N-SUBSTITUTED BENZAMIDES AND THEIR USE IN THE TREATMENT OF PAIN

[001] PRIORITY OF INVENTION

[002] This application claims priority to international patent application number PCT/IB2012/001324, filed 22 May 2012, and to United States Provisional Patent Application Number 61/650,934, filed 23 May 2012, and to United States Provisional Patent Application Number 61/785,601, filed 14 March 2013. The entire content of the applications referenced above are hereby incorporated by reference herein.

[003] FIELD OF THE INVENTION

[004] The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to inhibitors of sodium channel (e.g., NAV1.7) that are useful for treating sodium channel-mediated diseases or conditions, such as pain, as well as other diseases and conditions associated with the mediation of sodium channels.

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

[006] The hallmarks of sodium channels include rapid activation and inactivation when the voltage across the plasma membrane of an excitable cell is depolarized (voltage-dependent gating), and efficient and selective conduction of sodium ions through conducting pores intrinsic to the structure of the protein (Sato, C., et al., Nature (2001), 409:1047–1051). At negative or hyperpolarized membrane potentials, sodium channels are closed. Following membrane depolarization, sodium channels open rapidly and then inactivate. Channels only conduct currents in the open state and, once inactivated, have to return to the resting state, favoured by membrane hyperpolarization, before they can reopen. Different sodium channel subtypes vary in the voltage range over which they activate and inactivate as well as their activation and inactivation kinetics.

[007] The sodium channel family of proteins has been extensively studied and shown to be involved in a number of vital body functions. Research in this area has identified variants of the alpha subunits that result in major changes in channel function and activities, which can ultimately lead to major pathophysiological conditions. The members of this family of proteins are denoted NaV1.x, where x=1 to 9. NaV1.1 and NaV1.2 are highly expressed in the brain (Raymond, C.K., et al., J. Biol. Chem. (2004), 279(44):46234-41) and are vital to normal brain function. Some loss of function mutations in NaV1.1 in humans result in epilepsy, apparently because many of these channels are expressed in inhibitory neurons

(Yu, F. H., et al., Nat Neurosci (2006), 9 (9), 1142-9). Thus, block of NaV1.1 in the CNS may be counter-productive because it can produce hyperexcitability. However, NaV1.1 is also expressed in the peripheral nervous system and block may afford analgesic activity.

[008] NaV1.3 is expressed primarily in the fetal central nervous system. It is expressed at very low levels or not at all in the peripheral nervous system, but expression is upregulated in the dorsal horn sensory neurons of rats after nervous system injury (Hains, B.D., et al., J. Neurosci. (2003), 23(26):8881-92). Thus, it is an inducible target for treatment of pain following nerve injury.

[009] NaV1.4 is expressed primarily in skeletal muscle (Raymond, C.K., et al., op. cit.). Mutations in this gene have been shown to have profound effects on muscle function including paralysis, (Tamaoka A., Intern. Med. (2003), (9):769-70).

[010] NaV1.5, is expressed mainly in cardiac myocytes (Raymond, C.K., et al., op. cit.), including atria, ventricles, the sino-atrial node, atrio-ventricular node and cardiac Purkinje fibers. The rapid upstroke of the cardiac action potential and the rapid impulse conduction through cardiac tissue is due to the opening of NaV1.5. Abnormalities in the function of NaV1.5 can result inthe genesis of a variety of cardiac arrhythmias. Mutations in human NaV1.5 result in multiple arrhythmic syndromes, including, for example, long QT3 (LQT3), Brugada syndrome (BS), an inherited cardiac conduction defect, sudden unexpected nocturnal death syndrome (SUNDS) and sudden infant death syndrome (SIDS) (Liu, H., et al., Am. J. Pharmacogenomics (2003), 3(3):173-9). Sodium channel blocker therapy has been used extensively in treating cardiac arrhythmias.

[011] NaV1.6 is a widely distributed voltage-gated sodium channel found throughout the central and peripheral nervous systems. It is expressed at high density in the nodes of Ranvier of myelinated neurons (Caldwell, J.H., et al., Proc. Natl. Acad. Sci. USA (2000), 97(10): 5616-20).

[012] NaV1.7 is a tetrodotoxin-sensitive voltage-gated sodium channel encoded by the gene SCN9A. Human NaV1.7 was first cloned from neuroendocrine cells (Klugbauer, N., et al., 1995 EMBO J., 14 (6): 1084-90.) and rat NaV1.7 was cloned from a pheochromocytoma PC12 cell line (Toledo-Aral, J. J., et al., Proc. Natl.Acad. Sci. USA (1997), 94:1527–1532) and from rat dorsal root ganglia (Sangameswaran, L., et al., (1997), J. Biol. Chem., 272 (23): 14805-9). NaV1.7 is expressed primarily in the peripheral nervous system, especially nocieptors and olfactory neurons and sympathetic neurons. The inhibition, or blocking, of NaV1.7 has been shown to result in analgesic activity. Knockout of NaV1.7 expression in a subset of sensory neurons that are predominantly nociceptive results in resistance to inflammatory pain (Nassar, et al., op. cit.). Likewise, loss of function mutations in humans results in congenital indifference to pain (CIP), in which the individuals are resistant to both inflammatory and neuropathic pain (Cox, J.J., et al., Nature (2006);444:894-898; Goldberg, Y.P., et al., Clin. Genet. (2007);71:311-319). Conversely, gain of function mutations in NaV1.7 have been established in two human heritable pain conditions, primary erythromelalgia and familial rectal pain, (Yang, Y., et al., J. Med. Genet. (2004), 41(3):171-4). In addition, a single nucleotide polymorphism (R1150W) that has very subtle effects on the time- and

voltage-dependence of channel gating has large effects on pain perception (Estacion, M., et al., 2009. Ann Neurol 66: 862-6; Reimann, F., et al., Proc Natl Acad Sci U S A (2010), 107: 5148-53). About 10% of the patients with a variety of pain conditions have the allele conferring greater sensitivity to pain and thus might be more likely to respond to block of NaV1.7. Because NaV1.7 is expressed in both sensory and sympathetic neurons, one might expect that enhanced pain perception would be accompanied by cardiovascular abnormalities such as hypertension, but no correlation has been reported. Thus, both the CIP mutations and SNP analysis suggest that human pain responses are more sensitive to changes in NaV1.7 currents than are perturbations of autonomic function.

[013] NaV1.8 is expressed primarily in sensory ganglia of the peripheral nervous sytem, such as the dorsal root ganglia (Raymond, C.K., et al., op. cit.). There are no identified human mutations for NaV1.8 that produce altered pain responses. NaV1.8 differs from most neuronal NaV's in that it is insensitive to block by tetrodotoxin. Thus, one can isolate the current carried by this channel with tetrodotoxin. These studies have shown that a substantial portion of total sodium current is NaV1.8 in some dorsal root ganglion neurons (Blair, N.T., et al., J Neurosci (2002), 22: 10277-90). Knock-down of NaV1.8 in rats has been achieved by using antisense DNA or small interfering RNAs and virtually complete reversal of neuropathic pain was achieved in the spinal nerve ligation and chronic constriction injury models (Dong, X.W., et al., Neuroscience (2007),146: 812-21; Lai J., et al. Pain (2002), 95: 143-52). Thus, NaV1.8 is considered a promising target for analgesic agents based upon the limited tissue distribution of this NaV isoform and the analgesic activity produced by knock-down of channel expression.

[014] NaV1.9 is also a tetrodotoxin insensitive, sodium channel expressed primarily in dorsal root ganglia neurons (Dib-Hajj, S.D., et al. (see Dib-Hajj, S.D., et al., Proc. Natl. Acad. Sci. USA (1998), 95(15):8963-8). It is also expressed in enteric neurons, especially the myenteric plexus (Rugiero, F., et al., J Neurosci (2003), 23: 2715-25). The limited tissue distribution of this NaV isoform suggests that it may be a useful target for analgesic agents (Lai, J., et al., op. cit.; Wood, J.N., et al., op. cit.; Chung, J.M., et al., op. cit.). Knock-out of NaV1.9 results in resistance to some forms of inflammatory pain (Amaya, F., et al., J Neurosci (2006), 26: 12852-60; Priest, B.T., et al., Proc Natl Acad Sci U S A (2005), 102: 9382-7).

[015] This closely related family of proteins has long been recognized as targets for therapeutic intervention. Sodium channels are targeted by a diverse array of pharmacological agents. These include neurotoxins, antiarrhythmics, anticonvulsants and local anesthetics (England, S., et al., Future Med Chem (2010), 2: 775-90; Termin, A., et al., Annual Reports in Medicinal Chemistry (2008), 43: 43-60). All of the current pharmacological agents that act on sodium channels have receptor sites on the alpha subunits. At least six distinct receptor sites for neurotoxins and one receptor site for local anesthetics and related drugs have been identified (Cestèle, S., et al., Biochimie (2000), Vol. 82, pp. 883-892).

[016] The small molecule sodium channel blockers or the local anesthetics and related antiepileptic and antiarrhythmic drugs interact with overlapping receptor sites located in the inner cavity of the pore of the sodium channel (Catterall, W.A., Neuron (2000), 26:13-25). Amino acid residues in the S6 segments from

at least three of the four domains contribute to this complex drug receptor site, with the IVS6 segment playing the dominant role. These regions are highly conserved and as such most sodium channel blockers known to date interact with similar potency with all channel subtypes. Nevertheless, it has been possible to produce sodium channel blockers with therapeutic selectivity and a sufficient therapeutic window for the treatment of epilepsy (e.g., lamotrignine, phenytoin and carbamazepine) and certain cardiac arrhythmias (e.g., lignocaine, tocainide and mexiletine). However, the potency and therapeutic index of these blockers is not optimal and have limited the usefulness of these compounds in a variety of therapeutic areas where a sodium channel blocker would be ideally suited.

[017] Sodium channel blockers have been shown to be useful in the treatment of pain, including acute, chronic, inflammatory and/or neuropathic pain (see, e.g., Wood, J.N., et al., J. Neurobiol. (2004), 61(1), 55-71. Preclinical evidence demonstrates that sodium channel blockers can suppress neuronal firing in peripheral and central sensory neurons, and it is via this mechanism that they are considered to be useful for relieving pain. In some instances, abnormal or ectopic firing can original from injured or otherwise sensitized neurons. For example, it has been shown that sodium channels can accumulate in peripheral nerves at sites of axonal injury and may function as generators of ectopic firing (Devor et al., J. Neurosci.(1993), 132: 1976). Changes in sodium channel expression and excitability have also been shown in animal models of inflammatory pain where treatment with proinflammatory materials (CFA, Carrageenan) promoted pain-related behaviors and correlated with increased expression of sodium channel subunits (Gould et al., Brain Res., (1999), 824(2): 296-99; Black et al., Pain (2004), 108(3): 237-47). Alterations in either the level of exprssion or distribution of sodium channels, therefore, may have a major influence on neuronal excitability and pain-related behaviors.

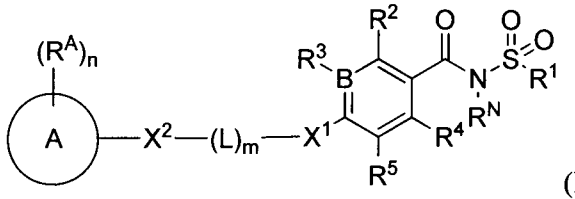
[018] Controlled infusions of lidocaine, a known sodium channel blocker, indicate that the drug is efficacious against neuropathic pain, but has a narrow therapeutic index. Likewise, the orally available local anesthetic, mexiletine, has dose-limiting side effects (Wallace, M.S., et al., Reg. Anesth. Pain Med. (2000), 25: 459-67). A major focus of drug discovery targeting voltage-gated sodium channels has been on strategies for improving the therapeutic index. One of the leading strategies is to identify selective sodium channel blockers designed to preferentially block NaV1.7, NaV1.8, NaV1.9 and/or NaV1.3. These are the sodium channel isoforms preferentially expressed in sensory neurons and unlikely to be involved in generating any dose-limiting side effects. For example, there is concern that blocking of NaV1.5 would be arrhythmogenic, so that selectivity of a sodium channel blocker against NaV1.5 is viewed as highly desirable. Furthermore, nearly 700 mutations of the SCN1A gene that codes for NaV1.1 have been identified in patients with Severe Myoclonic Epilepsy of Infancy (SMEI), making this the most commonly mutated gene in human epilepsy. Half of these mutations result in protein truncation (Meisler, M.H ., et al., The Journal of Physiology (2010), 588: 1841-8). Thus, selectivity of a sodium channel blocker against NaV1.1 is also desirable.

[019] In addition to the strategies of identifying selective sodium channel blockers, there is the continuing strategy of identifying therapeutic agents for the treatment of neuropathic pain. There has been some degree of success in treating neuropathic pain symptoms by using medications originally approved as anticonvulsants, such as gabapentin, and more recently pregabalin. However, pharmacotherapy for neuropathic pain has generally had limited success for a variety of reasons: sedation, especially by drugs first developed as anticonvulsants or anti-depressants, addiction or tachyphylaxis, especially by opiates, or lack of efficacy, especially by NSAIDs and anti-inflammatory agents. Consequently, there is still a considerable need to explore novel treatment modalities for neuropathic pain, which includes, but is not limited to, post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, and pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias.

[020] There are a limited number of effective sodium channel blockers for the treatment of pain with a minimum of adverse side effects which are currently in the clinic. There is also an unmet medical need to treat neuropathic pain and other sodium channel associated pathological states effectively and without adverse side effects due to the blocking of sodium channels not involved in nociception. The present invention provides methods to meet these critical needs.

[021] SUMMARY OF THE INVENTION

In one aspect the present invention provides for novel compounds. In a first embodiment of such compounds (Embodiment 1; abbreviated as "E1") the invention provides for compound selected from a compound of Formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein in Formula I:

[022] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 9 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$,

$-(X^{1R})_{0-1}-P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

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

[024] **B** is C or N;

[025] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[026] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-7} heterocycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

[027] **L** is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^L substituents selected from the group consisting of =O, -OH, -OCH2.phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

[028] the subscript m represents the integer 0 or 1;

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

[030] the subscript n is an integer from 0 to 5;

[031] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[032] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, heteroaryl, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and

R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2$N-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy, tetrahydronaphthalene and phenyl wherein phenyl is optionally substituted with 1-3 fluoro, chloro, bromo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy , C_{1-6} alkylamino, C_{1-6} or dialkylamino;

[033] with the proviso that a compound of Formula I is not
4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;
4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or
4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

[034] Further embodiments (E) of the first embodiment of compounds of the invention, are described below.

[035] E2 A compound of E1, wherein:

[036] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S as ring vertex and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8}

cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

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

[038] **B** is C or N;

[039] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[040] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

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

[042] the subscript m represents the integer 0 or 1;

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

[044] the subscript n is an integer from 0 to 5;

[045] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[046] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, heteroaryl, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6

membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)$_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene;

[047] with the proviso that a compound of Formula I is not

4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;

4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or

4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

[048] E3 A compound of E1, wherein:

[049] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatoms selected from N, O and S as ring vertex and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl;

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

[051] **B** is C or N;

[052] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[053] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3

heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

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

[055] the subscript m represents the integer 0 or 1;

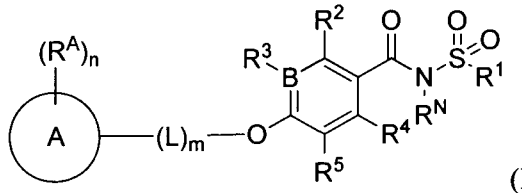
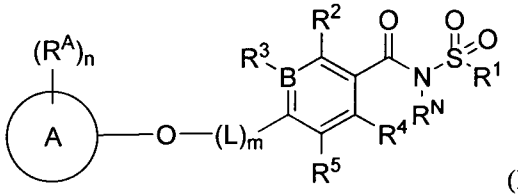
[056] $\mathbf{X^1}$ and $\mathbf{X^2}$ are each independently selected from the group consisting of absent, –O-, -S(O)-, $-S(O)_2-$ and $-N(R^X)-$ wherein R^x is C_{1-8} alkyl, C_{1-8} acyl or $-S(O)_2(C_{1-8}$ alkyl), and wherein if the subscript m is 0 then one of X^1 or X^2 is absent;

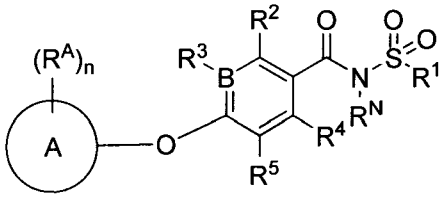
[057] the subscript n is an integer from 0 to 5;

[058] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[059] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2N$-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2N$-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene.

[060] E4 A compound of any one of E1-E3, wherein the compound has the formula I-I, I-II, or I-III:

[061]  (I-I),  (I-II)

or  (I-III).

[062] E5 A compound of E1, E2, E3, or E4 wherein B is N and R^3 is absent.

[063] E6 A compound of E1, E2, E3, or E4 wherein B is C.

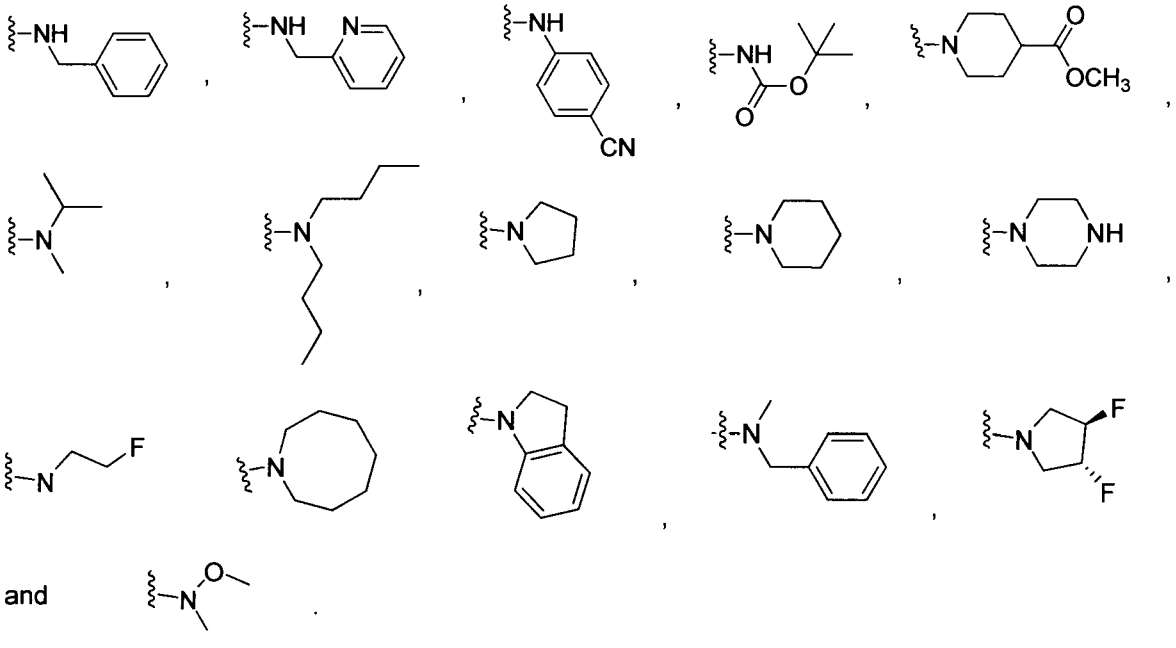
[064] E7 A compound of E1, E2, E3 E4, E5, or E6 wherein R^2, R^3 and R^4 are each independently selected from H, F, or Cl.

[065] E8 A compound of E1, E2, E3 E4, E5, E6, E7, or E8 wherein R^2 is H, F or Cl; R^3 and R^4 are each H; and R^5 is an optionally substituted group selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, and C_{1-8} alkoxy.

[066] E9 A compound of E1, E2, E3 E4, E5, E6, E7, or E8 wherein R^1 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl or $-NR^{1A}R^{1B}$.

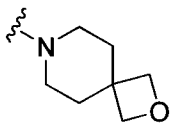
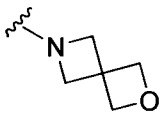
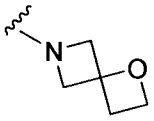
[067] E10 A compound of E9, wherein R^1 is selected from the group consisting of methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, monofluoromethyl, isopropyl and cyclopropyl.

[068] E11 A compound of E1, E2, E3 E4, E5, E6, E7, or E8 wherein R^1 is selected from the group consisting of: $-NH(CH_3)$, $-N(CH_3)_2$,



and .

[069] E12 A compound of E1, E2, E3 E4, E5, E6, E7, or E8 wherein R^1 is selected from the group consisting of: methyl, ethyl, *tert*-butyl, dimethylamino, methylamino, amino, morpholino, azetidino, imidazolyl, 3-hydroxyazetidino, 3-fluoroazetidino, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, N-methylimidazolyl, tetrahydorofuranyl, 2-isopropoxyethyl, 3-cyanoazetidino, 2-ethoxyethyl, 2-methoxypropyl, 2-hydroxypropyl, 4-hydroxypiperidinyl and 3-methoxypyrrolidinyl and the following formulas:


,

and

.

[070] E13 A compound of E1, E2, E3 E4, E5, E6, E7, or E8 wherein R^1 is selected from the group consisting of: methyl, ethyl, *tert*-butyl, dimethylamino, methylamino, amino, morpholino, azetidino, imidazolyl, 3-hydroxyazetidino, 3-fluoroazetidino, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, and N-methylimidazolyl.

[071] E14 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is an optionally substituted group selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene.

[072] E15 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–CH_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

[073] E16 A compound of E15, wherein X^1 is –O-; the subscript m is 1 and –(L)- is $–CH_2-$ or $–CH_2-CH_2-$.

[074] E17 The compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein X^1 is absent; X^2 is –O- or –N(H)-; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

[075] E18 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein X^1 and X^2 is absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

[076] E19 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein X^1 and X^2 is absent; the subscript m is 1; and –(L)- is an optionally substituted C_{1-4} heteroalkylene.

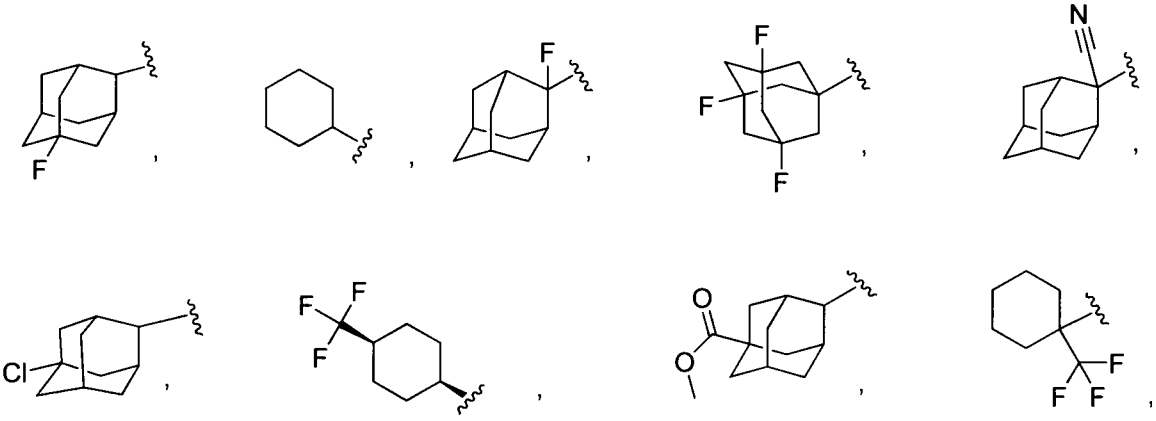
[077] E20 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein m is 0; X^1 is selected from –O-, and –N(H)-; and X^2 is absent.

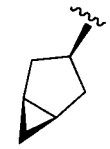
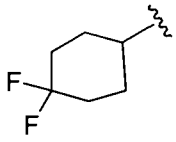
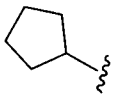
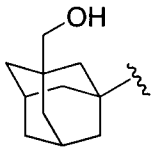
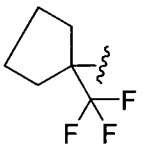
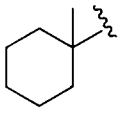
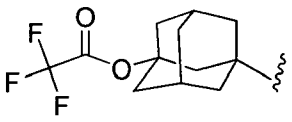
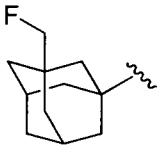
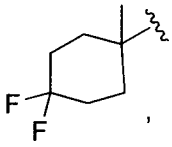
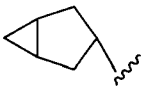
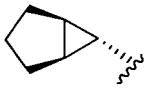
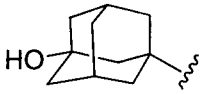
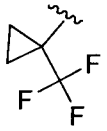
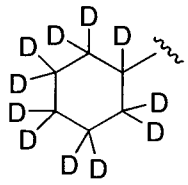
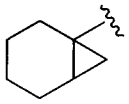
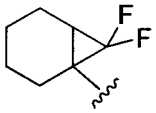
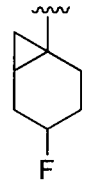
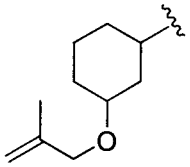
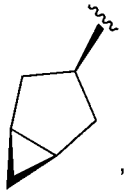
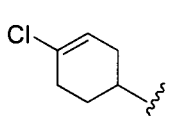
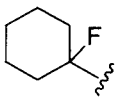
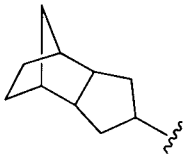
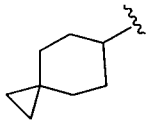
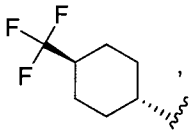
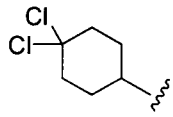
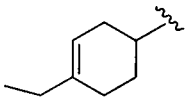
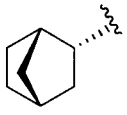
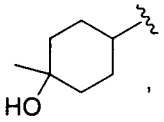
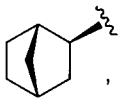
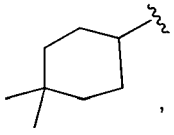
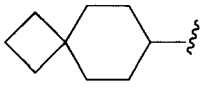
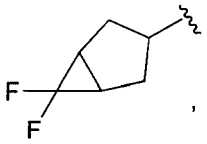
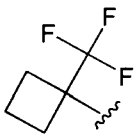
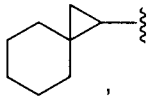
[078] E21 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, adamantane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, bicyclo[3.3.1]nonane and 1,2,3,4-tetrahydro-1,4-methanonaphthalene, 1,2,3,4-tetrahydroisoquinoline and chroman.

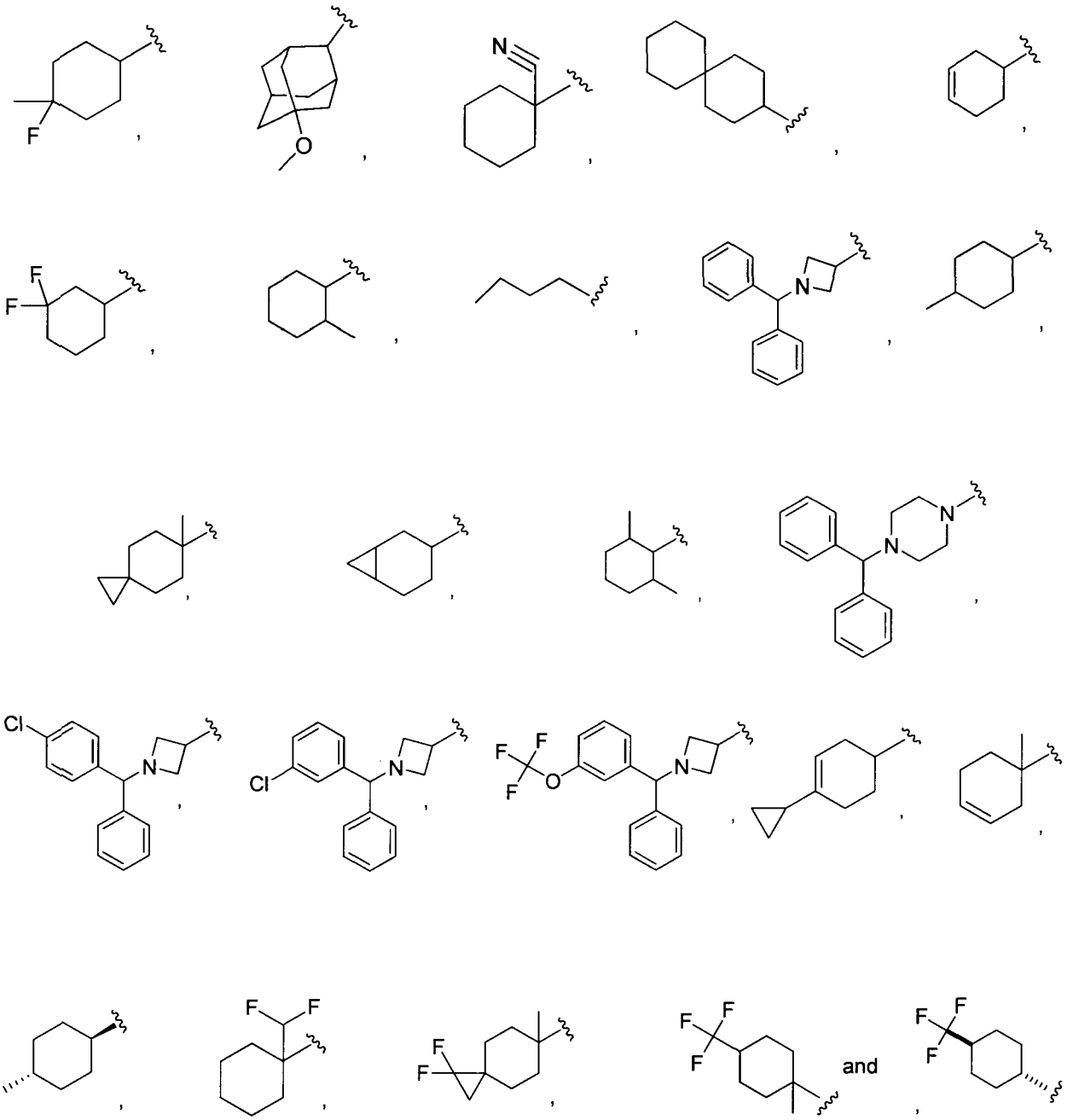
[079] E22 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein ring A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane, cubane, bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, piperidinyl, tetrahydrofuranyl, tetrahydronaphthyl, spiro[2,5]octanyl, norpinanyl, spiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, norbornanyl, spiro[4.5]decanyl, bicyclo[4.1.0]heptane and spiro[5.5]undecanyl.

[080] E23 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein ring A is an optionally substituted ring selected from the group consisting of azetidine, pyrrolidine, piperidine, homopiperidine, (1R,5S)-8-azabicyclo[3.2.1]octane, 3-oxa-9-azabicyclo[3.3.1]nonane, (1s,4s)-7-azabicyclo[2.2.1]heptane, (1R,4S)-5-azabicyclo[2.1.1]hexane, 7-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and quinuclidine.

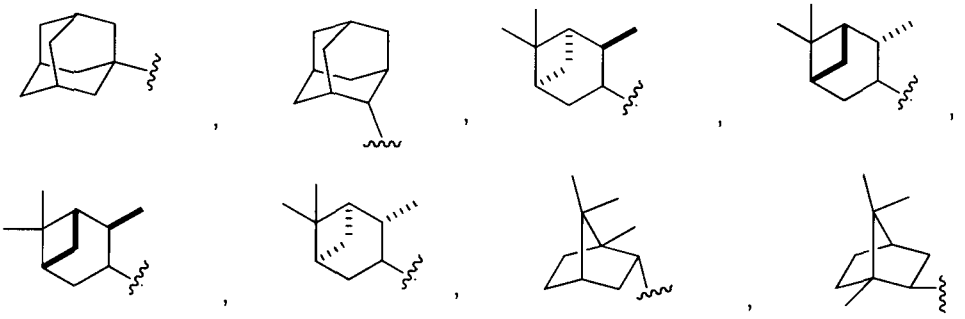
[081] E24 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein wherein ring A-$(R^A)_n$ is selected from the group consisting of

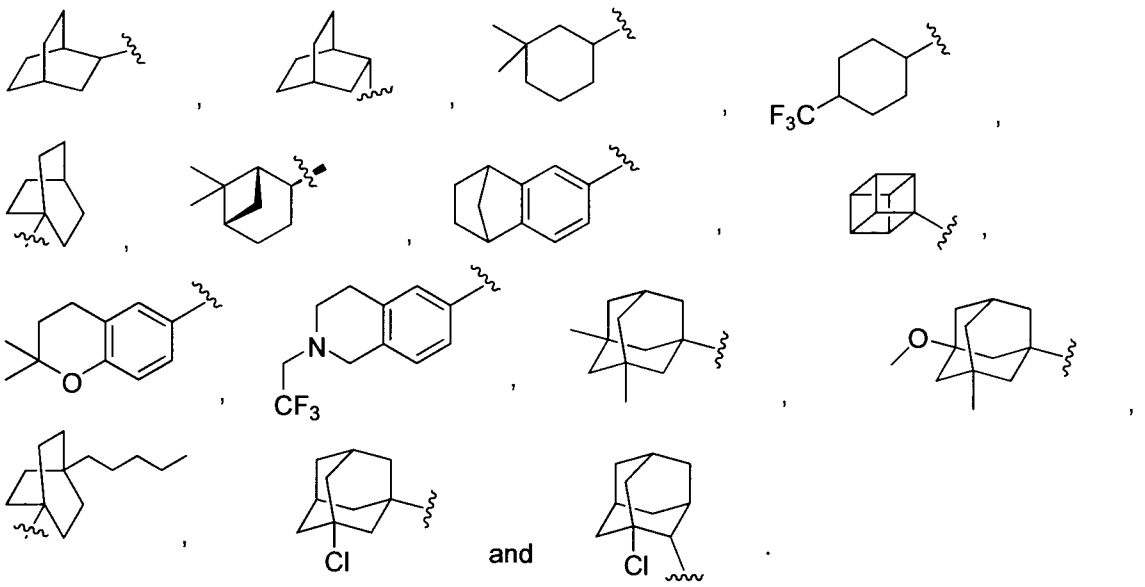



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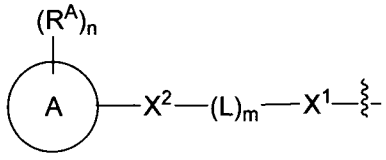


[082] E25 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein A-$(R^A)_n$ is is selected from the group consisting of

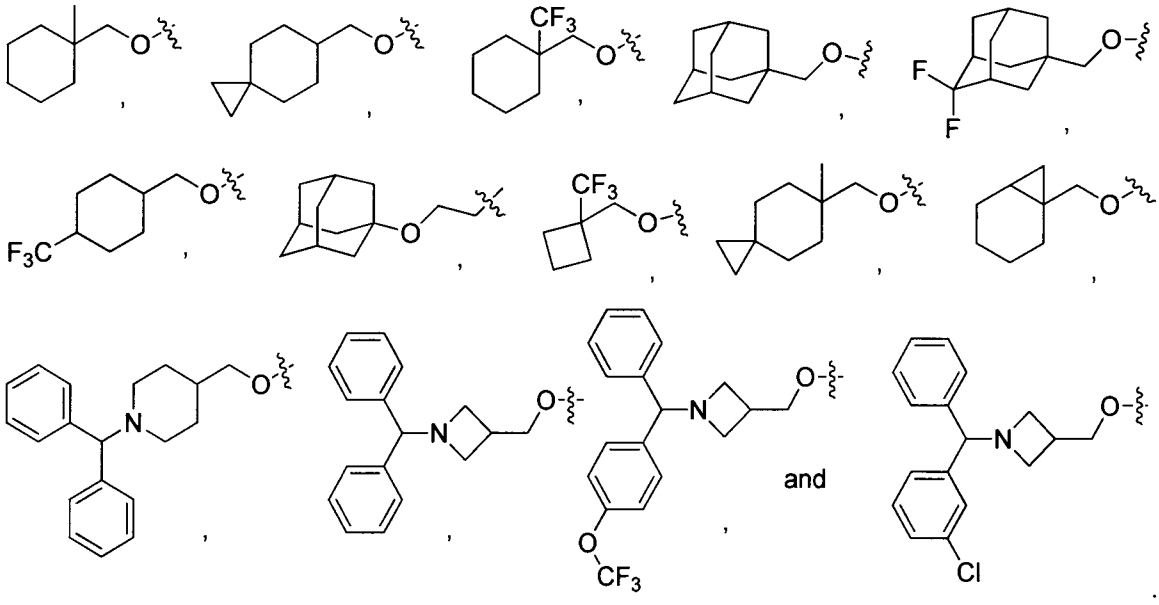




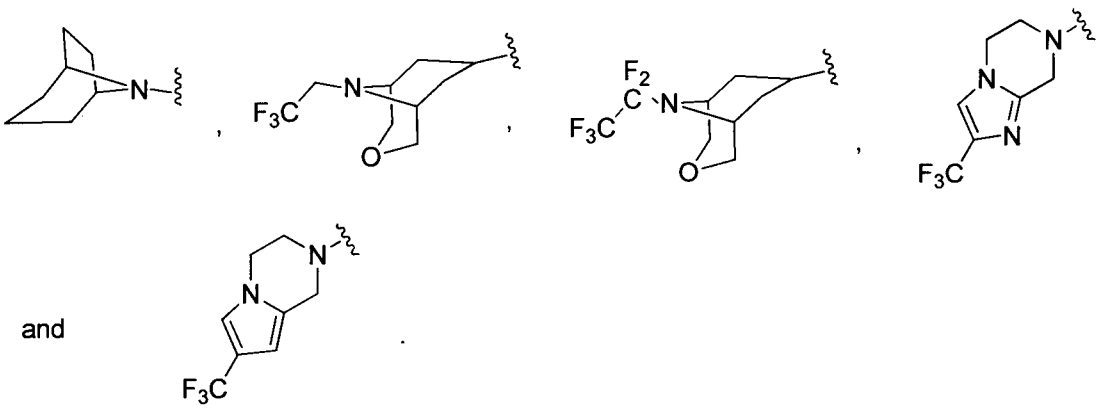
[083] E26 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, or E13 wherein the group:



is selected from the group consisting of



[084] E27 A compound of E1, E2 , E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, or E20 wherein A is selected from the group consisting of



and

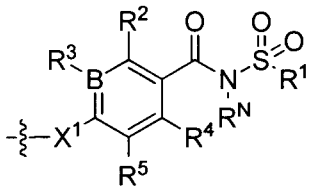
[085] E28 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E20, E21, E22, or E23 wherein R^A is selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{2-4} heterocycloalkyl, F, Cl, Br, I, -OH, $-NH_2$, -CN, $-NO_2$, C_{1-4} alkoxy, $-C(=O)-N(R^{A1})(R^{A2})$ and $-N(R^{A1})(R^{A2})$.

[086] E29 A compound of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E20, E21, E22, or E23 wherein R^A is methyl, trifluromethyl, difluoromethyl, monofluoromethyl, ethyl, pentafluoroethyl, cyclopropyl, -F, Cl, -OH, $-NH_2$ or –CN.

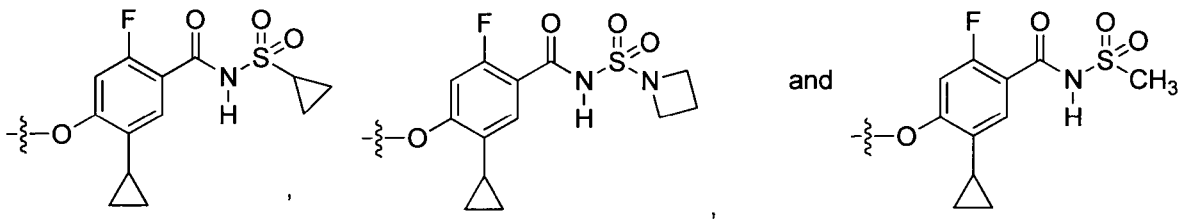
[087] E30 A compound of E1, E2, E3, E4, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E20, E21, E22, E23, E24, E25, E26, E27, E28, or E29 wherein B is C; R^3 is H, R^2 is F, Cl, Br, or I; R^4 is H; and R^5 is C_{3-8} cycloalkyl, wherein said C_{3-8} cycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, $-C_{1-4}$ alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy.

[088] E31 A compound of E30 wherein R^5 is C_{3-8} cycloalkyl.

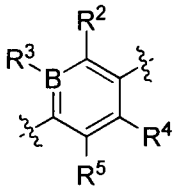
[089] E32 A compound of E1, E2, E3, E4, E21, E22, E23, E24, E25, E27, E28, or E29 wherein the group:



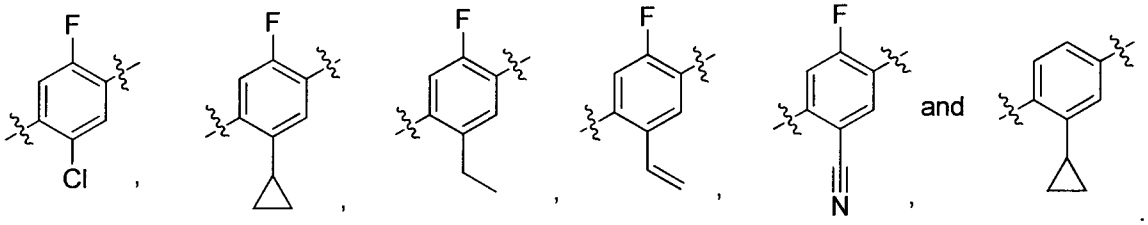
is selected from the group consisting of



[090] E33 A compound of E1, E2, E3, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E20, E21, E22, or E23 wherein the group:



is selected from the group consisting of



[091] E34 A compound of E1 selected from the group consisting of compounds set forth in Table 1 presented herein.

[092] In another aspect the present invention provides for a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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

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

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

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

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

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

[099] In another aspect of the invention, the present invention provides for a method for the treatment or prophylaxis of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, which method comprises administering an effective amount of a Formula I or a pharmaceutically acceptable salt thereof.

[0100] In another aspect of the invention, the present invention provides for a compound of formula I or a pharmaceutically acceptable salt thereof for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

[0101] In another aspect of the invention, the present invention provides for the use of a compound of any of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

[0102] In another aspect of the invention, the present invention provides for a compound of Formula I or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease.

[0103] In another aspect of the invention, the present invention provides for a compound of Formula I or a pharmaceutically acceptable salt thereof for use in medical therapy.

[0104] In one aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof with enhanced Nav1.7 potency. In another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof with reduced plasma protein interactions. In another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof with enhanced Nav1.7 potency without significantly reduced plasma protein interactions. For example, representative compounds of formula (I) wherein B is C; R^3 is H, R^2 is F, Cl, Br, or I; and R^5 is C_{3-8} cycloalkyl were found to possess enhanced Nav1.7 potency over similar compounds wherein R^5 is other than C_{3-8} cycloalkyl.

[0105] DETAILED DESCRIPTION OF THE INVENTION

[0106] Definitions

[0107] As used herein, the term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (i.e., C_{1-8} means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl radical having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl radical having one or more triple bonds. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "cycloalkyl," "carbocyclic," or "carbocycle" refers to hydrocarbon ringsystem having 3 to 10 overall number of ring atoms (e.g., 3-10 membered cycloalkyl is a cycloalkyl with 3 to 10 ring atoms, or C_{3-10} cycloalkyl is a cycloalkyl with 3-10 carbon ring atoms) and for a 3-5 membered cycloalkyl being fully saturated or having no more than one double bond between ring vertices and for a 6 membered cycloalkyl or larger being fully saturated or having no more than two double bonds between ring vertices. As used

herein, "cycloalkyl," "carbocyclic," or "carbocycle" is also meant to refer to bicyclic, polycyclic and spirocyclic hydrocarbon ring system, such as, for example, bicyclo[2.2.1]heptane, pinane, bicyclo[2.2.2]octane, adamantane, norborene, spirocyclic C_{5-12} alkane, etc. As used herein, the terms, "alkenyl," "alkynyl," "cycloalkyl,", "carbocycle," and "carbocyclic," are meant to include mono and polyhalogenated variants thereof.

[0108] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain hydrocarbon radical, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N and S can be placed at any interior position of the heteroalkyl group. The heteroatom Si can be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. A "heteroalkyl" can contain up to three units of unsaturation, and also include mono- and poly-halogenated variants, or combinations thereof. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CF_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH=N(CH_3)-CH_3$. Up to two heteroatoms can be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[0109] The term "heterocycloalkyl," "heterocyclic," or "heterocycle" refers to a saturated or partially unsaturated ring system radical having the overall having from 3-10 ring atoms (e.g., 3-10 membered heterocycloalkyl is a heterocycloalkyl radical with 3-10 ring atoms, a C_{2-9} heterocycloalkyl is a heterocycloalkyl having 3-10 ring atoms with between 2-9 ring atoms being carbon) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, nitrogen atom(s) are optionally quaternized, as ring atoms. Unless otherwise stated, a "heterocycloalkyl," "heterocyclic," or "heterocycle" ring can be a monocyclic, a bicyclic, spirocyclic or a polycylic ring system. Non limiting examples of "heterocycloalkyl," "heterocyclic," or "heterocycle" rings include pyrrolidine, piperidine, N-methylpiperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, pyrimidine-2,4(1H,3H)-dione, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrhydrothiophene, quinuclidine, tropane, 2-azaspiro[3.3]heptane, (1R,5S)-3-azabicyclo[3.2.1]octane, (1s,4s)-2-azabicyclo[2.2.2]octane, (1R,4R)-2-oxa-5-azabicyclo[2.2.2]octane and the like A "heterocycloalkyl," "heterocyclic," or "heterocycle" group can be attached to the remainder of the molecule through one or more ring carbons or heteroatoms. A "heterocycloalkyl," "heterocyclic," or "heterocycle" can include mono- and poly-halogenated variants thereof.

[0110] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane (including branched alkane), as exemplified by $-CH_2CH_2CH_2CH_2-$ and $-CH(CH_2)CH_2CH_2-$.

Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. "Alkenylene" and "alkynylene" refer to the unsaturated forms of "alkylene" having double or triple bonds, respectively. "Alkylene", "alkenylene" and "alkynylene" are also meant to include mono and poly-halogenated variants.

[0111] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical, saturated or unsaturated or polyunsaturated, derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$, $-O-CH_2-CH=CH-$, $-CH_2-CH=C(H)CH_2-O-CH_2-$ and $-S-CH_2-C\equiv C-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). The term "heteroalkylene" is also meant to include mono and poly-halogenated variants.

[0112] The terms "alkoxy," "alkylamino" and "alkylthio", are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom ("oxy"), an amino group ("amino") or thio grou, and further include mono- and poly-halogenated variants thereof. Additionally, for dialkylamino groups, the alkyl portions can be the same or different.

[0113] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. The term "(halo)alkyl" is meant to include both a "alkyl" and "haloalkyl" substituent. Additionally, the term "haloalkyl," is meant to include monohaloalkyl and polyhaloalkyl. For example, the term "C_{1-4} haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, difluoromethyl, and the like.

[0114] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon ring radical, which can be a single ring or multiple rings (up to three rings) which are fused together and having the stated number of aryl ring atoms. The term "heteroaryl" refers to aryl ring(s) that contain from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl groups include phenyl, naphthyl and biphenyl, while non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalaziniyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like. Optional substituents for each of the above noted aryl and heteroaryl ring systems can be selected from the group of acceptable substituents described further below.

[0115] The above terms (e.g., "alkyl," "aryl" and "heteroaryl"), in some embodiments, will include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0116] Substituents for the alkyl radicals (including those groups often referred to as alkylene, alkenyl, alkynyl, heteroalkyl, cycloalkyl and heterocycloalkyl) can be a variety of groups including,but not limited to,

-halogen, -OR', -NR'R", -SR', -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'"C(O)NR'R", -NR"C(O)$_2$R', -NHC(NH_2)=NH, -NR'C(NH_2)=NH, -NHC(NH_2)=NR', -NR'"C(NR'R")=N-CN, -NR'"C(NR'R")=NOR', -NHC(NH_2)=NR',-S(O)R', -S(O)$_2$R', -S(O)$_2$NR'R", -NR'S(O)$_2$R", -NR'"S(O)$_2$NR'R", -CN, -NO_2, -(CH_2)$_{1-4}$-OR', -(CH_2)$_{1-4}$-NR'R", -(CH_2)$_{1-4}$-SR', -(CH_2)$_{1-4}$-SiR'R"R'", -(CH_2)$_{1-4}$-OC(O)R', -(CH_2)$_{1-4}$-C(O)R', -(CH_2)$_{1-4}$-CO_2R', -(CH_2)$_{1-4}$CONR'R", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R" and R'" each independently refer groups including, for example, hydrogen, unsubstituted C_{1-6} alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups, unsubstituted heteroaryl, substituted heteroaryl, among others. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. Other substitutents for alkyl radicals, including heteroalkyl, alkylene, include for example, =O, =NR', =N-OR', =N-CN, =NH, wherein R' include substituents as described above.

[0117] Similarly, substituents for the aryl and heteroaryl groups are varied and are generally selected from the group including, but not limited to,

-halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"C(O)$_2$R', -NR'C(O)NR"R'", -NHC(NH_2)=NH, -NR'C(NH_2)=NH, -NHC(NH_2)=NR', -S(O)R', -S(O)$_2$R', -S(O)$_2$NR'R", -NR'S(O)$_2$R", -N_3, perfluoro-C_{1-4} alkoxy, and perfluoro-C_{1-4} alkyl, -(CH_2)$_{1-4}$-OR', -(CH_2)$_{1-4}$-NR'R", -(CH_2)$_{1-4}$-SR', -(CH_2)$_{1-4}$-SiR'R"R'", -(CH_2)$_{1-4}$-OC(O)R', -(CH_2)$_{1-4}$-C(O)R', -(CH_2)$_{1-4}$-CO_2R', -(CH_2)$_{1-4}$CONR'R", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R'" are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-C_{1-4} alkyl, and unsubstituted aryloxy-C_{1-4} alkyl. Other suitable substituents include each of the above aryl substituents attached to a ring atom by an alkylene tether of from 1-4 carbon atoms. When a substituent for the aryl or heteroaryl group contains an alkylene linker (e.g., -(CH_2)$_{1-4}$-NR'R"), the alkylene linker includes halo variants as well. For example, the linker "-(CH_2)$_{1-4}$-" when used as part of a substituent is meant to include difluoromethylene, 1,2-difluoroethylene, etc.

[0118] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0119] As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0120] As used herein, the term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0121] As used herein a wavy line " ~~~ " that intersects a bond in a chemical structure indicates the point of attachment of the bond that the wavy bond intersects in the chemical structure to the remainder of a molecule.

[0122] As used herein, the term "C-linked" means that the group that the term describes is attached the remainder of the molecule through a ring carbon atom.

[0123] As used herein, the term "N-linked" means that the group that the term describes is attached to the remainder of the molecule through a ring nitrogen atom.

[0124] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0125] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0126] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0127] As used herein, the term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0128] As used herein, the term "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[0129] As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis 4th edition, Wiley-Interscience, New York, 2006.

[0130] As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep

[0131] As used herein, the term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine,

triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0132] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0133] In addition to salt forms, the present invention provides compounds which are in a prodrug form. As used herein the term "prodrug" refers to those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0134] Prodrugs of the invention include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of a compound of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes phosphoserine, phosphothreonine, phosphotyrosine, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, gamma-carboxyglutamate, hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, methionine sulfone and tert-butylglycine.

[0135] Additional types of prodrugs are also encompassed. For instance, a free carboxyl group of a compound of the invention can be derivatized as an amide or alkyl ester. As another example, compounds of this invention comprising free hydroxy groups can be derivatized as prodrugs by converting the hydroxy

group into a group such as, but not limited to, a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl group, as outlined in Fleisher, D. et al., (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs Advanced Drug Delivery Reviews, 19:115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group can be an alkyl ester optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem., (1996), 39:10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-((C_{1-6})alkanoyloxy)ethyl, 1-methyl-1-((C_{1-6})alkanoyloxy)ethyl, (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, alpha-amino(C_{1-4})alkanoyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0136] For additional examples of prodrug derivatives, see, for example, a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs," by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, Advanced Drug Delivery Reviews, 8:1-38 (1992); d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77:285 (1988); and e) N. Kakeya, et al., Chem. Pharm. Bull., 32:692 (1984), each of which is specifically incorporated herein by reference.

[0137] Additionally, the present invention provides for metabolites of compounds of the invention. As used herein, a "metabolite" refers to a product produced through metabolism in the body of a specified compound or salt thereof. Such products can result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

[0138] Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well

known to those skilled in the art. The metabolite products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

[0139] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention can exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0140] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention.

[0141] The compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but the for the fact that one or more atoms are replace by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention, and their uses. Exemplary isotopes that can be incorporated in to compounds of the invention include istopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Certain isotopically labeled compounds of the present invention (e.g., those labeled with ^{3}H or ^{14}C) are useful in compound and /or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes are usefule for their ease of preparation and detectability. Further substituteion with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resuting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0142] The terms "treat" and "treatment" refer to both therapeutic treatment and/or prophylactic treatment or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as, for example, the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease or disorder, stabilized (i.e., not worsening) state of disease or disorder, delay or slowing of disease progression, amelioration or palliation of the disease state or disorder,

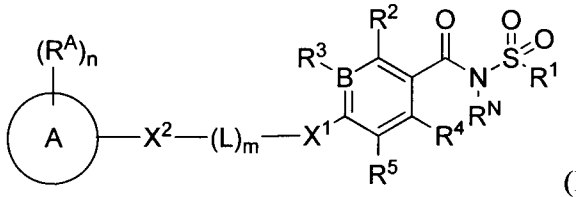
and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the disease or disorder as well as those prone to have the disease or disorder or those in which the disease or disorder is to be prevented.

[0143] The phrase "therapeutically effective amount" or "effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

[0144] The term "bioavailability" refers to the systemic availability (i.e., blood/plasma levels) of a given amount of drug administered to a patient. Bioavailability is an absolute term that indicates measurement of both the time (rate) and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

[0145] A. COMPOUNDS

In one aspect the present invention provides for compounds of Formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein in Formula I:

[0146] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 9 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8}

cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

[0147] $\mathbf{R^N}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

[0148] **B** is C or N;

[0149] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[0150] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-7} heterocycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

[0151] **L** is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^L substituents selected from the group consisting of =O, -OH, -OCH2.phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

[0152] the subscript m represents the integer 0 or 1;

[0153] $\mathbf{X^1}$ and $\mathbf{X^2}$ are each independently selected from the group consisting of absent, –O-, -S(O)-, -$S(O)_2$- and -$N(R^X)$- wherein R^x is H, C_{1-8} alkyl, C_{1-8} acyl or -$S(O)_2$(C_{1-8} alkyl), and wherein if the subscript m is 0 then at least one of X^1 or X^2 is absent;

[0154] the subscript n is an integer from 0 to 5;

[0155] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[0156] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, =O, heteroaryl, -$(X^{RA})_{0-1}NR^{A1}R^{A2}$, -$(X^{RA})_{0-1}OR^{A1}$, -$(X^{RA})_{0-1}SR^{A1}$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, -$(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, -$(X^{RA})_{0-1}C(=O)OR^{A1}$, -$(X^{RA})_{0-1}OC(=O)R^{A1}$, -$P(=O)(OR^{A1})(OR^{A2})$, -$(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, -$(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and -$(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or

monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2N$-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2N$-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy, tetrahydronaphthalene and phenyl wherein phenyl is optionally substituted with 1-3 fluoro, chloro, bromo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy , C_{1-6} alkylamino, C_{1-6} or dialkylamino;

[0157] with the proviso that a compound of Formula I is not

4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;

4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or

4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

[0158] In another aspect the present invention provides for a compound offormula (I) and pharmaceutically acceptable salts thereof, wherein in Formula I:

[0159] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S as ring vertex and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

[0160] $\mathbf{R^N}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

[0161] **B** is C or N;

[0162] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[0163] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

[0164] **L** is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^L substituents selected from the group consisting of =O, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

[0165] the subscript m represents the integer 0 or 1;

[0166] $\mathbf{X^1}$ and $\mathbf{X^2}$ are each independently selected from the group consisting of absent, –O-, -S(O)-, $-S(O)_2-$ and $-N(R^X)-$ wherein R^x is H, C_{1-8} alkyl, C_{1-8} acyl or $-S(O)_2(C_{1-8}$ alkyl), and wherein if the subscript m is 0 then one of X^1 or X^2 is absent;

[0167] the subscript n is an integer from 0 to 5;

[0168] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[0169] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, heteroaryl, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2$N-C(=O)-, C_{1-4}

(halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene;

[0170] with the proviso that a compound of Formula I is not

4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;

4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or

4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

[0171] In another aspect the present invention provides for a compound offormula (I) and pharmaceutically acceptable salts thereof, wherein in Formula I:

[0172] $\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl or –$NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatoms selected from N, O and S as ring vertex and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, -$(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, -$(X^{1R})_{0-1}OR^{R1a}$, -$(X^{1R})_{0-1}SR^{R1a}$, -$(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, -$(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, -$(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, -$(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, -$(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, -$(X^{1R})_{0-1}C(=O)OR^{R1a}$, -$(X^{1R})_{0-1}OC(=O)R^{R1a}$, -$(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, -$(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, -$(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, -$(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and -$(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl;

[0173] $\mathbf{R^N}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

[0174] **B** is C or N;

[0175] $\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

[0176] $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

[0177] **L** is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^L substituents selected from the group consisting of =O, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

[0178] the subscript m represents the integer 0 or 1;

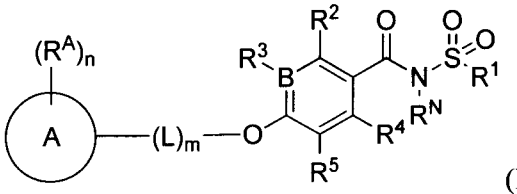
[0179] $\mathbf{X^1}$ and $\mathbf{X^2}$ are each independently selected from the group consisting of absent, –O-, -S(O)-, $-S(O)_2-$ and $-N(R^X)-$ wherein R^x is C_{1-8} alkyl, C_{1-8} acyl or $-S(O)_2(C_{1-8}$ alkyl), and wherein if the subscript m is 0 then one of X^1 or X^2 is absent;

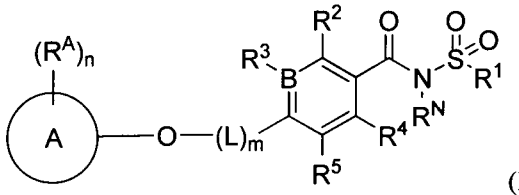
[0180] the subscript n is an integer from 0 to 5;

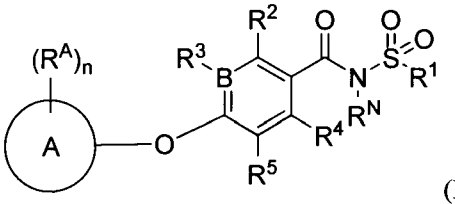
[0181] **A** is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

[0182] $\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2N$-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2N$-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene.

[0183] In another embodiment, a compound of formula I has the formula


(I-I),


(I-II) or


(I-III)

[0184] In another embodiment, in compounds of formula I, B is N and R^3 is absent.

[0185] In another embodiment, in compounds of formula I, B is carbon.

[0186] In another embodiment, in compounds of formula I, R^2, R^3 and R^4 are each independently selected from H, F, or Cl.

[0187] In another embodiment, in compounds of formula I, R^2 is H, F or Cl; R^3 and R^4 are each H; and R^5 is an optionally substituted group selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, and C_{1-8} alkoxy.

[0188] In another embodiment, in compounds of formula I, R^2 is H, F or Cl; R^3 and R^4 are each H; and R^5

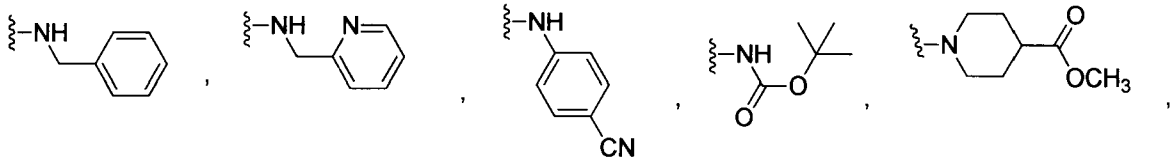
[0189] is an optionally substituted group selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{1-8} alkoxy.

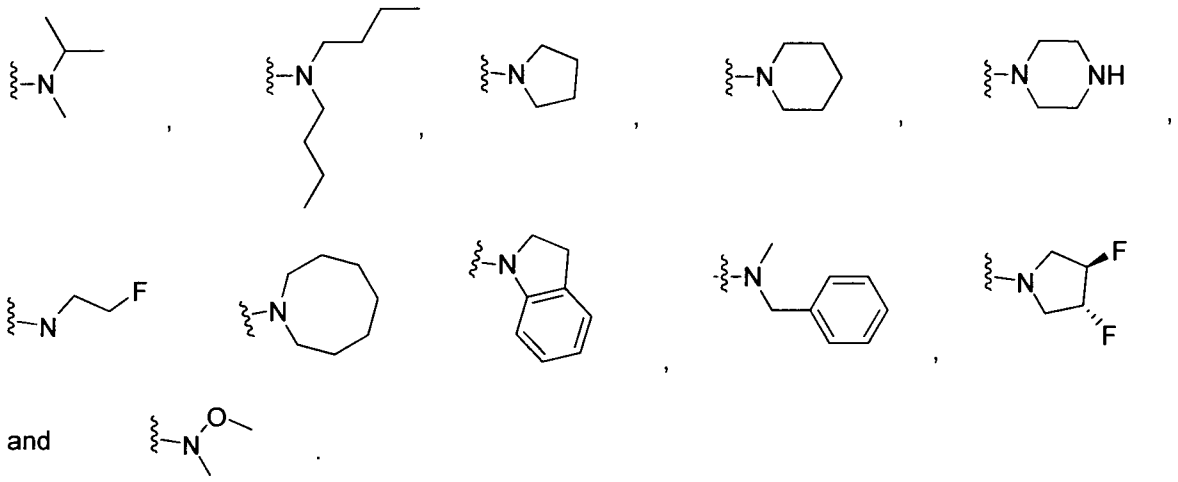
[0190] In another embodiment, in compounds of formula I, R^1 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl or $-NR^{1A}R^{1B}$.

[0191] In another embodiment, in compounds of formula I, R^1 is selected from the group consisting of methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, monofluoromethyl, isopropyl and cyclopropyl.

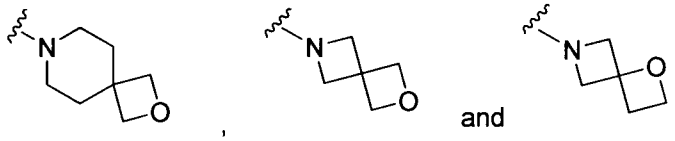
[0192] In another embodiment, in compounds of formula I, R^1 is selected from the group consisting of methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, monofluoromethyl, isopropyl, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, and N-methylimidazolyl.

[0193] In another embodiment, in compounds of formula I, R^1 is selected from the group consisting of: $-NH(CH_3)$, $-N(CH_3)_2$,





In another embodiment, in compounds of formula I, R^1 is selected from the group consisting of: methyl, ethyl, *tert*-butyl, dimethylamino, methylamino, amino, morpholino, azetidino, imidazolyl, 3-hydroxyazetidino, 3-fluoroazetidino, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, N-methylimidazolyl, tetrahydorofuranyl, 2-isopropoxyethyl, 3-cyanoazetidino, 2-ethoxyethyl, 2-methoxypropyl, 2-hydroxypropyl, 4-hydroxypiperidinyl and 3-methoxypyrrolidinyl and the following formulas:



[0194] In another embodiment, in compounds of formula I, X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is an optionally substituted group selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene.

[0195] In another embodiment, in compounds of formula I, X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–CH_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

[0196] In another embodiment, in compounds of formula I, X^1 is –O-; the subscript m is 1 and –(L)- is $–CH_2-$ or $–CH_2-CH_2-$.

[0197] In another embodiment, in compounds of formula I, X^1 is absent; X^2 is –O- or –N(H)-; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

[0198] In another embodiment, in compounds of formula I, X^1 and X^2 is absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, $–C(=O)-$, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

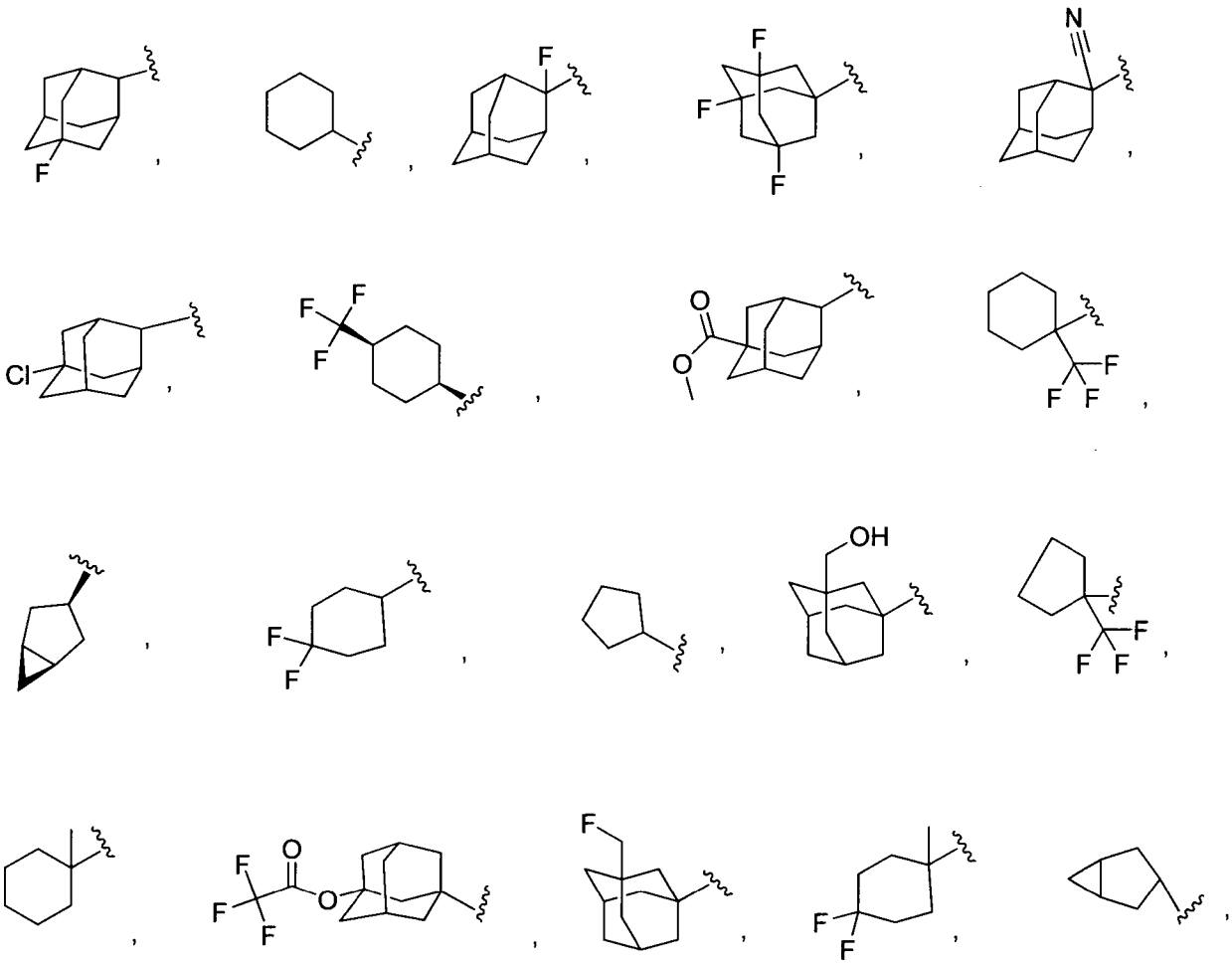
[0199] In another embodiment, in compounds of formula I, X^1 and X^2 is absent; the subscript m is 1; and –(L)- is an optionally substituted C_{1-4} heteroalkylene.

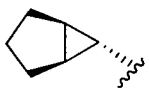
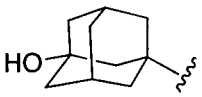
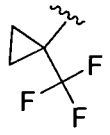
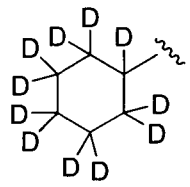
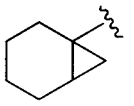
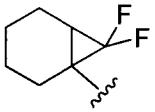
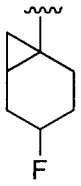
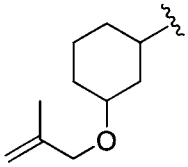
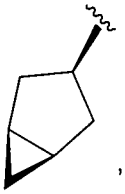
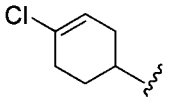
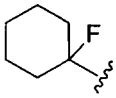
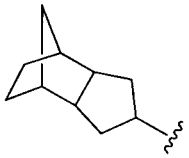
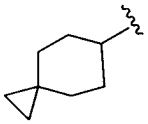
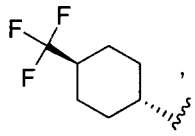
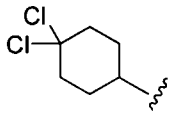
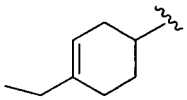
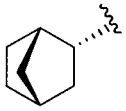
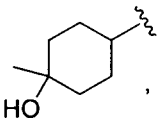
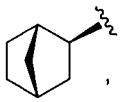
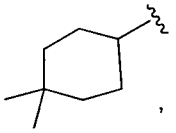
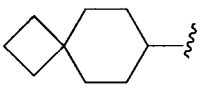
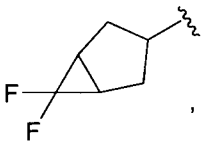
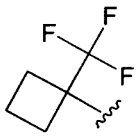
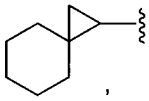
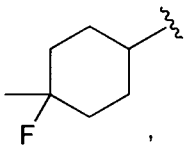
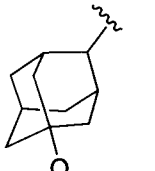
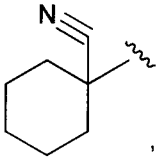
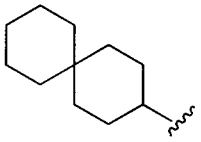
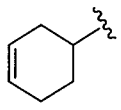
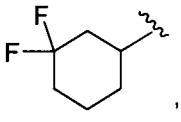
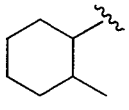
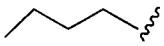
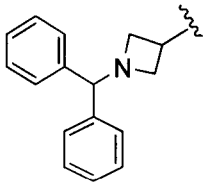
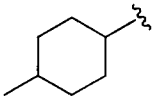
[0200] In another embodiment, in compounds of formula I, m is 0; X^1 is selected from –O-, and –N(H)-; and X^2 is absent.

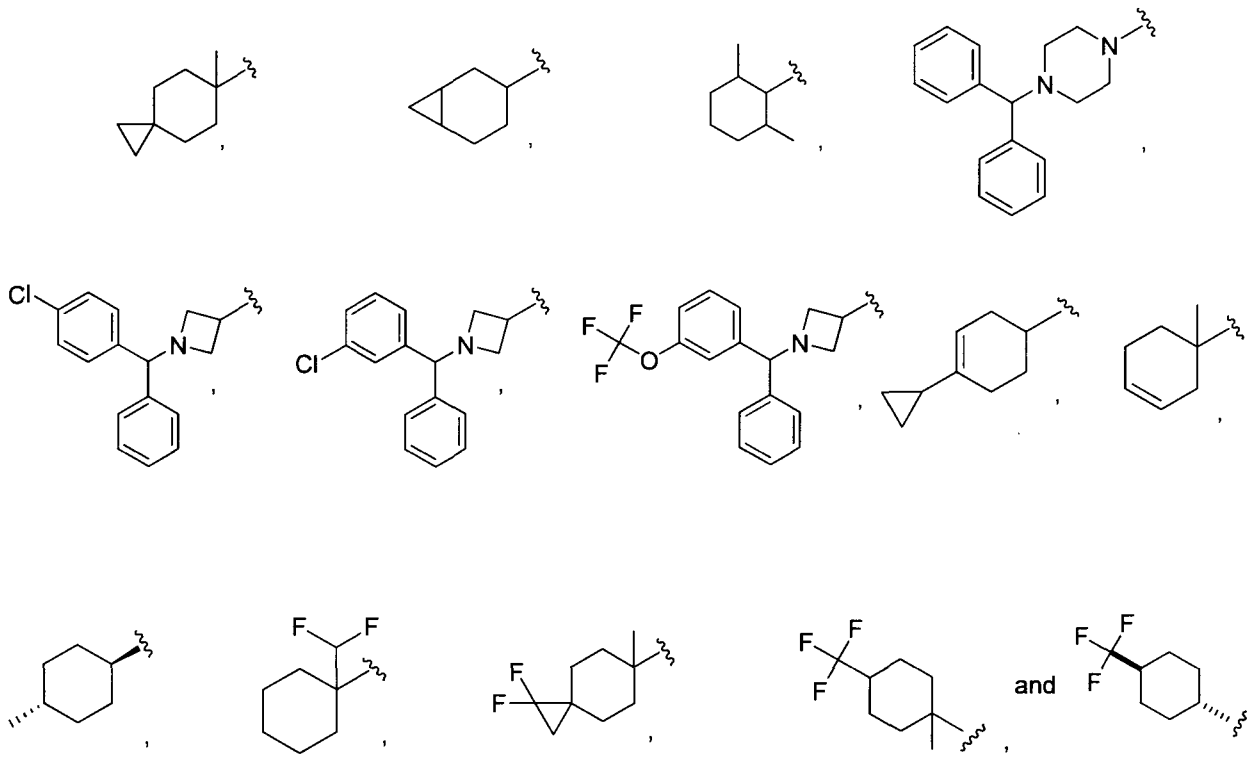
[0201] In another embodiment, in compounds of formula I, A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, adamantane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, bicyclo[3.3.1]nonane 1,2,3,4-tetrahydro-1,4-methanonaphthalene, 1,2,3,4-tetrahydroisoquinoline and chroman.

[0202] In another embodiment, in compounds of formula I, ring A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane, cubane, bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane piperidinyl, tetrahydrofuranyl, tetrahydronaphthyl, spiro[2,5]octanyl, norpinanyl, spiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, norbornanyl, spiro[4.5]decanyl, bicyclo[4.1.0]heptane and spiro[5.5]undecanyl.

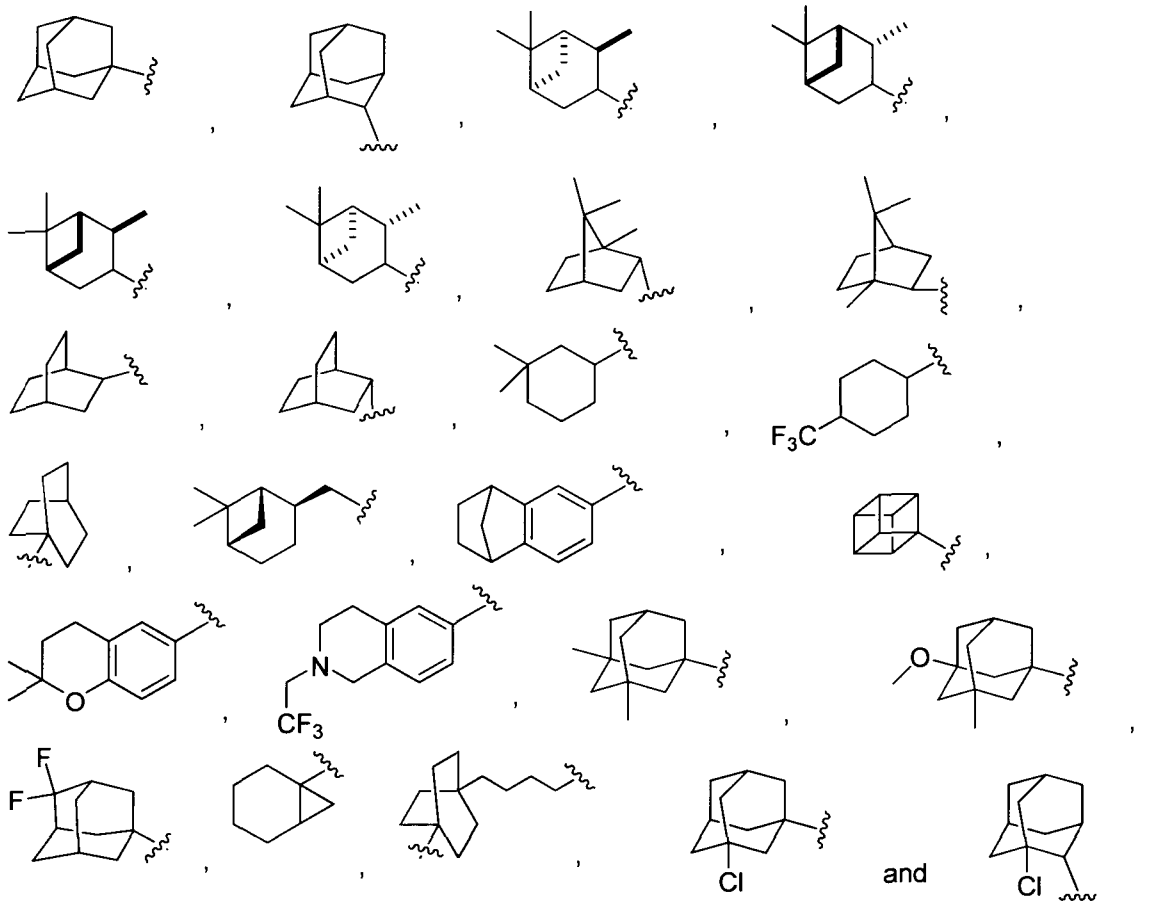
[0203] In another embodiment, in compounds of formula I, ring A-$(R^A)_n$ is selected from the group consisting of




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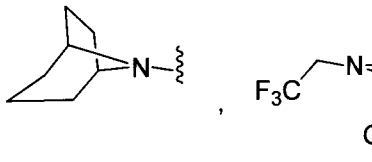
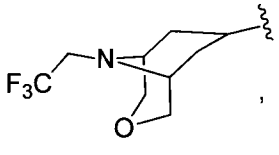
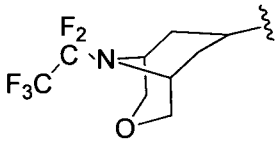
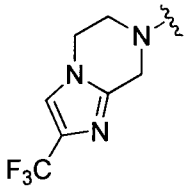


[0204] In another embodiment, in compounds of formula I, ring A-$(R^A)_n$ is selected from the group consisting of

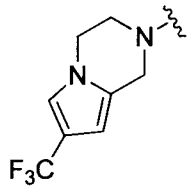


[0205] In another embodiment, in compounds of formula I, ring A is an optionally substituted ring selected from the group consisting of azetidine, pyrrolidine, piperidine, homopiperidine, (1R,5S)-8-azabicyclo[3.2.1]octane, 3-oxa-9-azabicyclo[3.3.1]nonane, (1s,4s)-7-azabicyclo[2.2.1]heptane, (1R,4S)-5-azabicyclo[2.1.1]hexane, 7-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and quinuclidine

[0206] In another embodiment, in compounds of formula I, A is selected from the group consisting of

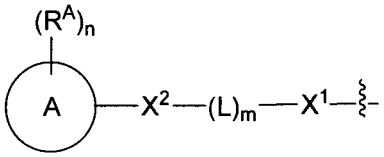
and



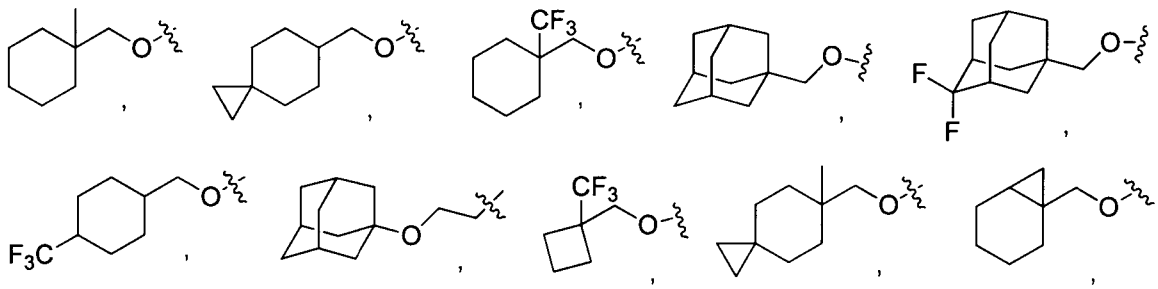
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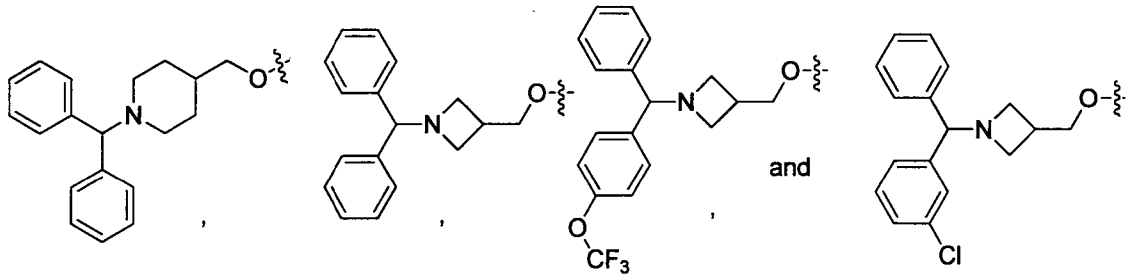
[0207] In another embodiment, in compounds of formula I, R^A is selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{2-4} heterocycloalkyl, F, Cl, Br, I, -OH, $-NH_2$, -CN, $-NO_2$, C_{1-4} alkoxy, $-C(=O)-N(R^{A1})(R^{A2})$ and $-N(R^{A1})(R^{A2})$.

[0208] In another embodiment, in compounds of formula I, wherein the group:

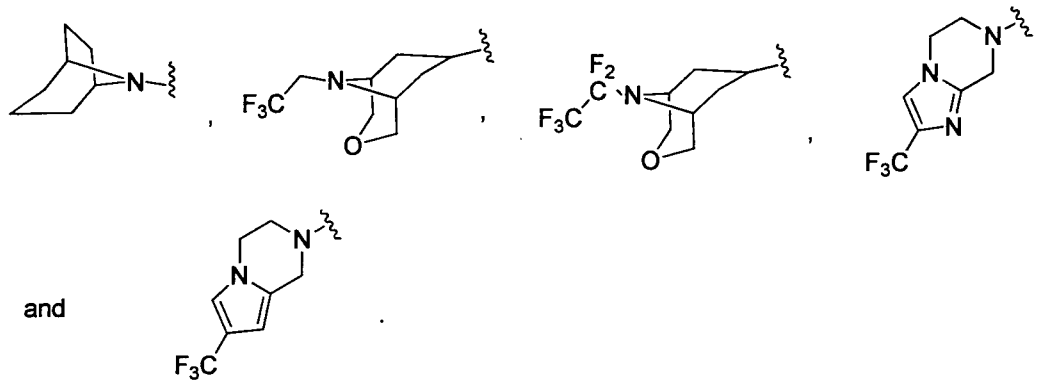


is selected from the group consisting of





[0209] In another embodiment, in compounds of formula I, ring A is selected from the group consisting of

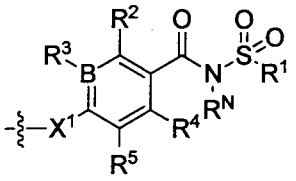


[0210] In another embodiment, in compounds of formula I, R^A is methyl, trifluromethyl, difluoromethyl, monofluoromethyl, ethyl, pentafluoroethyl, cyclopropyl, -F, Cl, -OH, $-NH_2$ or –CN.

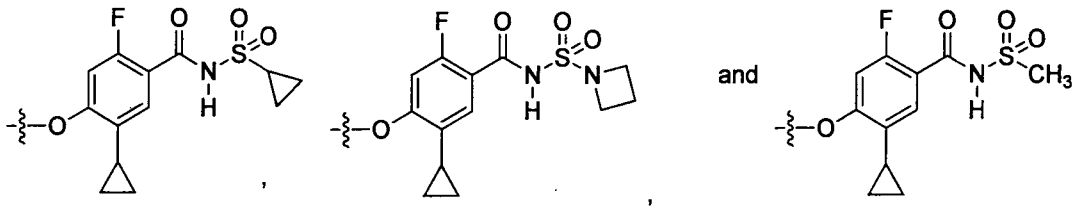
[0211] In another embodiment, in compounds of formula I, B is C; R^3 is H, R^2 is F, Cl, Br, or I; and R^5 is C_{3-8} cycloalkyl, wherein said C_{3-8} cycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy.

[0212] In another embodiment, in compounds of formula I, R^5 is C_{3-8} cycloalkyl.

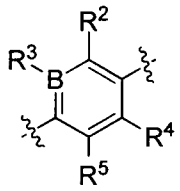
[0213] In another embodiment, in compounds of formula I, the group:



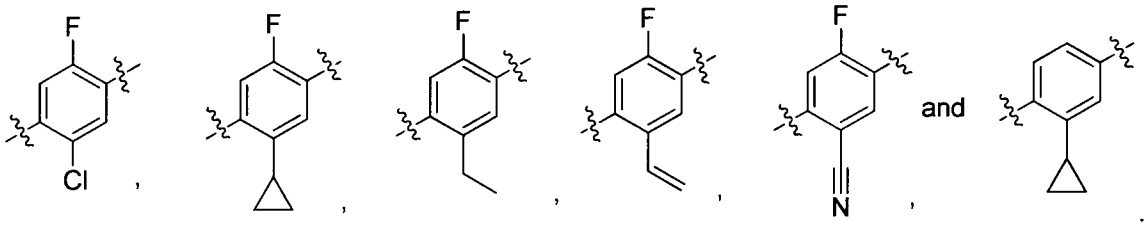
is selected from the group consisting of



[0213] In another embodiment, in compounds of formula I,the group:

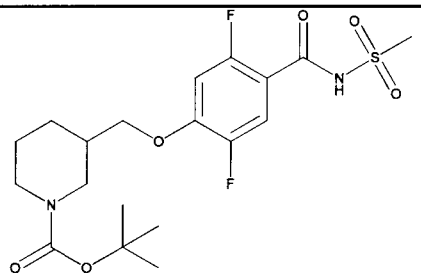
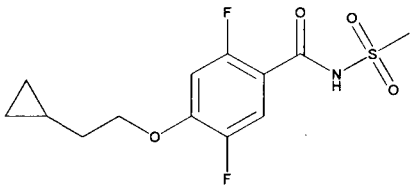
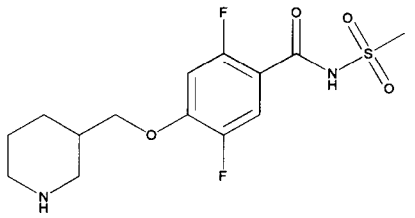
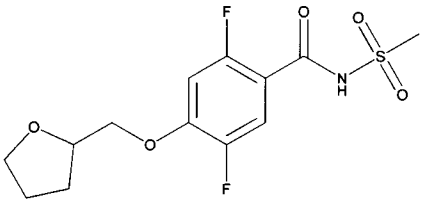
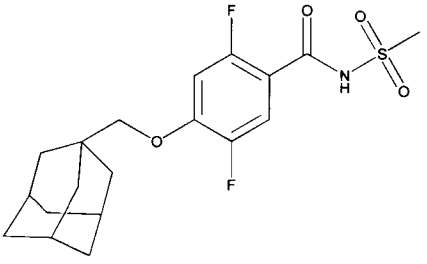


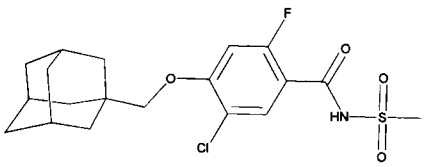
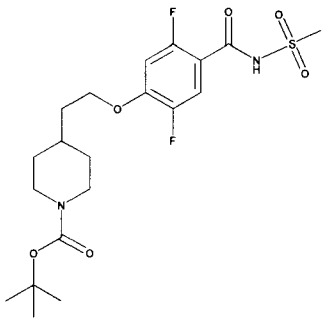
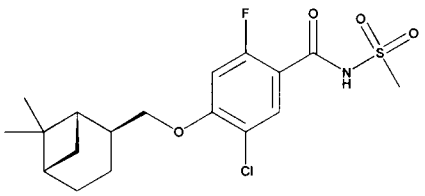
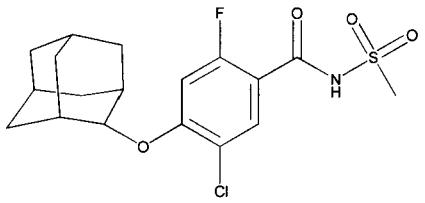
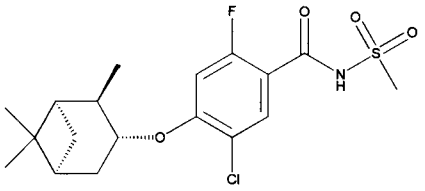
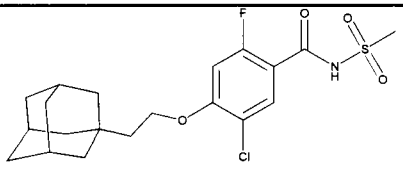
is selected from the group consisting of

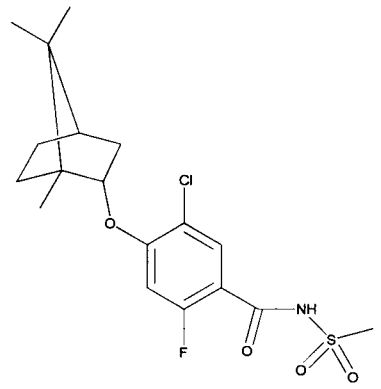
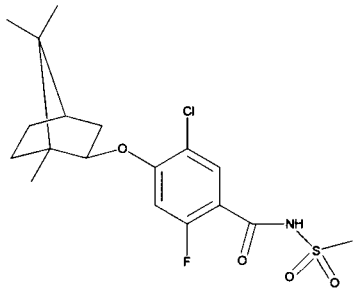
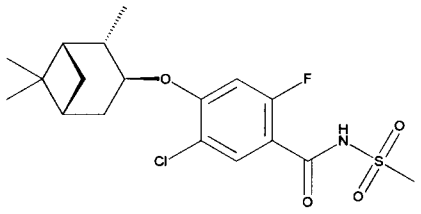
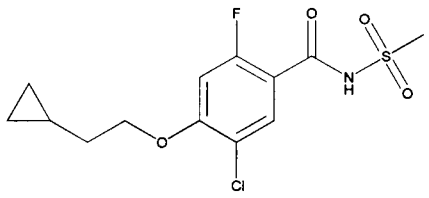
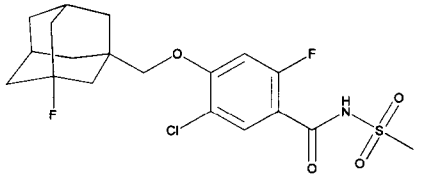


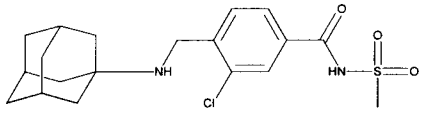
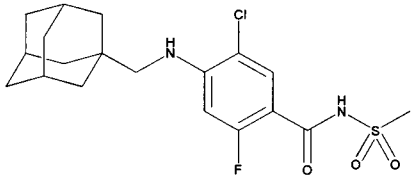
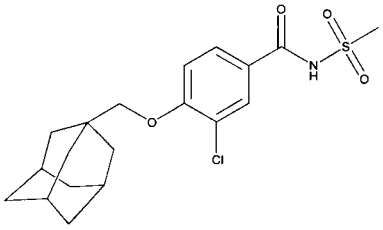
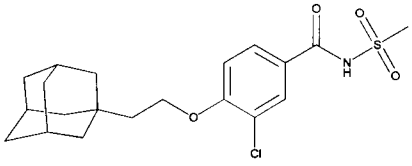
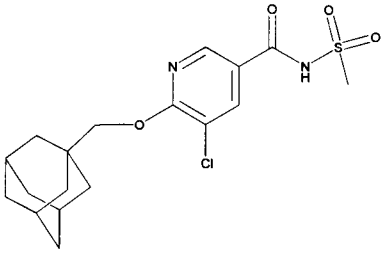
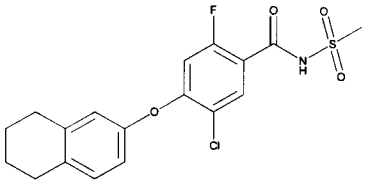
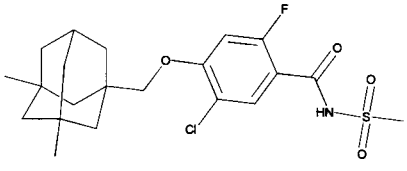
[0214] In another embodiment, in compounds of formula I, the compound is selected from the group consisting of compounds set forth in Table 1.

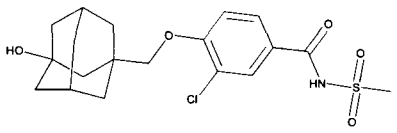
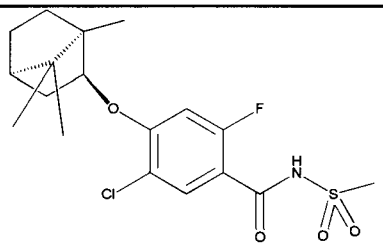
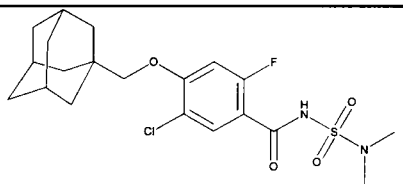
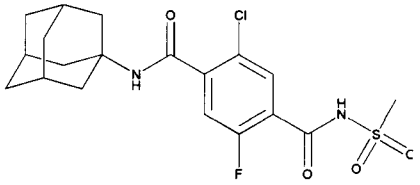
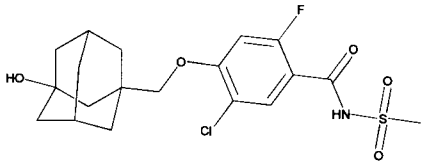
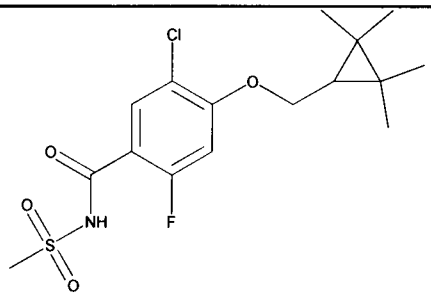
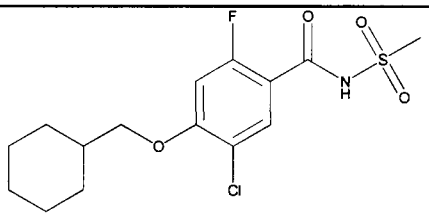
[0215] Table 1

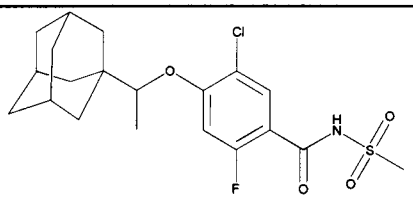
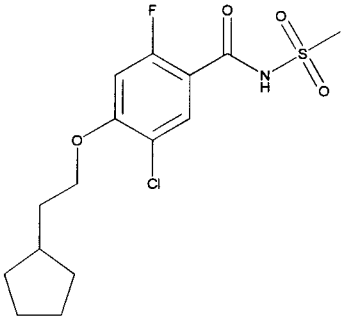
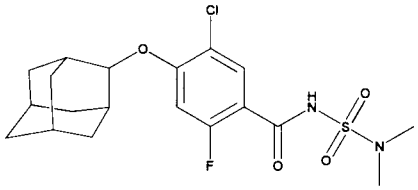
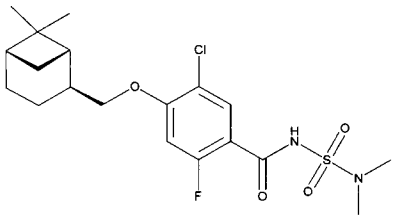
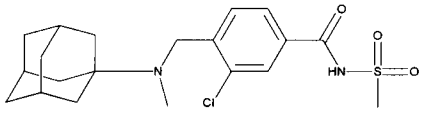
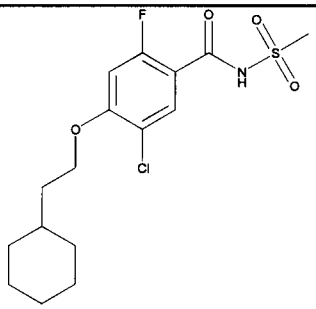
No	Structure	Name
1		tert-butyl 3-((2,5-difluoro-4-((methylsulfonyl)carbamoyl)phenoxy)methyl)piperidine-1-carboxylate
2		4-(2-cyclopropylethoxy)-2,5-difluoro-*N*-(methylsulfonyl)benzamide
3		2,5-difluoro-N-(methylsulfonyl)-4-(piperidin-3-ylmethoxy)benzamide
4		2,5-difluoro-N-(methylsulfonyl)-4-((tetrahydrofuran-2-yl)methoxy)benzamide
5		4-((adamantan-1-ylmethoxy)-2,5-difluoro-*N*-(methylsulfonyl)benzamide

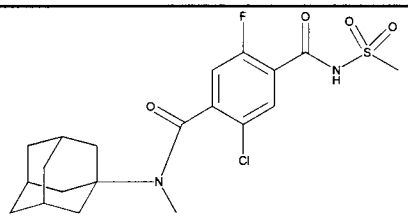
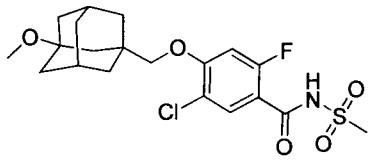
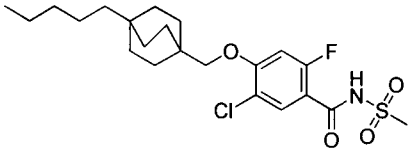
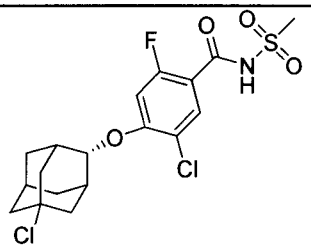
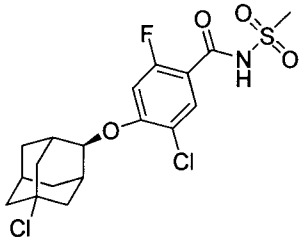
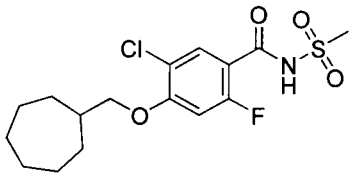
No	Structure	Name
6		4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide
7		tert-butyl 4-(2-(2,5-difluoro-4-((methylsulfonyl)carbamoyl)phenoxy)ethyl)piperidine-1-carboxylate
8		5-chloro-4-(((1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide
9		4-(adamantan-2-yloxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide
10		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)oxy)benzamide
11		4-(2-(adamantan-1-yl)ethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide

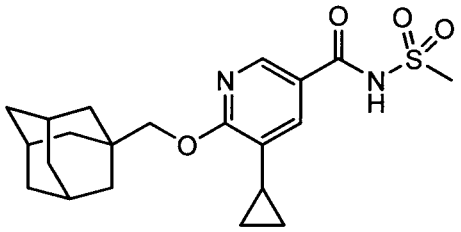
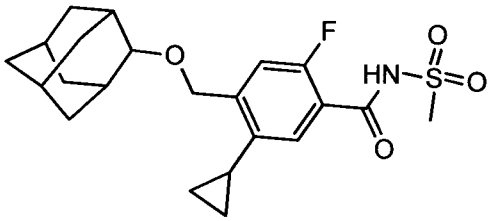
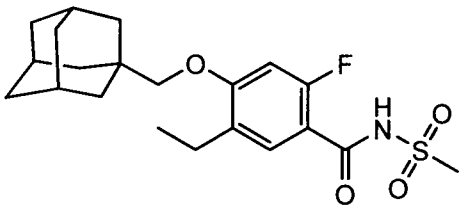
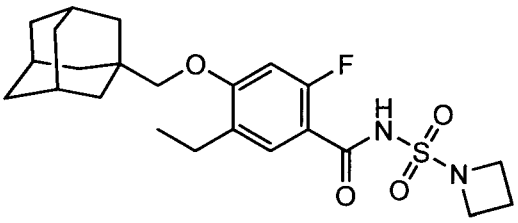
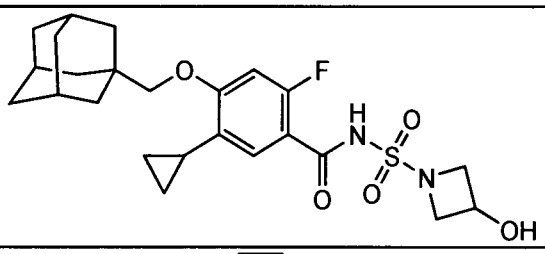
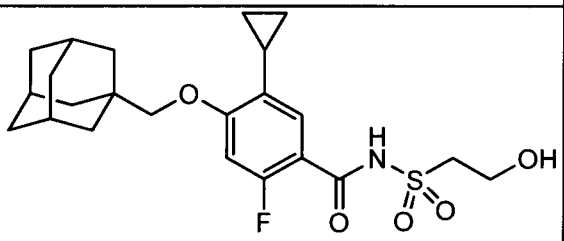
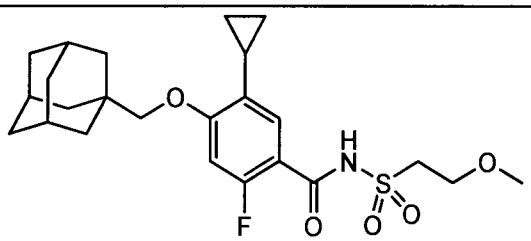
No	Structure	Name
12		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide
13		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((*exo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide
14		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)oxy)benzamide
15		5-chloro-4-(2-cyclopropylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide
16		5-chloro-2-fluoro-4-((3-fluoroadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide

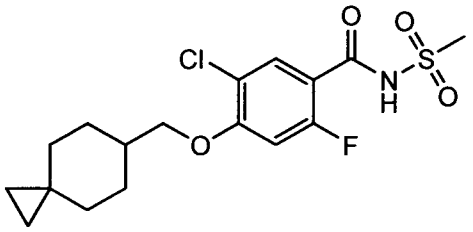
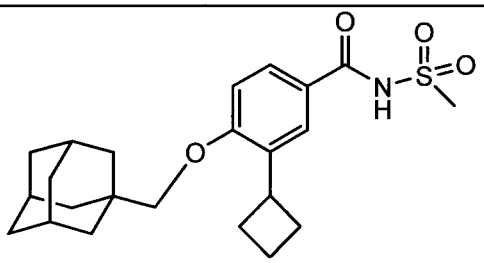
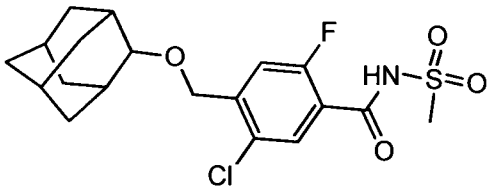
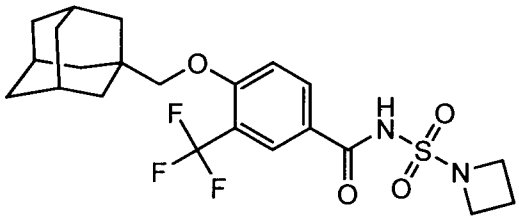
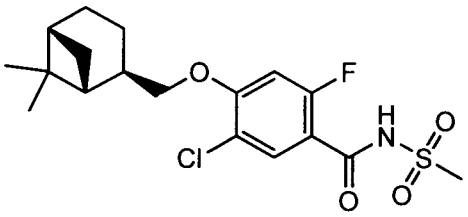
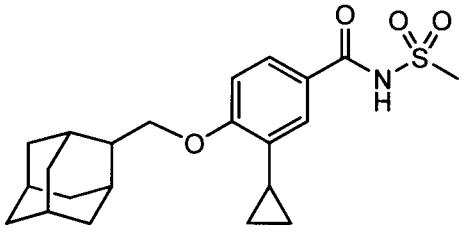
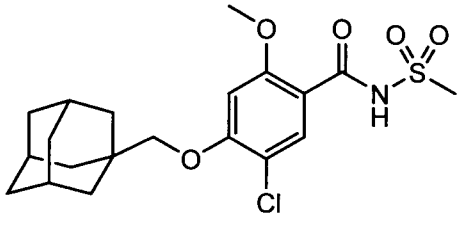
No	Structure	Name
17		4-(((3s,5s,7s)-adamantan-1-ylamino)methyl)-3-chloro-N-(methylsulfonyl)benzamide
18		4-((-adamantan-1-ylmethyl) amino)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide
19		4-(adamantan-1-ylmethoxy) -3-chloro-*N*-(methylsulfonyl)benzamide
20		4-(2-(adamantan-1-yl)ethox y)-3-chloro-*N*-(methylsulfon yl)benzamide
21		6-(adamantan-1-ylmethoxy) -5-chloro-N-methanesulfony lpyridine-3-carboxamide
22		5-chloro-2-fluoro-N-(methyl sulfonyl)-4-(5,6,7,8-tetrahyd ronaphthalen-2-yloxy)benza mide
23		5-chloro-4-((-3, 5-dimethyladamantan-1-yl) methoxy)-2-fluoro-*N*-(meth ylsulfonyl)benzamide

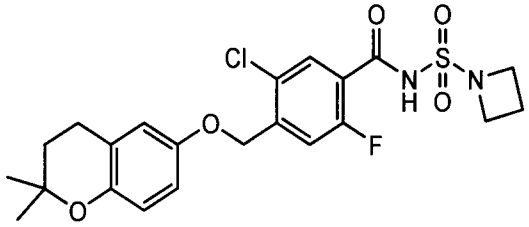
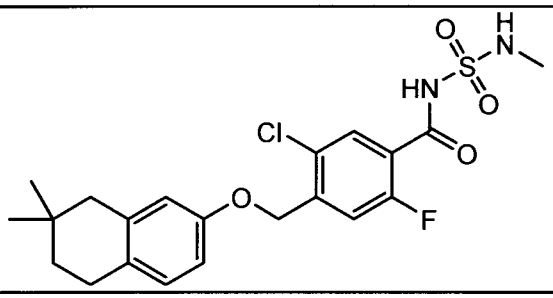
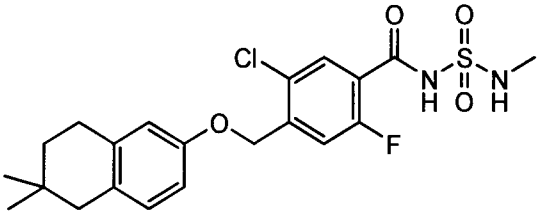
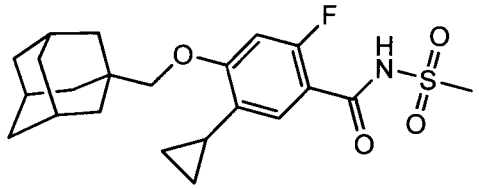
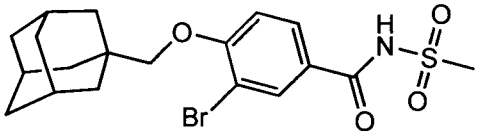
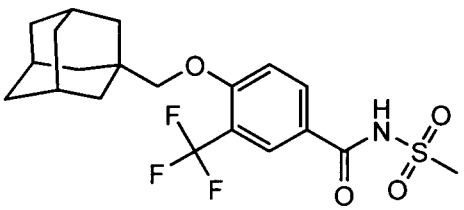
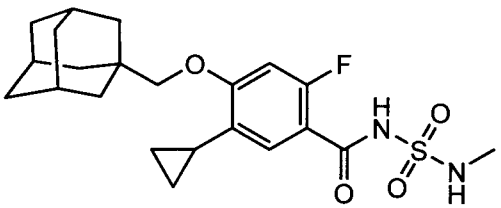
No	Structure	Name
24		3-chloro-4-(((1r,3s,5R,7S)-3-hydroxyadamantan-1-yl)methoxy)-N-(methylsulfonyl)benzamide
25		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide
26		4-(adamantan-1-ylmethoxy)-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide
27		N1-((3s,5s,7s)-adamantan-1-yl)-2-chloro-5-fluoro-N4-(methylsulfonyl)terephthalamide
28		5-chloro-2-fluoro-4-((3-hydroxyadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide
29		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((2,2,3,3-tetramethylcyclopropyl)methoxy)benzamide
30		5-chloro-4-(cyclohexylmethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide

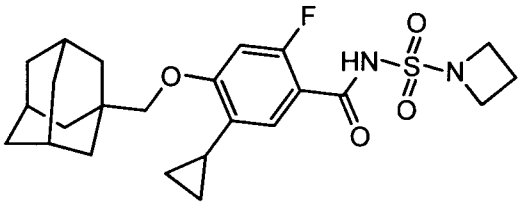
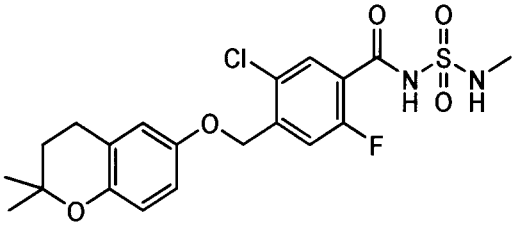
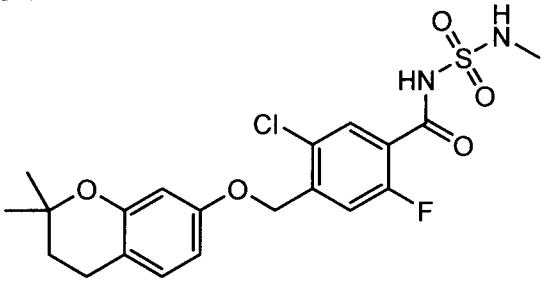
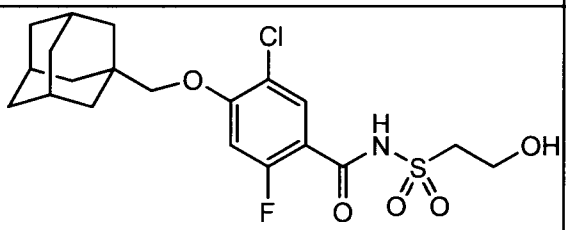
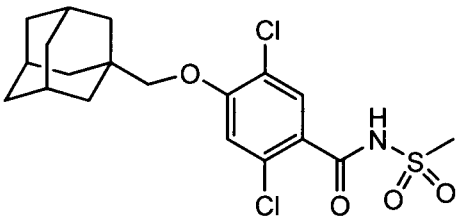
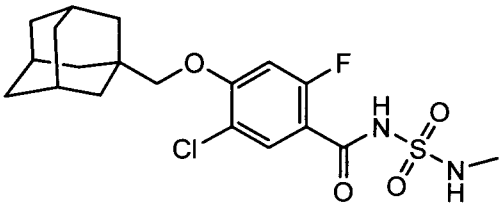
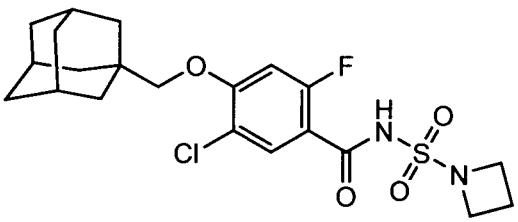
No	Structure	Name
31		4-(1-(adamantan-1-yl)ethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide
32		5-chloro-4-(2-cyclopentylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide
33		4-(adamantan-2-yloxy)-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide
34		5-chloro-4-(((1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methoxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide
35		4-(((3s,5s,7s)-adamantan-1-yl(methyl)amino)methyl)-3-chloro-N-(methylsulfonyl)benzamide
36		5-chloro-4-(2-cyclohexylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide

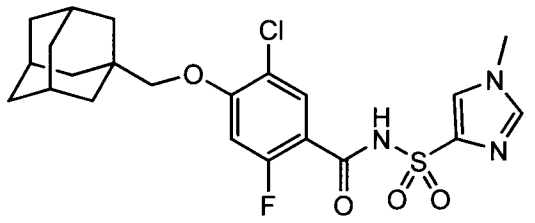
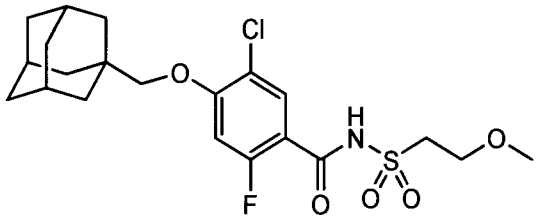
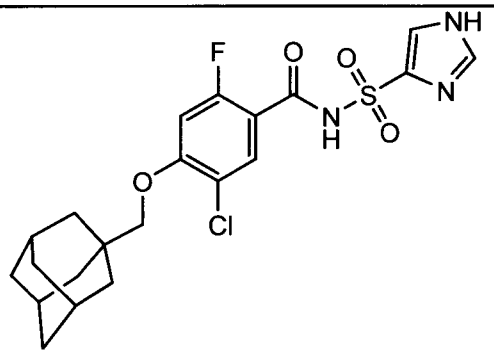
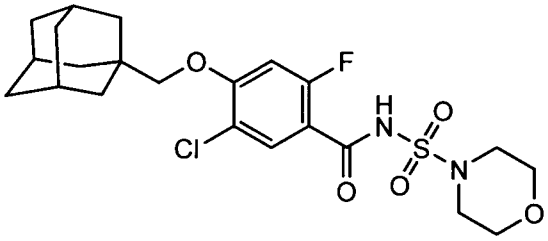
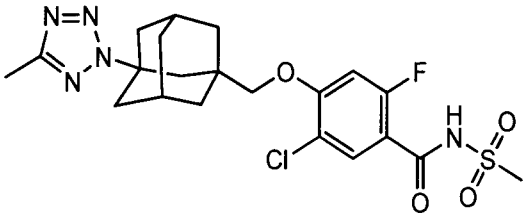
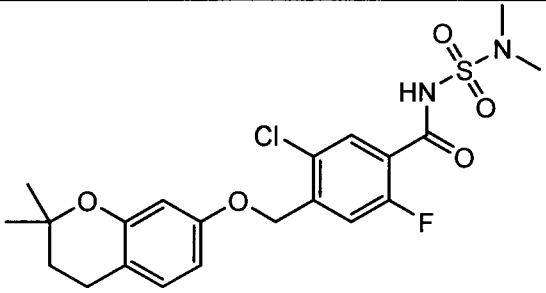
No	Structure	Name
37		N1-((3s,5s,7s)-adamantan-1-yl)-2-chloro-5-fluoro-N1-methyl-N4-(methylsulfonyl)terephthalamide
38		5-chloro-2-fluoro-4-((3-methoxyadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide
39		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4-pentylbicyclo[2.2.2]octan-1-yl)methoxy)benzamide
40		5-chloro-4-(((1*R*,2s,3*S*,5s,7s)-5-chloroadamantan-2-yl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide
41		5-chloro-4-(((1*R*,2r,3*S*,5s,7s)-5-chloroadamantan-2-yl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide
42		5-chloro-4-(2-cycloheptylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide

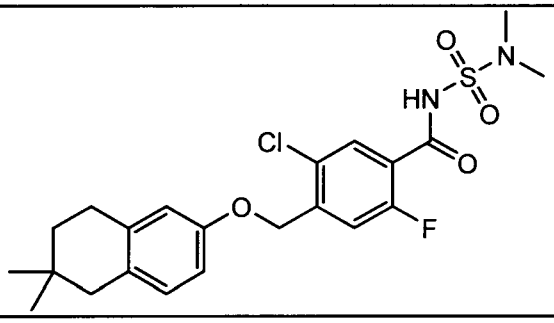
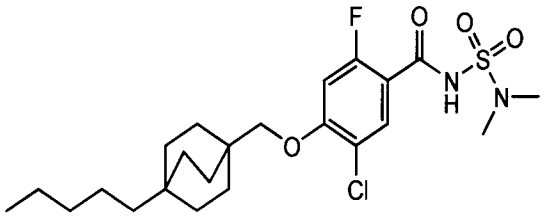
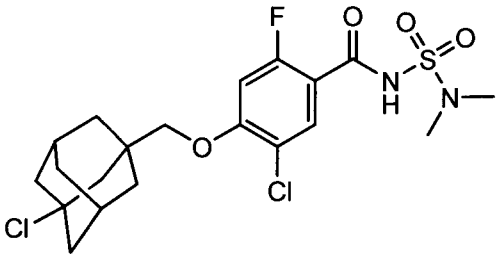
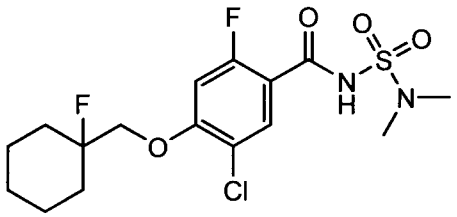
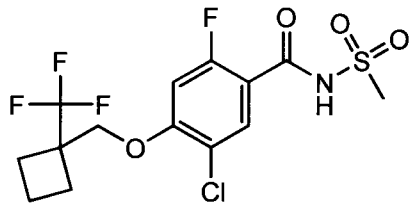
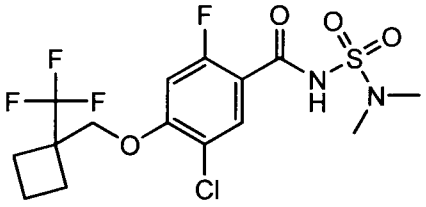
No	Structure	Name
43		6-(1-adamantylmethoxy)-5-cyclopropyl-N-methylsulfonyl-pyridine-3-carboxamide
44		4-(2-adamantyloxymethyl)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
45		4-(1-adamantylmethoxy)-5-ethyl-2-fluoro-N-methylsulfonyl-benzamide
46		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-ethyl-2-fluoro-benzamide
47		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-hydroxyazetidin-1-yl)sulfonyl-benzamide
48		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-hydroxyethylsulfonyl)benzamide
49		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide

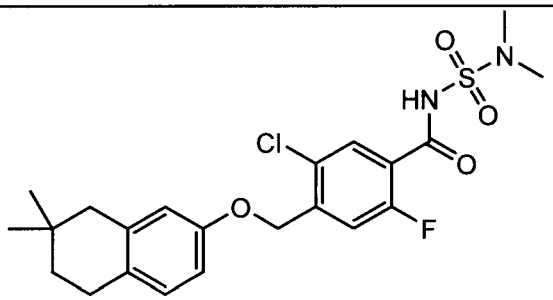
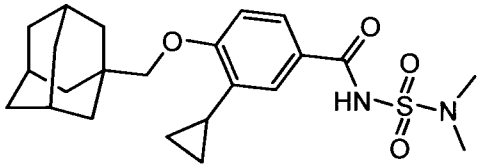
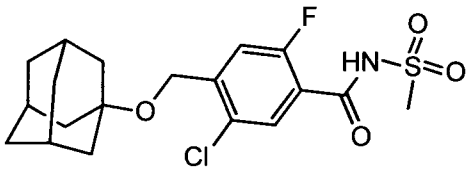
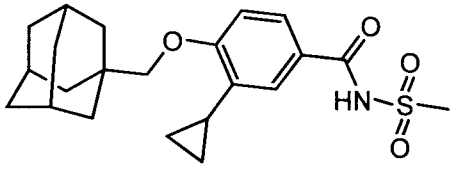
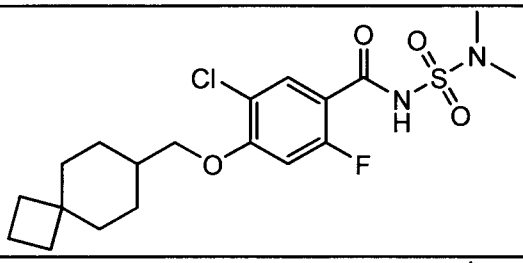
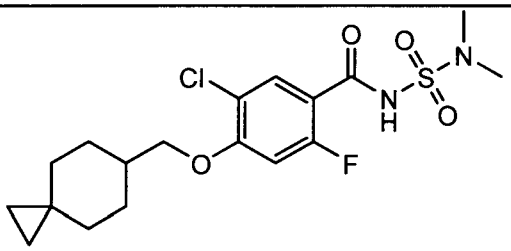
No	Structure	Name
50		5-chloro-2-fluoro-N-methyl sulfonyl-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
51		4-(1-adamantylmethoxy)-3-cyclobutyl-N-methylsulfony l-benzamide
52		4-(2-adamantyloxymethyl)-5-chloro-2-fluoro-N-methyl sulfonyl-benzamide
53		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-3-(tri fluoromethyl)benzamide
54		5-chloro-4-[[(1R,2R,5R)-6,6-dimethylnorpinan-2-yl]met hoxy]-2-fluoro-N-methylsul fonyl-benzamide
55		4-(2-adamantylmethoxy)-3-cyclopropyl-N-methylsulfon yl-benzamide
56		4-(1-adamantylmethoxy)-5-chloro-2-methoxy-N-methyl sulfonyl-benzamide

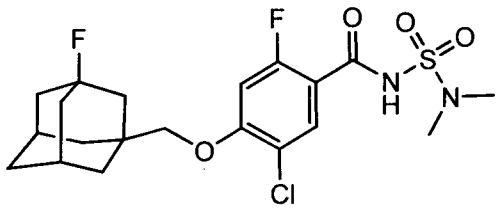
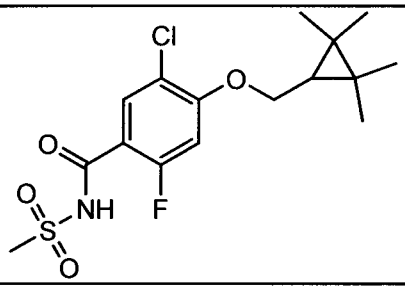
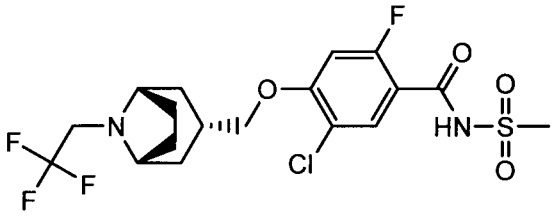
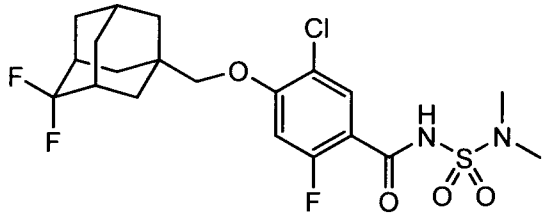
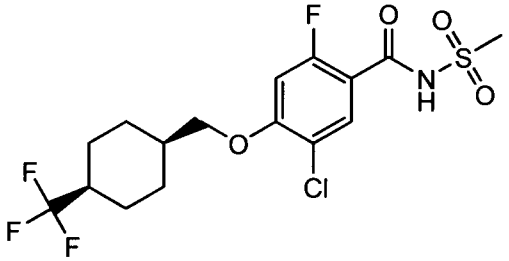
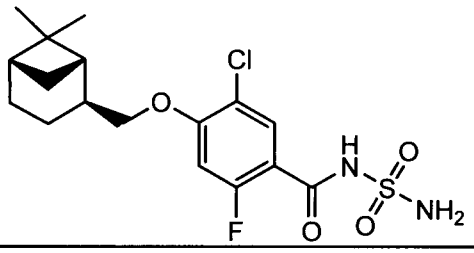
No	Structure	Name
57		N-(azetidin-1-ylsulfonyl)-5-chloro-4-[(2,2-dimethylchroman-6-yl)oxymethyl]-2-fluoro-benzamide
58		5-chloro-4-[(3,3-dimethyltetralin-6-yl)oxymethyl]-2-fluoro-N-(methylsulfamoyl)benzamide
59		5-chloro-4-[(2,2-dimethyltetralin-6-yl)oxymethyl]-2-fluoro-N-(methylsulfamoyl)benzamide
60		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
61		4-(1-adamantylmethoxy)-3-bromo-N-methylsulfonyl-benzamide
62		4-(1-adamantylmethoxy)-N-methylsulfonyl-3-(trifluoromethyl)benzamide
63		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfamoyl)benzamide

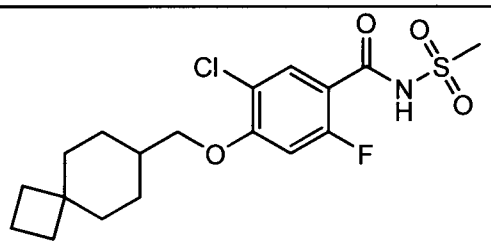
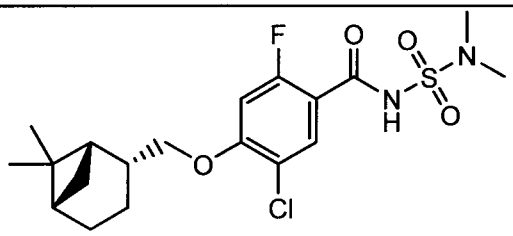
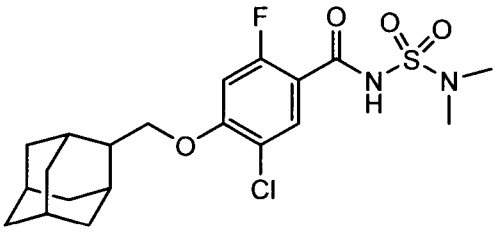
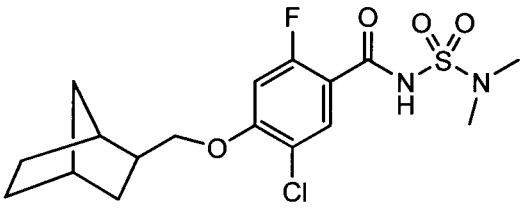
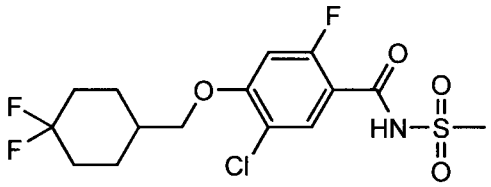
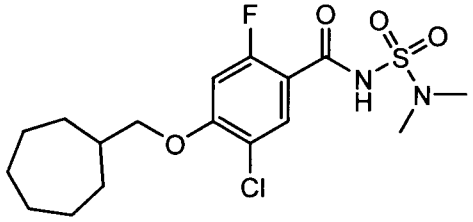
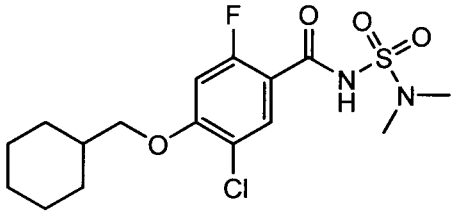
No	Structure	Name
64		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-benzamide
65		5-chloro-4-[(2,2-dimethylchroman-6-yl)oxymethyl]-2-fluoro-N-(methylsulfamoyl)benzamide
66		5-chloro-4-[(2,2-dimethylchroman-7-yl)oxymethyl]-2-fluoro-N-(methylsulfamoyl)benzamide
67		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(2-hydroxyethylsulfonyl)benzamide
68		4-(1-adamantylmethoxy)-2,5-dichloro-N-methylsulfonyl-benzamide
69		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(methylsulfamoyl)benzamide
70		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-benzamide

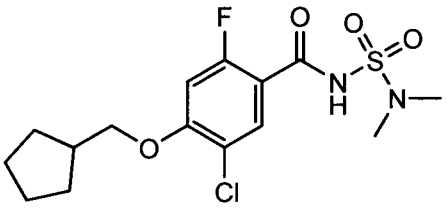
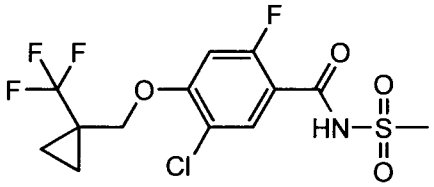
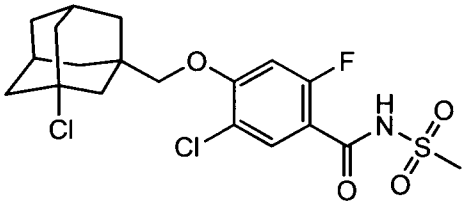
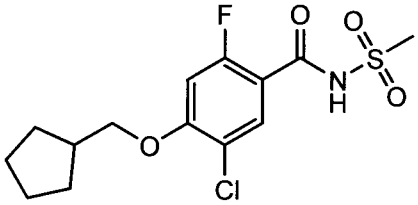
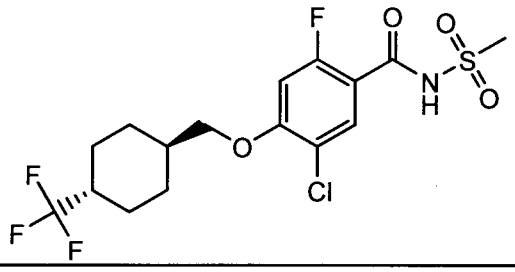
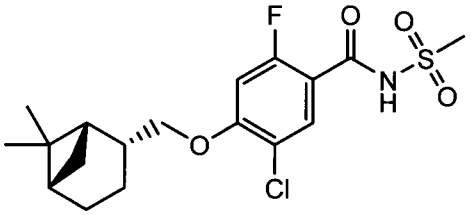
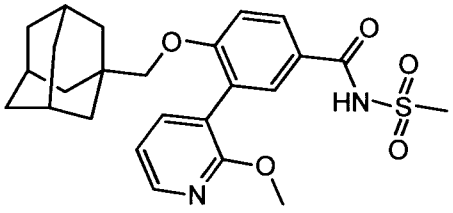
No	Structure	Name
71		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(1-methyl imidazol-4-yl)sulfonyl-benzamide
72		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
73		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(1H-imidazol-4-ylsulfonyl)benzamide
74		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-morpholinosulfonyl-benzamide
75		5-chloro-2-fluoro-N-methylsulfonyl-4-[[3-(5-methyltetrazol-2-yl)-1-adamantyl]methoxy]benzamide
76		5-chloro-4-[(2,2-dimethylchroman-7-yl)oxymethyl]-N-(dimethylsulfamoyl)-2-fluoro-benzamide

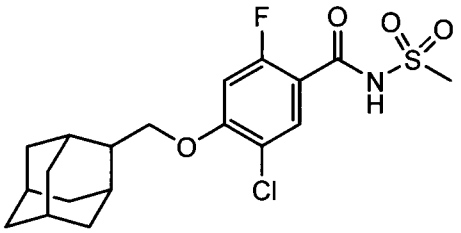
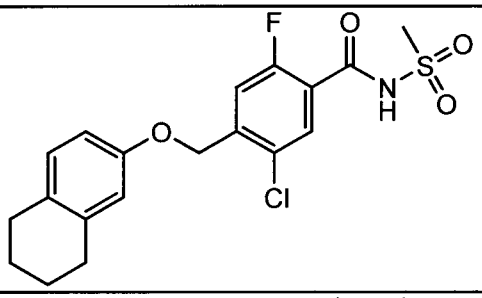
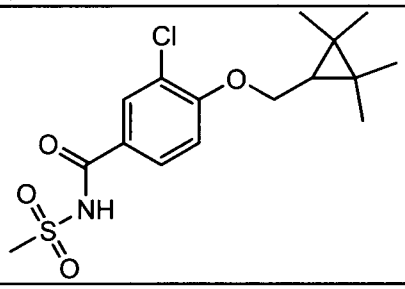
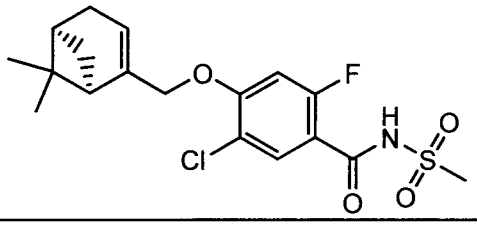
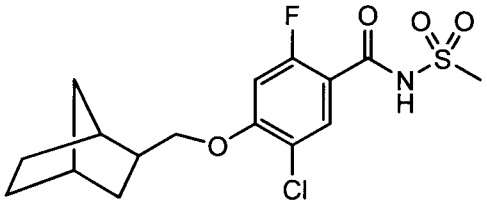
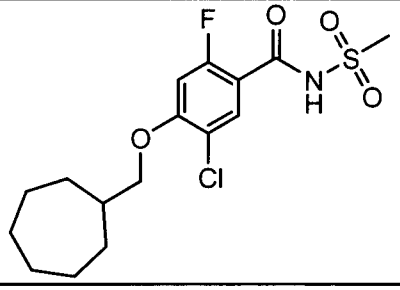
No	Structure	Name
77		5-chloro-N-(dimethylsulfamoyl)-4-[(2,2-dimethyltetralin-6-yl)oxymethyl]-2-fluoro-benzamide
78		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[(1-pentyl-4-bicyclo[2.2.2]octanyl)methoxy]benzamide
79		5-chloro-4-[(3-chloro-1-adamantyl)methoxy]-N-(dimethylsulfamoyl)-2-fluoro-benzamide
80		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[(1-fluorocyclohexyl)methoxy]benzamide
81		5-chloro-2-fluoro-N-methylsulfonyl-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide
82		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide

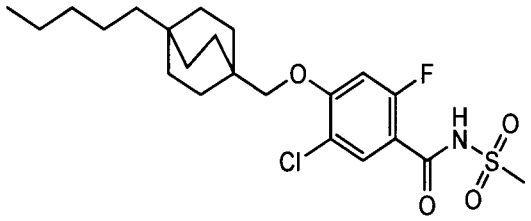
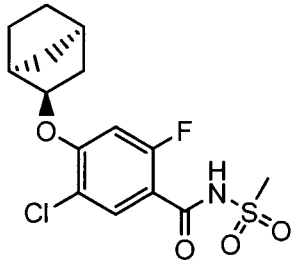
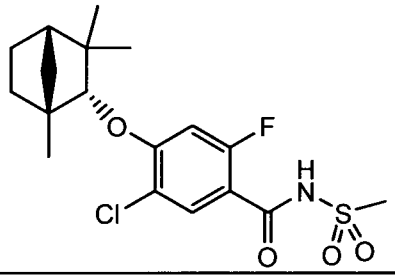
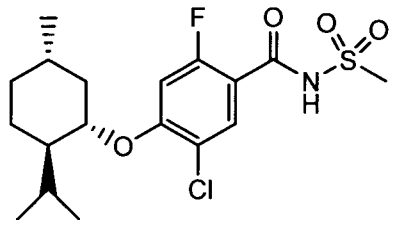
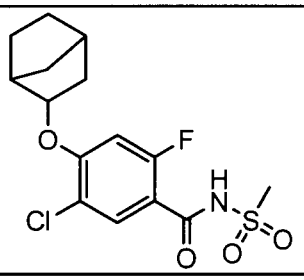
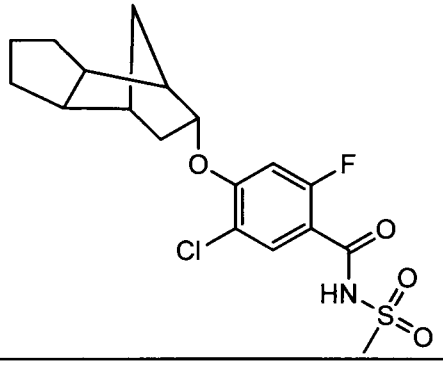
No	Structure	Name
83		5-chloro-N-(dimethylsulfamoyl)-4-[(3,3-dimethyltetralin-6-yl)oxymethyl]-2-fluoro-benzamide
84		4-(1-adamantylmethoxy)-3-cyclopropyl-N-(dimethylsulfamoyl)benzamide
85		4-(1-adamantyloxymethyl)-5-chloro-2-fluoro-N-methylsulfonyl-benzamide
86		4-(1-adamantylmethoxy)-3-cyclopropyl-N-methylsulfonyl-benzamide
87		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide
88		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide

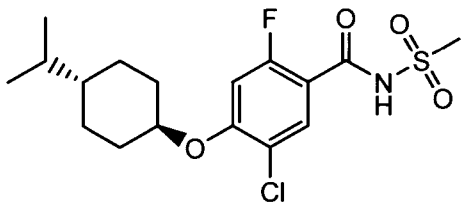
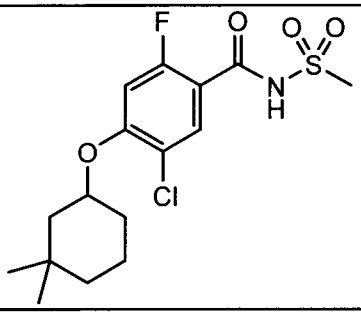
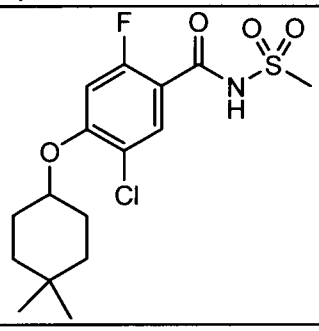
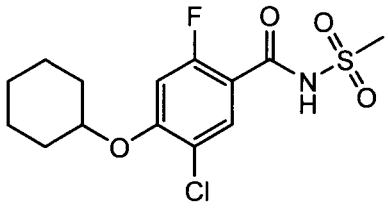
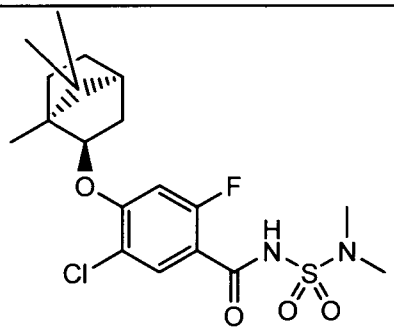
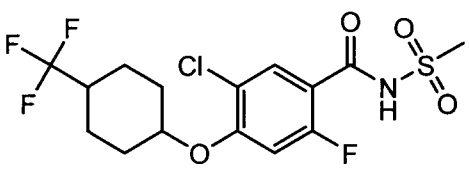
No	Structure	Name
89		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[(3-fluoro-1-adamantyl)methoxy]benzamide
90		5-chloro-2-fluoro-N-methylsulfonyl-4-[(2,2,3,3-tetramethylcyclopropyl)methoxy]benzamide
91		5-chloro-2-fluoro-N-methylsulfonyl-4-[[(1S,5R)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl]methoxy]benzamide
92		5-chloro-4-[(4,4-difluoro-1-adamantyl)methoxy]-N-(dimethylsulfamoyl)-2-fluoro-benzamide
93		5-chloro-2-fluoro-N-methylsulfonyl-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
94		5-chloro-4-[[(1S,2S,5S)-6,6-dimethylnorpinan-2-yl]methoxy]-2-fluoro-N-sulfamoyl-benzamide

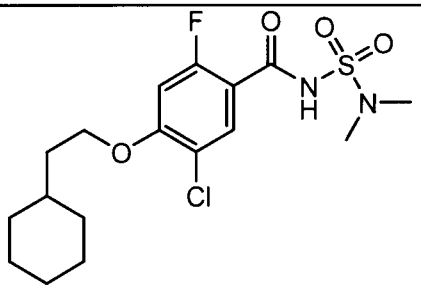
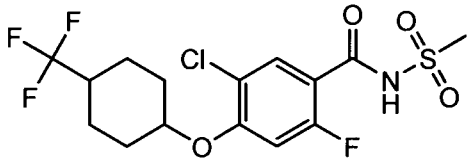
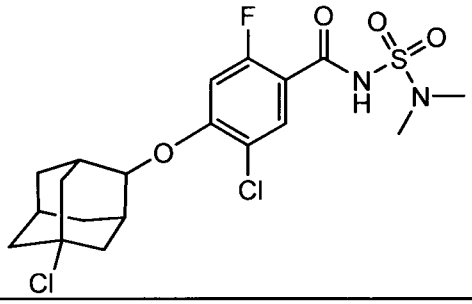
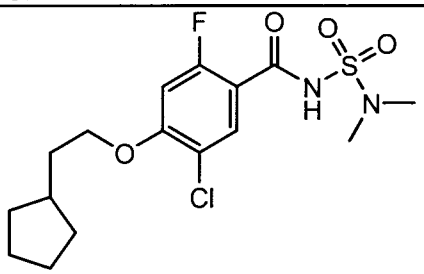
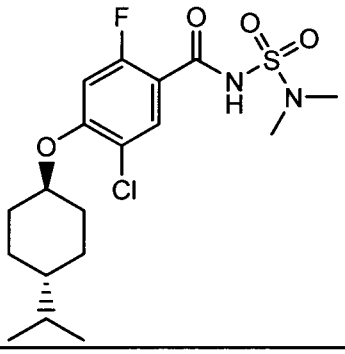
No	Structure	Name
95		5-chloro-2-fluoro-N-methyl sulfonyl-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide
96		5-chloro-4-[[(1S,2R,5S)-6,6-dimethylnorpinan-2-yl]methoxy]-N-(dimethylsulfamoyl)-2-fluoro-benzamide
97		4-(2-adamantylmethoxy)-5-chloro-N-(dimethylsulfamoyl)-2-fluoro-benzamide
98		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-(norbornan-2-ylmethoxy)benzamide
99		5-chloro-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
100		5-chloro-4-(cycloheptylmethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
101		5-chloro-4-(cyclohexylmethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide

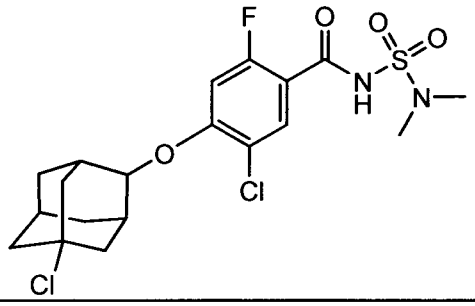
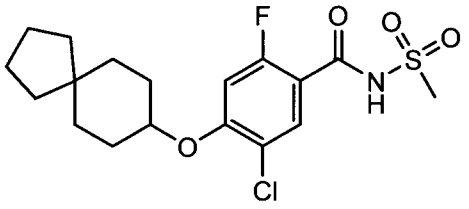
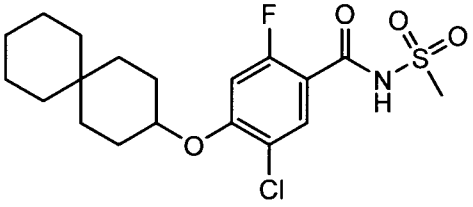
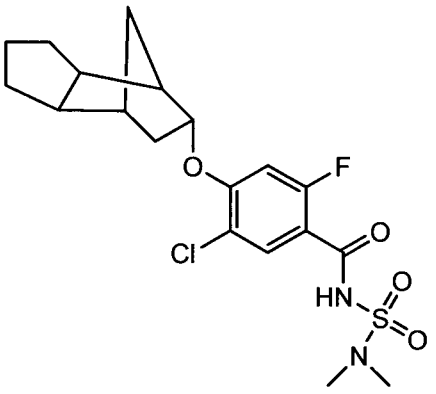
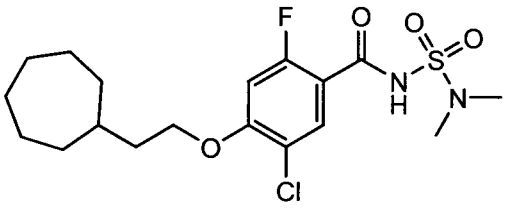
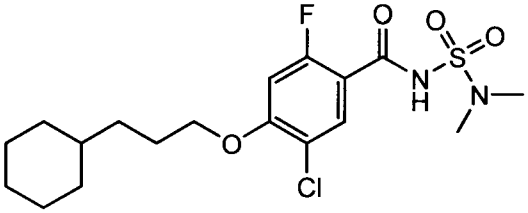
No	Structure	Name
102		5-chloro-4-(cyclopentylmethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
103		5-chloro-2-fluoro-N-methylsulfonyl-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]benzamide
104		5-chloro-4-[(3-chloro-1-adamantyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
105		5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-methylsulfonyl-benzamide
106		5-chloro-2-fluoro-N-methylsulfonyl-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
107		5-chloro-4-[[(1S,2R,5S)-6,6-dimethylnorpinan-2-yl]methoxy]-2-fluoro-N-methylsulfonyl-benzamide
108		4-(1-adamantylmethoxy)-3-(2-methoxy-3-pyridyl)-N-methylsulfonyl-benzamide

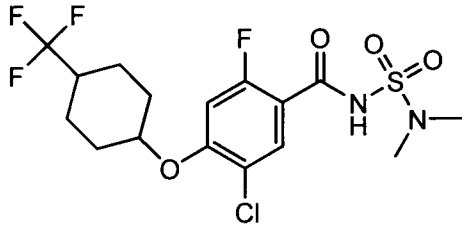
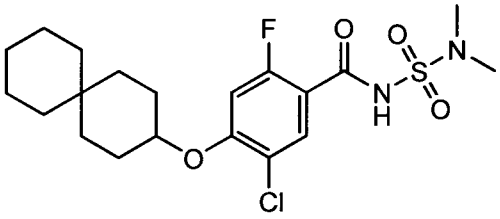
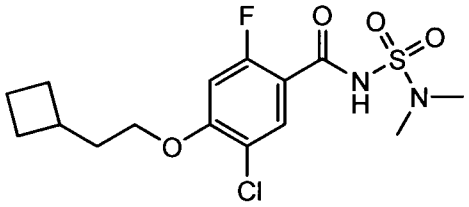
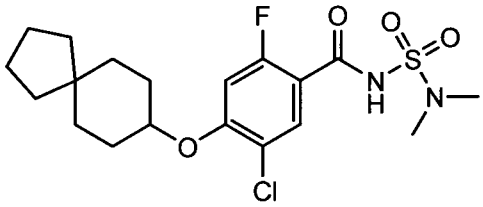
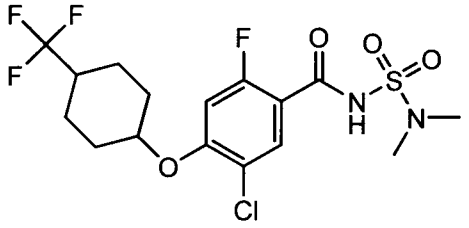
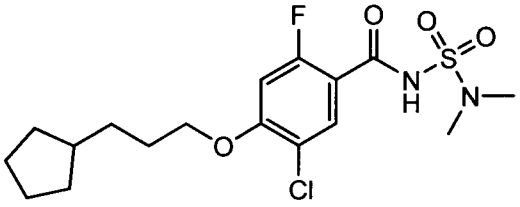
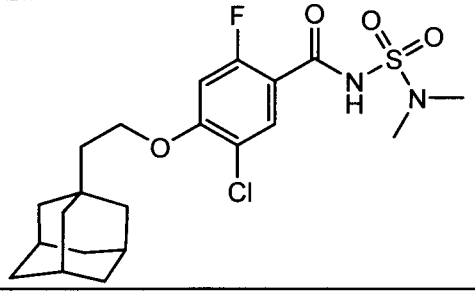
No	Structure	Name
109		4-(2-adamantylmethoxy)-5-chloro-2-fluoro-N-methylsulfonyl-benzamide
110		5-chloro-2-fluoro-N-methylsulfonyl-4-(tetralin-6-yloxymethyl)benzamide
111		3-chloro-N-methylsulfonyl-4-[(2,2,3,3-tetramethylcyclopropyl)methoxy]benzamide
112		5-chloro-4-[[(1S,5R)-6,6-dimethyl-4-bicyclo[3.1.1]hept-3-enyl]methoxy]-2-fluoro-N-methylsulfonyl-benzamide
113		5-chloro-2-fluoro-N-methylsulfonyl-4-(norbornan-2-ylmethoxy)benzamide
114		5-chloro-4-(cycloheptylmethoxy)-2-fluoro-N-methylsulfonyl-benzamide

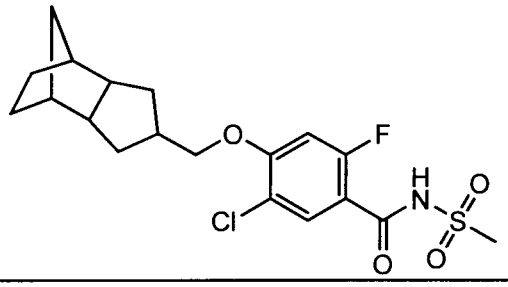
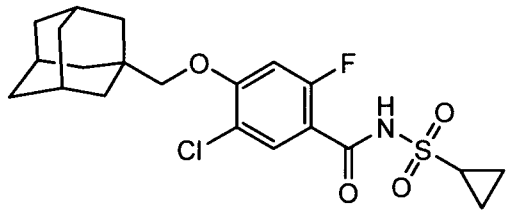
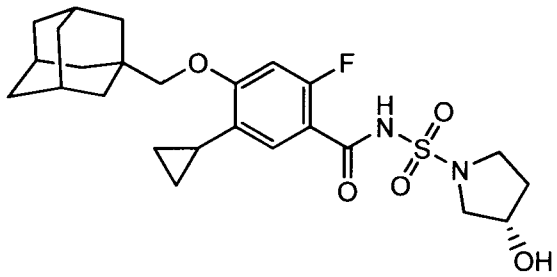
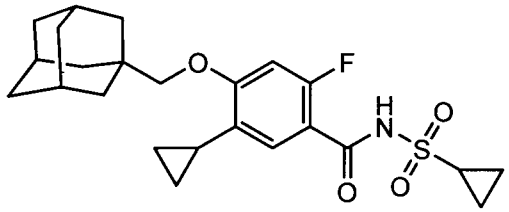
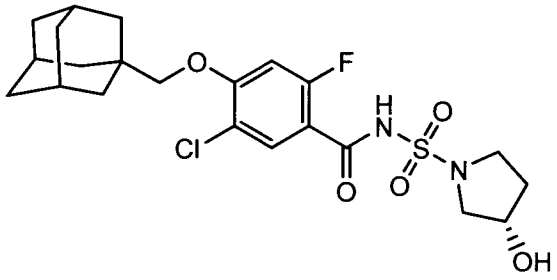
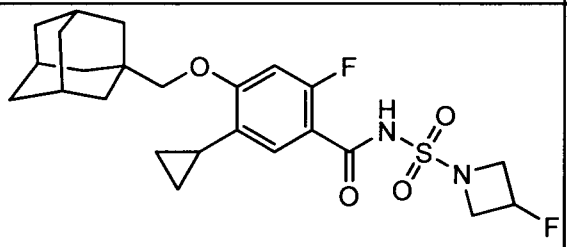
No	Structure	Name
115		5-chloro-2-fluoro-N-methyl sulfonyl-4-[(1-pentyl-4-bicyclo[2.2.2]octanyl)methoxy]benzamide
116		5-chloro-2-fluoro-N-methylsulfonyl-4-[(1S,2R,4R)-norbornan-2-yl]oxy-benzamide
117		5-chloro-2-fluoro-N-methylsulfonyl-4-[(1R,2R,4S)-1,3,3-trimethylnorbornan-2-yl]oxy-benzamide
118		5-chloro-2-fluoro-4-[(1S,2R,5S)-2-isopropyl-5-methyl-cyclohexoxy]-N-methylsulfonyl-benzamide
119		5-chloro-2-fluoro-N-methylsulfonyl-4-norbornan-2-yloxy-benzamide
120		

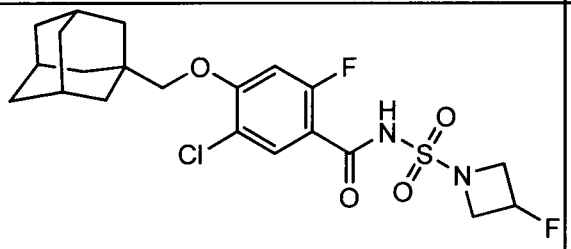
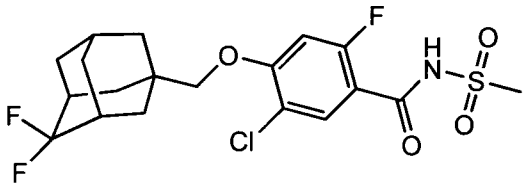
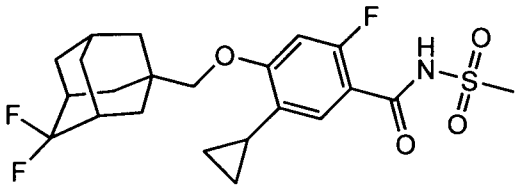
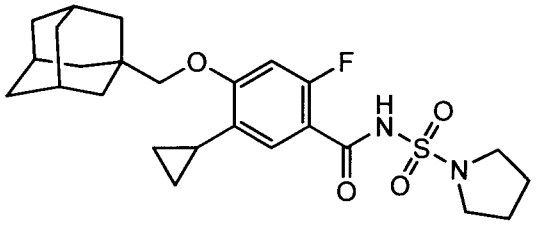
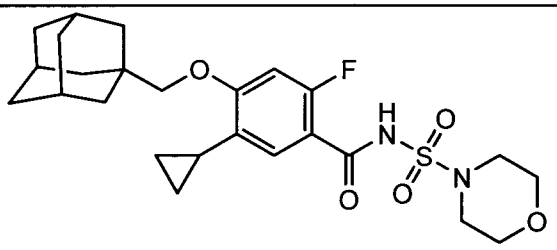
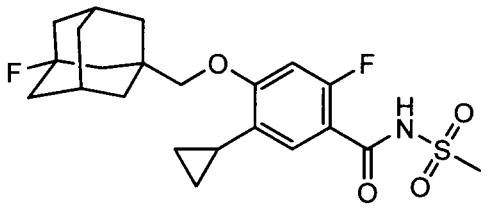
No	Structure	Name
121		5-chloro-2-fluoro-4-(4-isopropylcyclohexoxy)-N-methylsulfonyl-benzamide
122		5-chloro-4-(3,3-dimethylcyclohexoxy)-2-fluoro-N-methylsulfonyl-benzamide
123		5-chloro-4-(4,4-dimethylcyclohexoxy)-2-fluoro-N-methylsulfonyl-benzamide
124		5-chloro-4-(cyclohexoxy)-2-fluoro-N-methylsulfonyl-benzamide
125		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[(1S,2R,4S)-1,7,7-trimethylnorbornan-2-yl]oxy-benzamide
126		5-chloro-2-fluoro-N-methylsulfonyl-4-[4-(trifluoromethyl)cyclohexoxy]benzamide

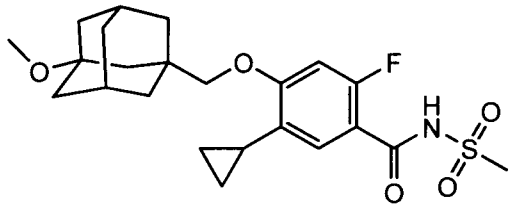
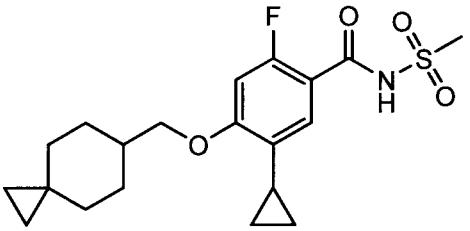
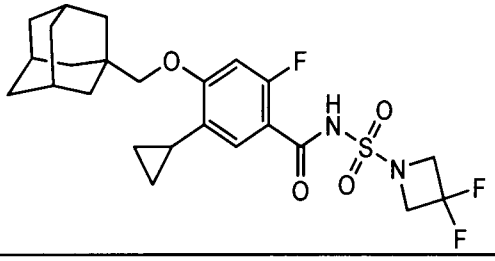
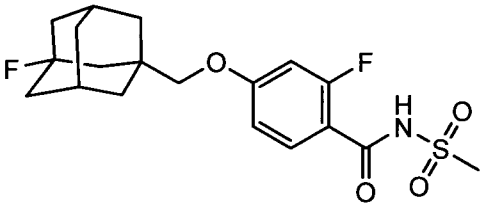
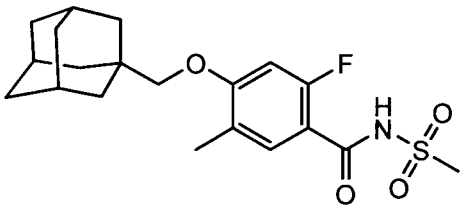
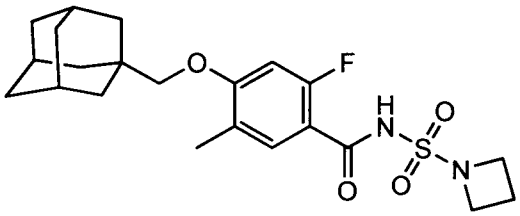
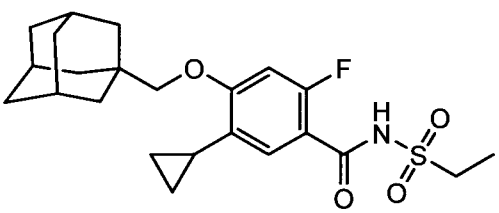
No	Structure	Name
127		5-chloro-4-(2-cyclohexylethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
128		5-chloro-2-fluoro-N-methylsulfonyl-4-[4-(trifluoromethyl)cyclohexoxy]benzamide
129		5-chloro-4-[(5-chloro-2-adamantyl)oxy]-N-(dimethylsulfamoyl)-2-fluoro-benzamide
130		5-chloro-4-(2-cyclopentylethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
131		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-(4-isopropylcyclohexoxy)benzamide

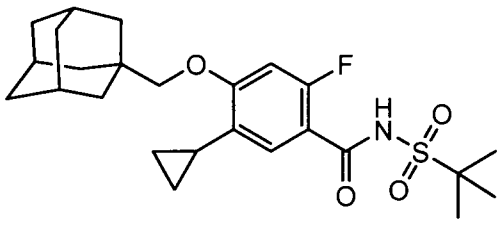
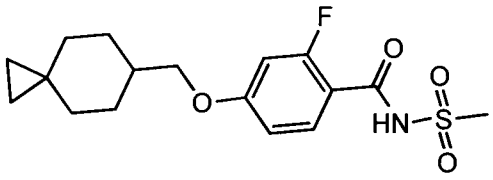
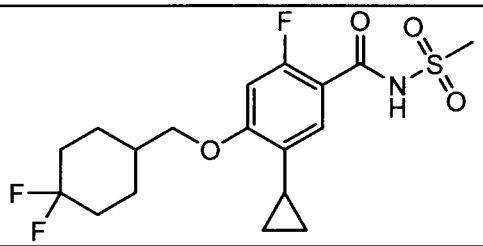
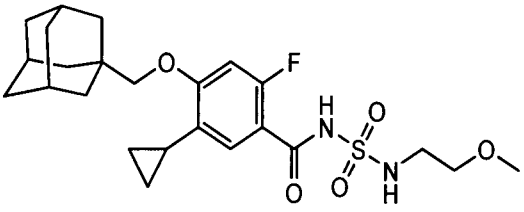
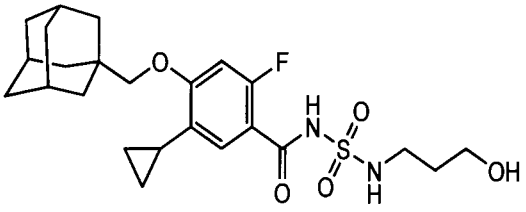
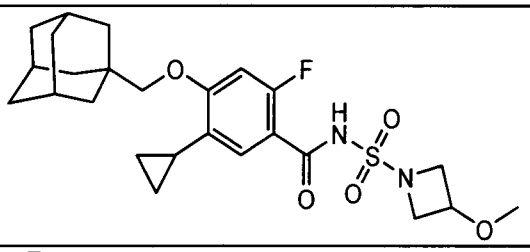
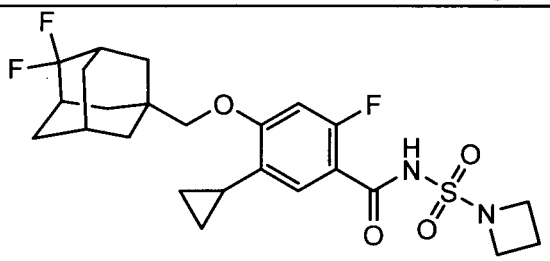
No	Structure	Name
132		5-chloro-4-[(5-chloro-2-adamantyl)oxy]-N-(dimethylsulfamoyl)-2-fluoro-benzamide
133		5-chloro-2-fluoro-N-methylsulfonyl-4-spiro[4.5]decan-8-yloxy-benzamide
134		5-chloro-2-fluoro-N-methylsulfonyl-4-spiro[5.5]undecan-3-yloxy-benzamide
135		
136		5-chloro-4-(2-cycloheptylethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
137		5-chloro-4-(3-cyclohexylpropoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide

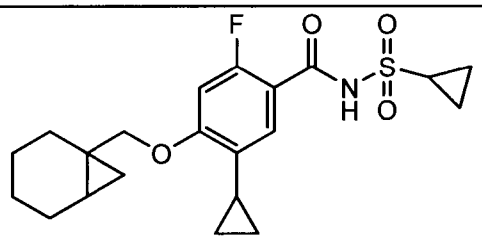
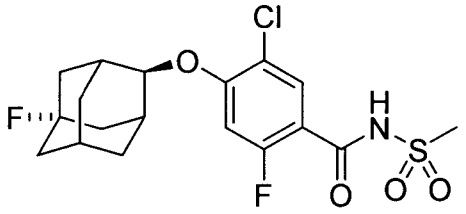
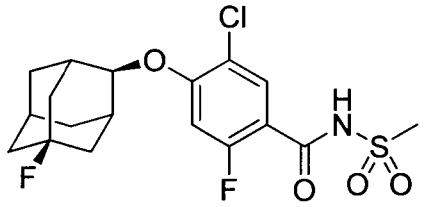
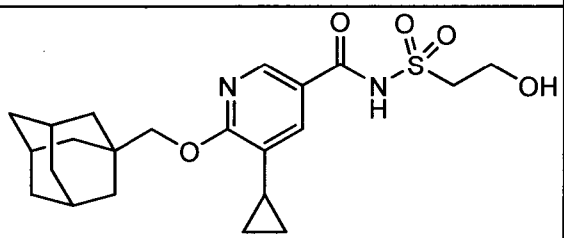
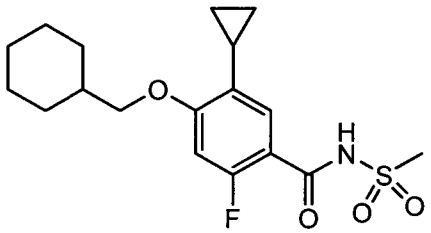
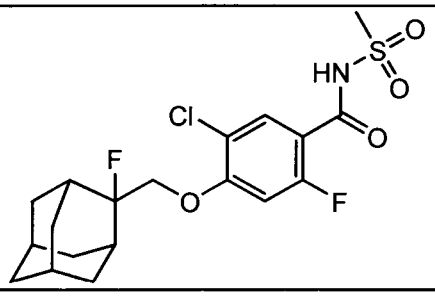
No	Structure	Name
138		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[4-(trifluoromethyl)cyclohexoxy]benzamide
139		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-spiro[5.5]undecan-3-yloxy-benzamide
140		5-chloro-4-(2-cyclobutylethoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
141		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-spiro[4.5]decan-8-yloxy-benzamide
142		5-chloro-N-(dimethylsulfamoyl)-2-fluoro-4-[4-(trifluoromethyl)cyclohexoxy]benzamide
143		5-chloro-4-(3-cyclopentylpropoxy)-N-(dimethylsulfamoyl)-2-fluoro-benzamide
144		4-[2-(1-adamantyl)ethoxy]-5-chloro-N-(dimethylsulfamoyl)-2-fluoro-benzamide

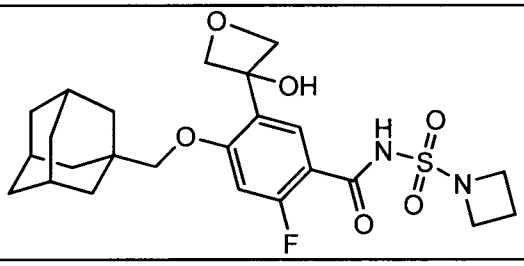
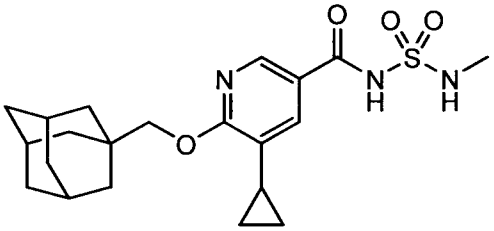
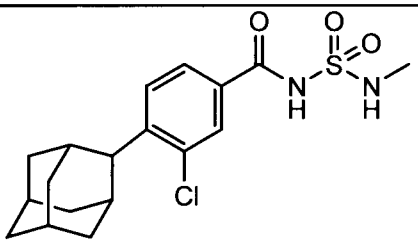
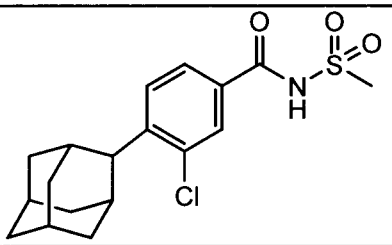
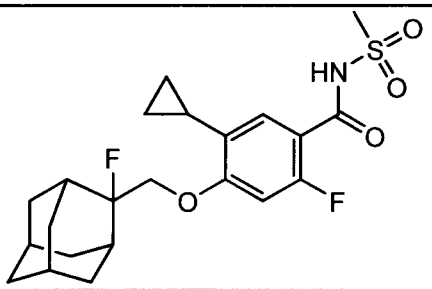
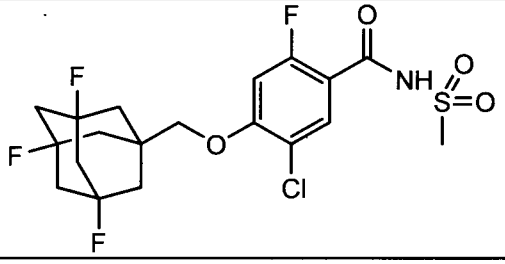
No	Structure	Name
145		
146		4-(1-adamantylmethoxy)-5-chloro-N-cyclopropylsulfonyl-2-fluoro-benzamide
147		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-[(3S)-3-hydroxypyrrolidin-1-yl]sulfonyl-benzamide
148		4-(1-adamantylmethoxy)-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide
149		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-[(3S)-3-hydroxypyrrolidin-1-yl]sulfonyl-benzamide
150		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide

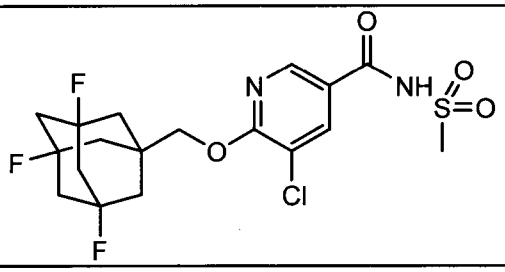
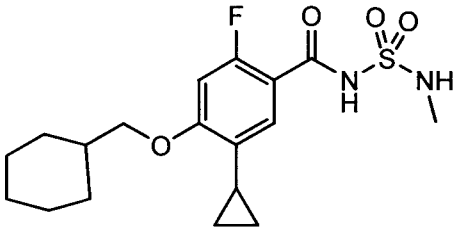
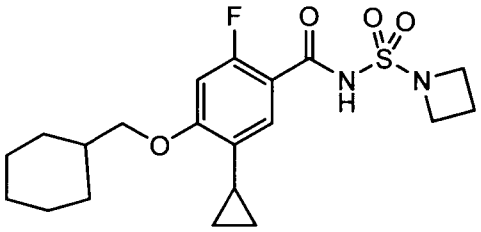
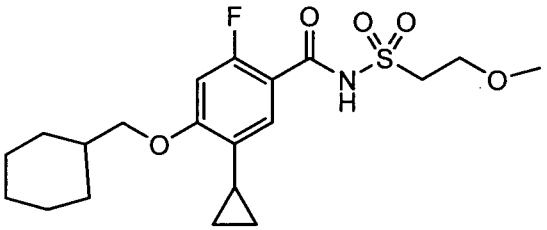
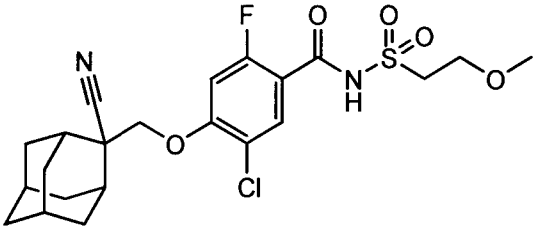
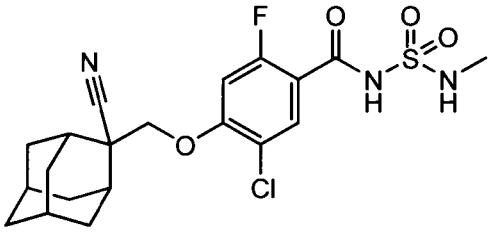
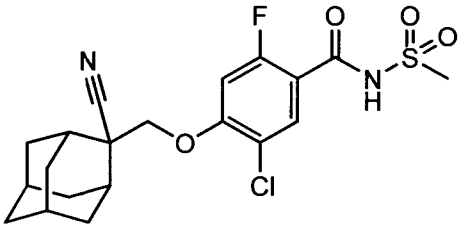
No	Structure	Name
151		4-(1-adamantylmethoxy)-5-chloro-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide
152		5-chloro-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
153		5-cyclopropyl-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
154		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-pyrrolidin-1-ylsulfonyl-benzamide
155		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-morpholinosulfonyl-benzamide
156		5-cyclopropyl-2-fluoro-4-[(3-fluoro-1-adamantyl)methoxy]-N-methylsulfonyl-benzamide

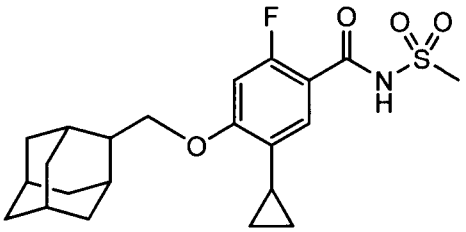
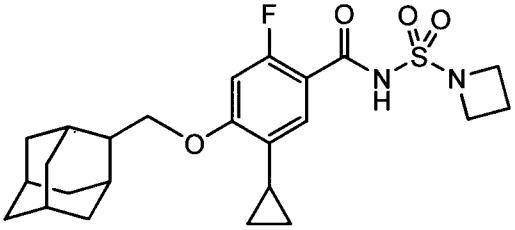
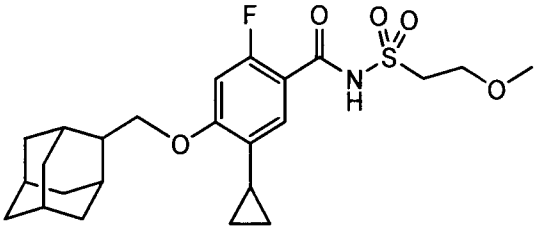
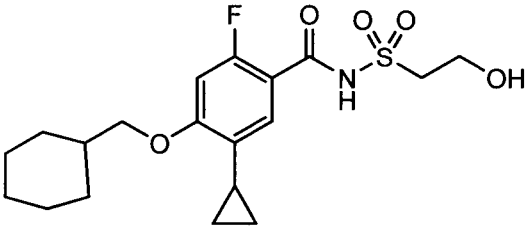
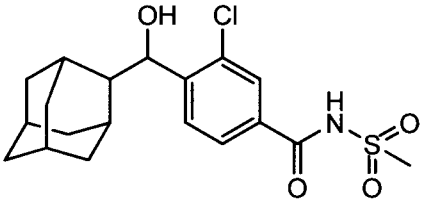
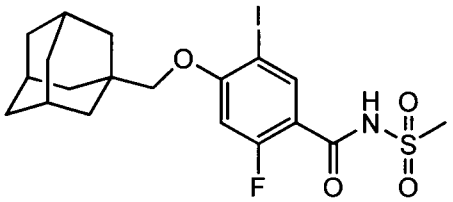
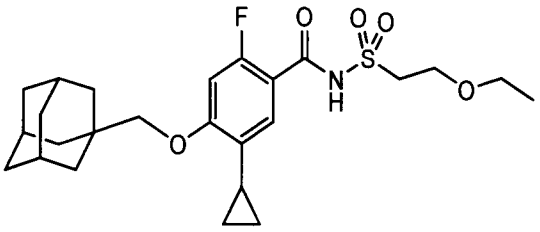
No	Structure	Name
157		5-cyclopropyl-2-fluoro-4-[(3-methoxy-1-adamantyl)methoxy]-N-methylsulfonyl-benzamide
158		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
159		4-(1-adamantylmethoxy)-5-cyclopropyl-N-(3,3-difluoroazetidin-1-yl)sulfonyl-2-fluoro-benzamide
160		2-fluoro-4-[(3-fluoro-1-adamantyl)methoxy]-N-methylsulfonyl-benzamide
161		4-(1-adamantylmethoxy)-2-fluoro-5-methyl-N-methylsulfonyl-benzamide
162		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-methyl-benzamide
163		4-(1-adamantylmethoxy)-5-cyclopropyl-N-ethylsulfonyl-2-fluoro-benzamide

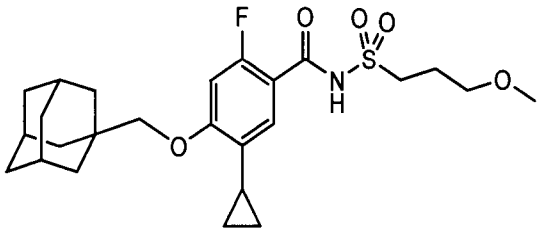
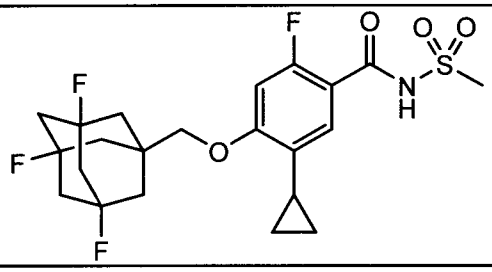
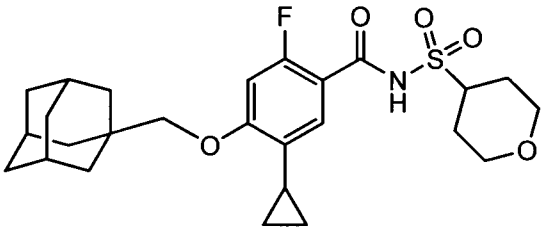
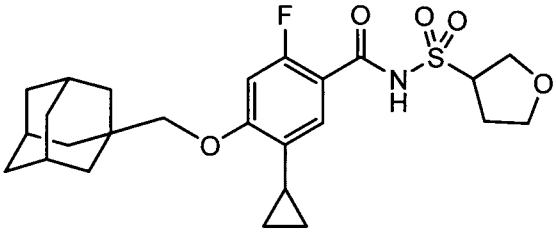
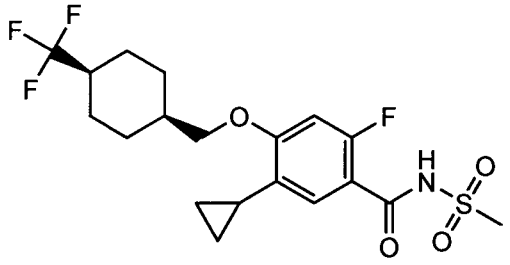
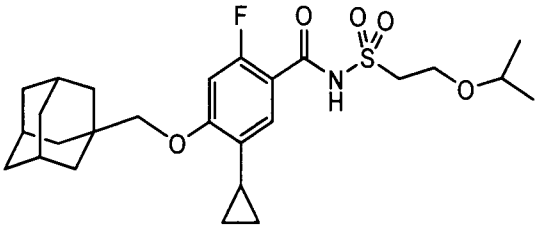
No	Structure	Name
164		4-(1-adamantylmethoxy)-N-tert-butylsulfonyl-5-cyclopropyl-2-fluoro-benzamide
165		2-fluoro-N-methylsulfonyl-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
166		5-cyclopropyl-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
167		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfamoyl)benzamide
168		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-hydroxypropylsulfamoyl)benzamide
169		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-methoxyazetidin-1-yl)sulfonyl-benzamide
170		Azetidine-1-sulfonic acid 5-cyclopropyl-4-(4,4-difluoro-adamantan-1-ylmethoxy)-2-fluoro-benzoylamide

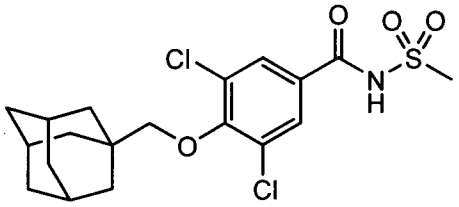
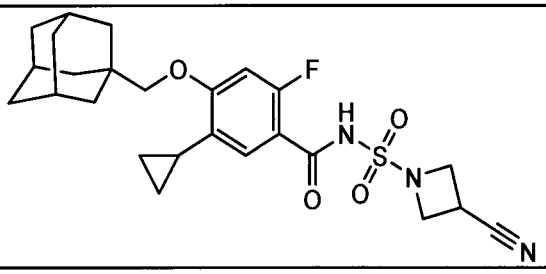
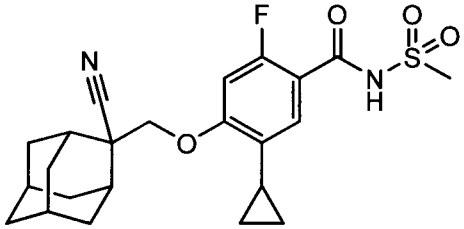
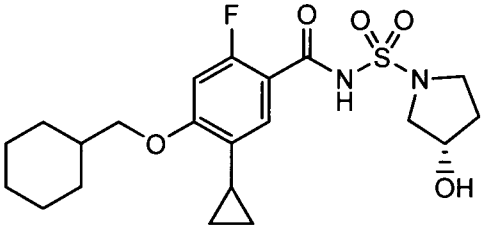
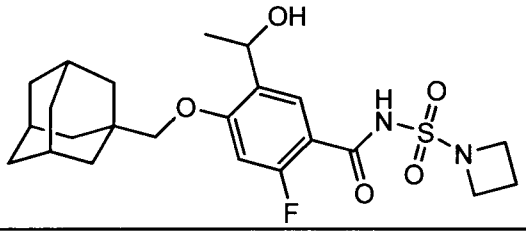
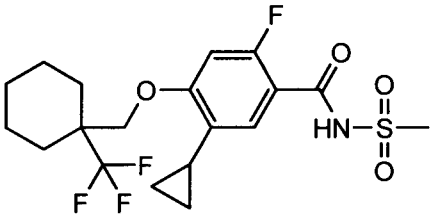
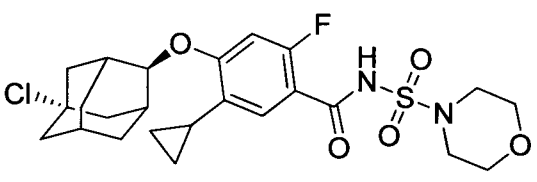
No	Structure	Name
171		Cyclopropanesulfonic acid 4-(bicyclo[4.1.0]hept-1-ylmethoxy)-5-cyclopropyl-2-fluoro-benzoylamide
172		trans-2-fluoro-4-[(5-fluoro-2-adamantyl)oxy]-5-methyl-N-methylsulfonyl-benzamide
173		cis-5-chloro-2-fluoro-4-[(5-fluoro-2-adamantyl)oxy]-N-methylsulfonyl-benzamide
174		6-(1-adamantylmethoxy)-5-cyclopropyl-N-(2-hydroxyethylsulfonyl)pyridine-3-carboxamide
175		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
176		5-chloro-2-fluoro-4-[(2-fluoro-2-adamantyl)methoxy]-N-methylsulfonyl-benzamide

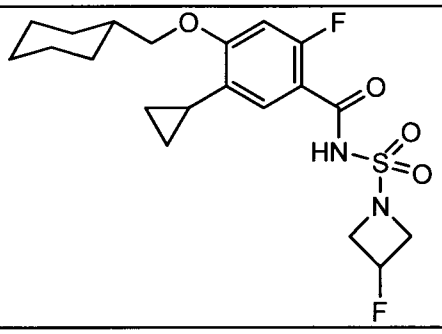
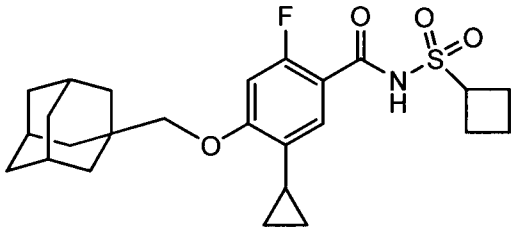
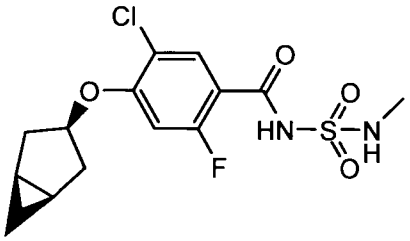
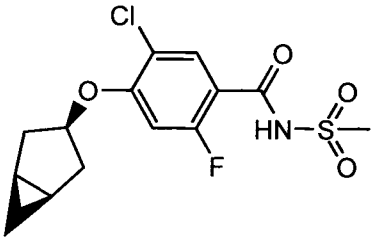
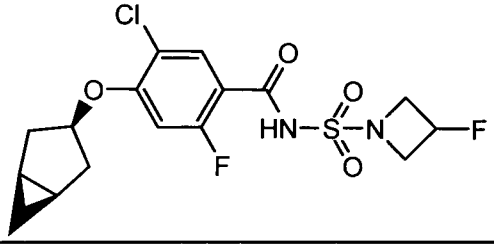
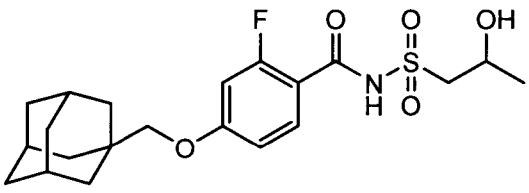
No	Structure	Name
177		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzamide
178		6-(1-adamantylmethoxy)-5-cyclopropyl-N-(methylsulfamoyl)pyridine-3-carboxamide
179		4-(2-adamantyl)-3-chloro-N-(methylsulfamoyl)benzamide
180		4-(2-adamantyl)-3-chloro-N-methylsulfonyl-benzamide
181		5-cyclopropyl-2-fluoro-4-[(2-fluoro-2-adamantyl)methoxy]-N-methylsulfonyl-benzamide
182		5-chloro-2-fluoro-N-methylsulfonyl-4-[(3,5,7-trifluoro-1-adamantyl)methoxy]benzamide

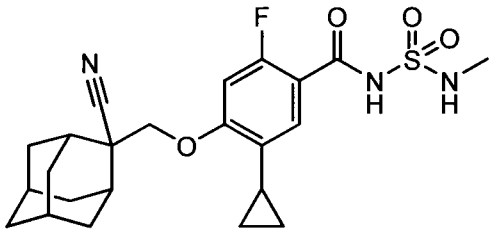
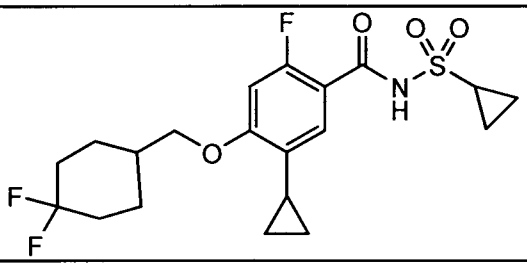
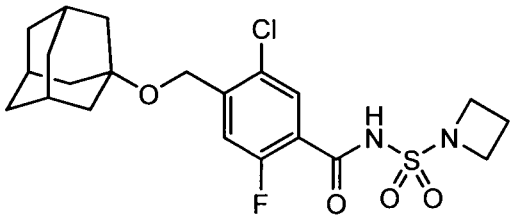
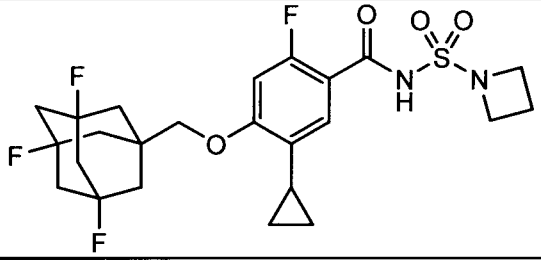
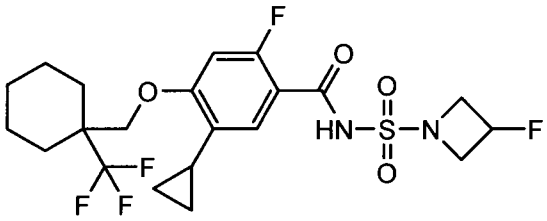
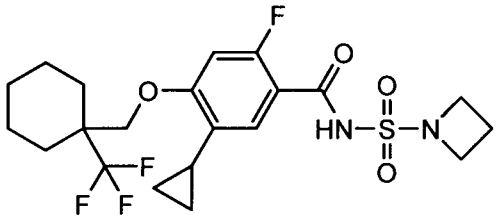
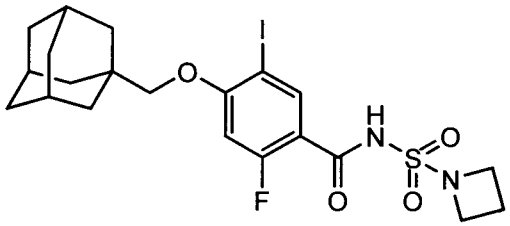
No	Structure	Name
183		5-chloro-N-methylsulfonyl-6-[(3,5,7-trifluoro-1-adamantyl)methoxy]pyridine-3-carboxamide
184		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfamoyl)benzamide
185		N-(azetidin-1-ylsulfonyl)-4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-benzamide
186		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
187		5-chloro-4-[(2-cyano-2-adamantyl)methoxy]-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
188		5-chloro-4-[(2-cyano-2-adamantyl)methoxy]-2-fluoro-N-(methylsulfamoyl)benzamide
189		5-chloro-4-[(2-cyano-2-adamantyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide

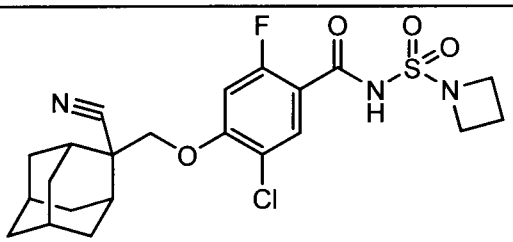
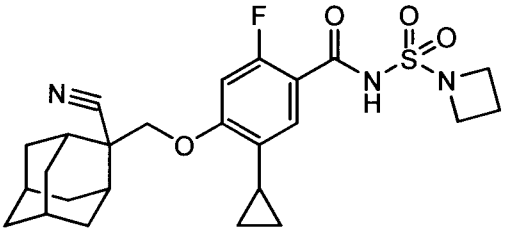
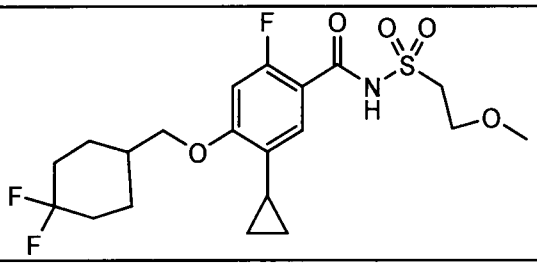
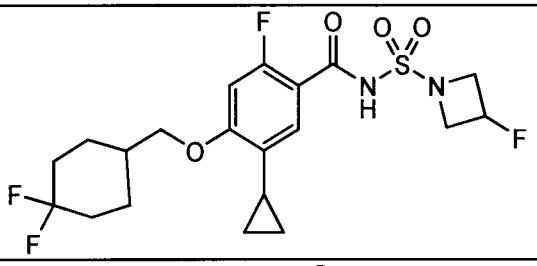
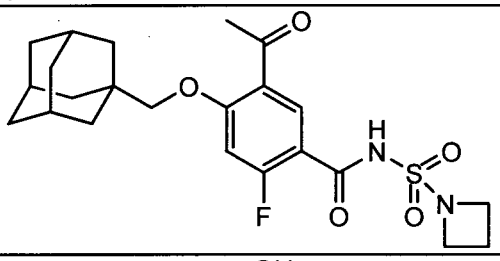
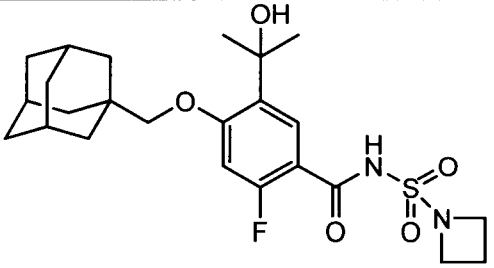
No	Structure	Name
190		4-(2-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
191		4-(2-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-benzamide
192		4-(2-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
193		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-hydroxyethylsulfonyl)benzamide
194		4-[2-adamantyl(hydroxy)methyl]-3-chloro-N-methylsulfonyl-benzamide
195		4-(1-adamantylmethoxy)-2-fluoro-5-iodo-N-methylsulfonyl-benzamide
196		4-(1-adamantylmethoxy)-5-cyclopropyl-N-(2-ethoxyethylsulfonyl)-2-fluoro-benzamide

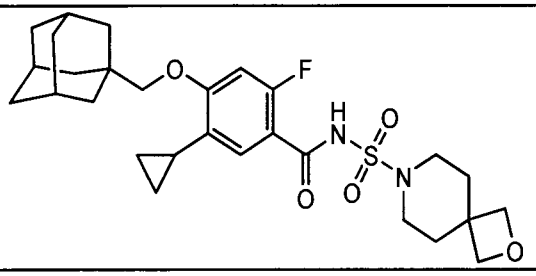
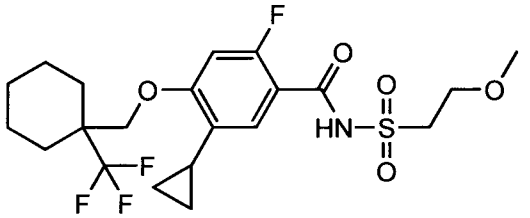
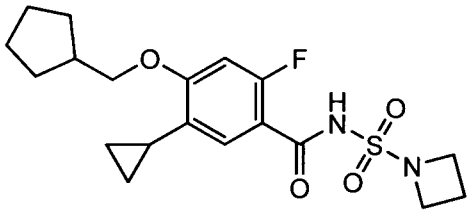
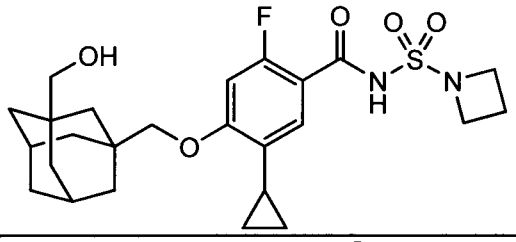
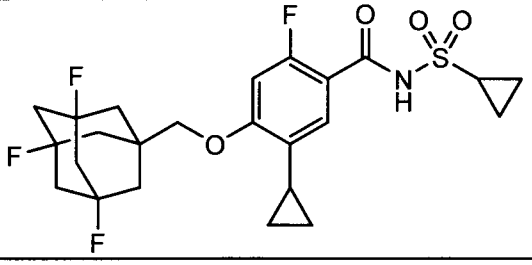
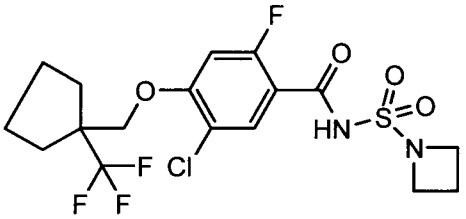
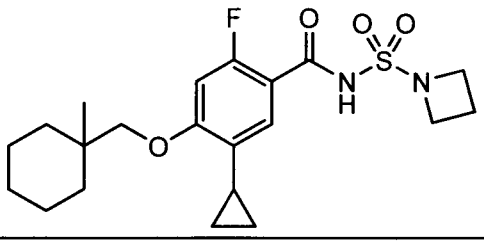
No	Structure	Name
197		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-methoxypropylsulfonyl)benzamide
198		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[(3,5,7-trifluoro-1-adamantyl)methoxy]benzamide
199		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-tetrahydropyran-4-ylsulfonyl-benzamide
200		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-tetrahydrofuran-3-ylsulfonyl-benzamide
201	 (rel-cis)	cis-5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
202		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-isopropoxyethylsulfonyl)benzamide

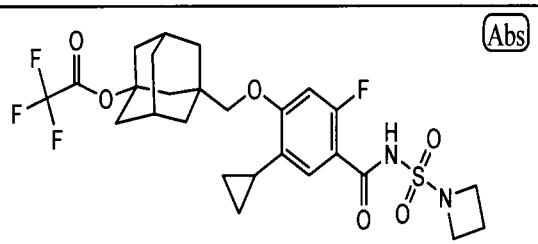
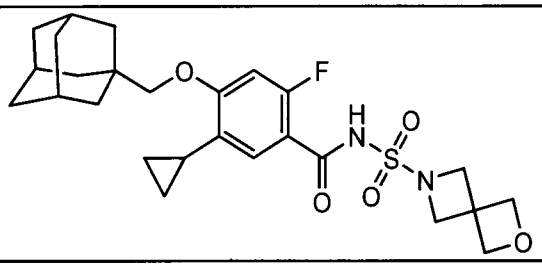
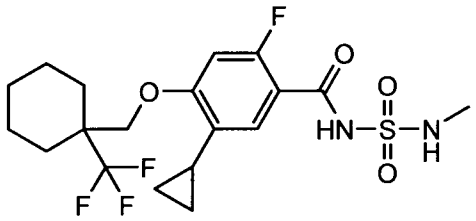
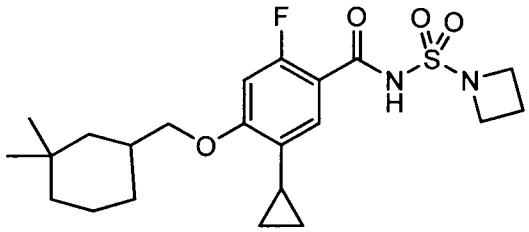
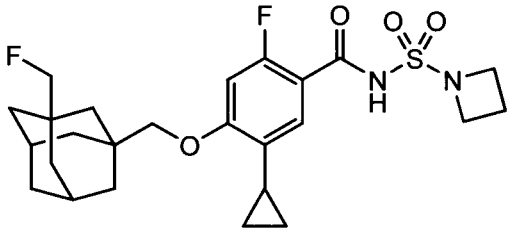
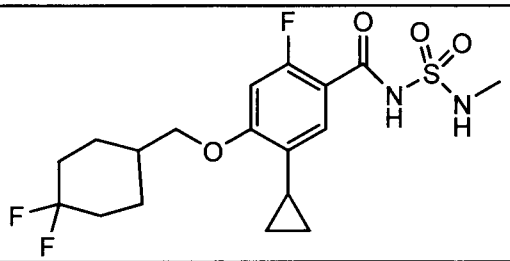
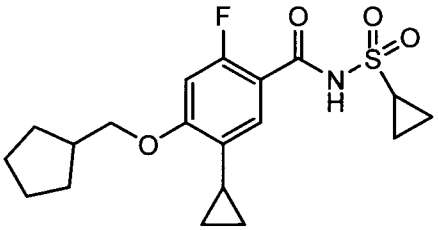
No	Structure	Name
203		4-(1-adamantylmethoxy)-3,5-dichloro-N-methylsulfonyl-benzamide
204		4-(1-adamantylmethoxy)-N-(3-cyanoazetidin-1-yl)sulfonyl-5-cyclopropyl-2-fluoro-benzamide
205		4-[(2-cyano-2-adamantyl)methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
206		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-[(3S)-3-hydroxypyrrolidin-1-yl]sulfonyl-benzamide
207		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxyethyl)benzamide
208		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[1-(trifluoromethyl)cyclohexyl]methoxy]benzamide
209		trans-4-[(5-chloro-2-adamantyl)oxy]-5-cyclopropyl-2-fluoro-N-morpholinosulfonyl-benzamide

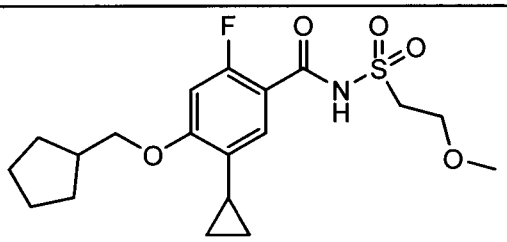
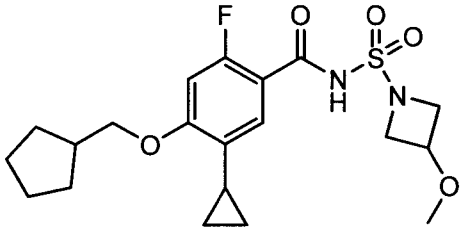
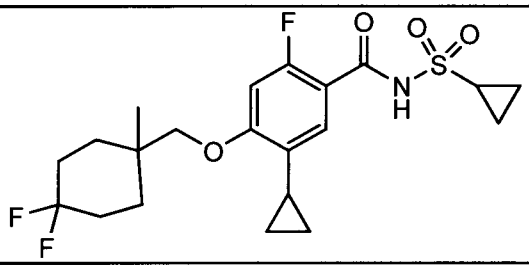
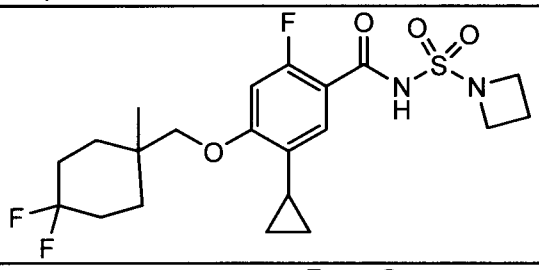
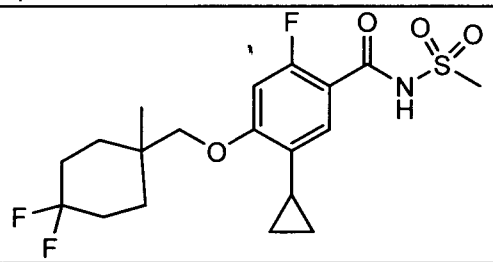
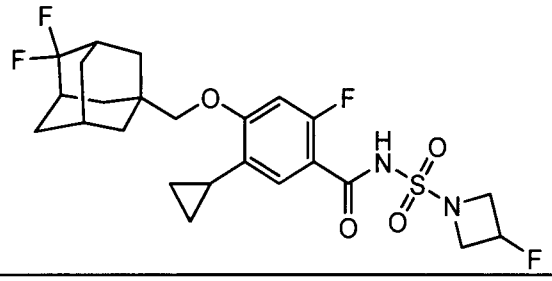
No	Structure	Name
210		4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide
211		4-(1-adamantylmethoxy)-N-cyclobutylsulfonyl-5-cyclopropyl-2-fluoro-benzamide
212		4-[[(1R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-5-chloro-2-fluoro-N-(methylsulfamoyl)benzamide
213		4-[[(1R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-5-chloro-2-fluoro-N-methylsulfonyl-benzamide
214		4-[[(1R,5S)-3-bicyclo[3.1.0]hexanyl]oxy]-5-chloro-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide
215		4-(1-adamantylmethoxy)-2-fluoro-N-(2-hydroxypropylsulfonyl)benzamide

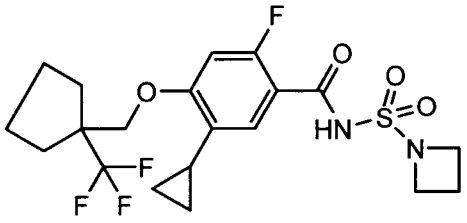
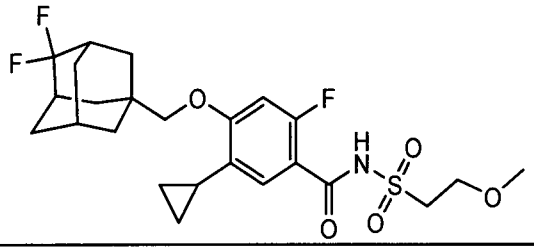
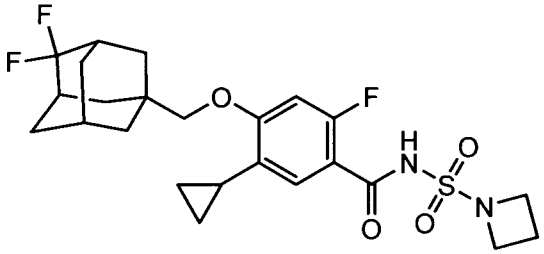
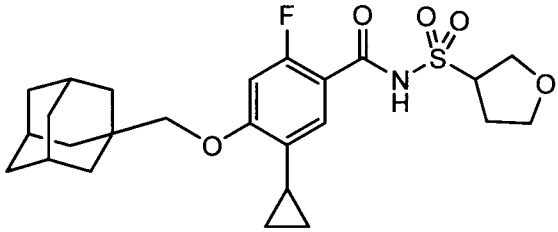
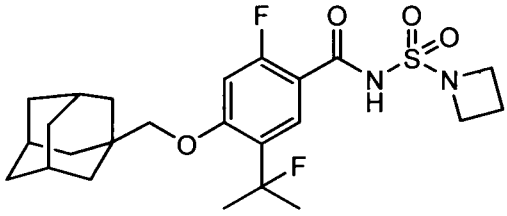
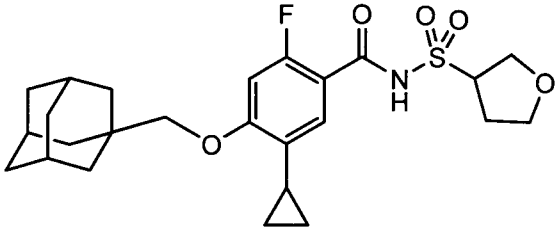
No	Structure	Name
216		4-[(2-cyano-2-adamantyl)methoxy]-5-cyclopropyl-2-fluoro-N-(methylsulfamoyl)benzamide
217		5-cyclopropyl-N-cyclopropylsulfonyl-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-benzamide
218		4-(1-adamantyloxymethyl)-N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-benzamide
219		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(3,5,7-trifluoro-1-adamantyl)methoxy]benzamide
220		5-cyclopropyl-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-4-[[1-(trifluoromethyl)cyclohexyl]methoxy]benzamide
221		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[1-(trifluoromethyl)cyclohexyl]methoxy]benzamide
222		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-iodo-benzamide

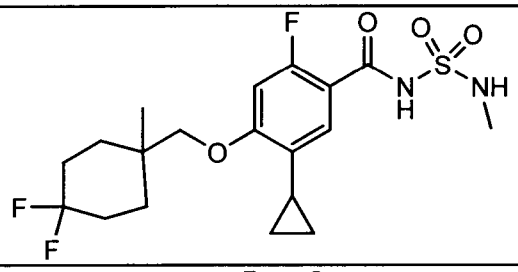
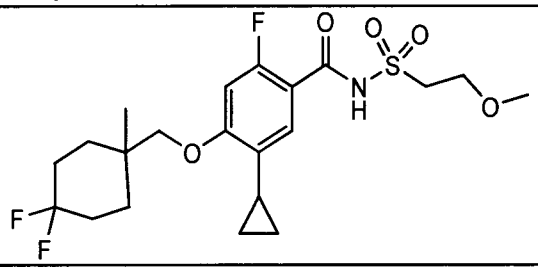
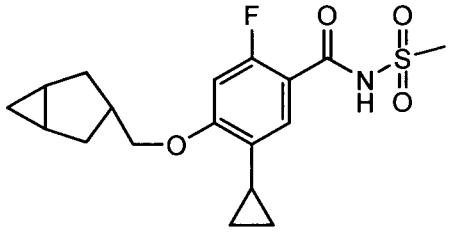
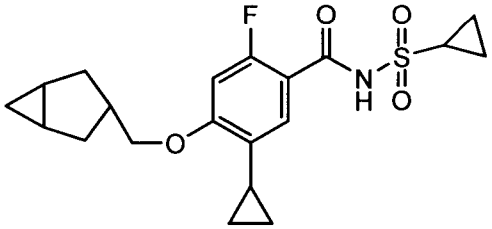
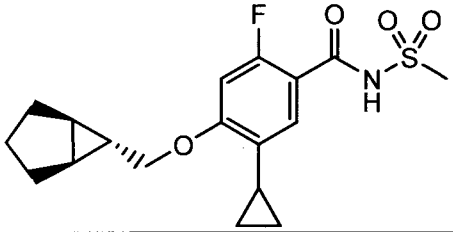
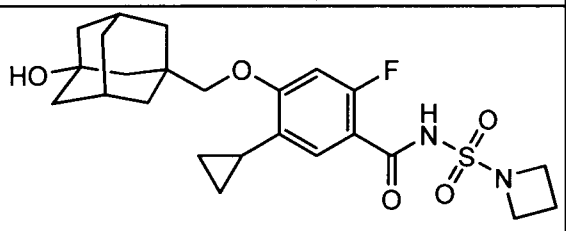
No	Structure	Name
223		N-(azetidin-1-ylsulfonyl)-5-chloro-4-[(2-cyano-2-adamantyl)methoxy]-2-fluoro-benzamide
224		N-(azetidin-1-ylsulfonyl)-4-[(2-cyano-2-adamantyl)methoxy]-5-cyclopropyl-2-fluoro-benzamide
225		5-cyclopropyl-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
226		5-cyclopropyl-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide
227		5-acetyl-4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-benzamide
228		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxy-1-methyl-ethyl)benzamide

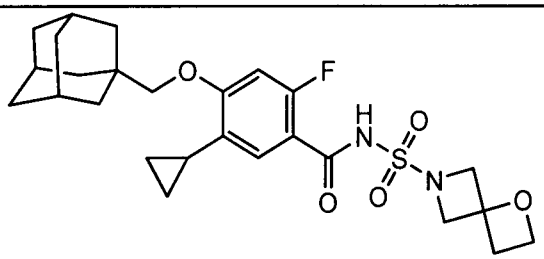
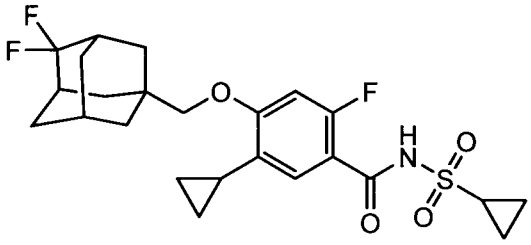
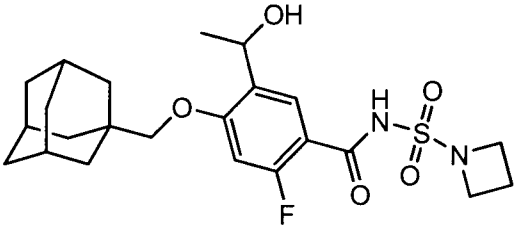
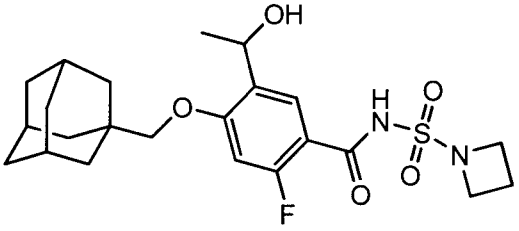
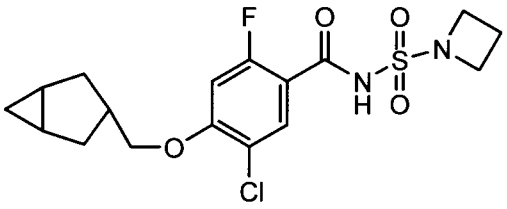
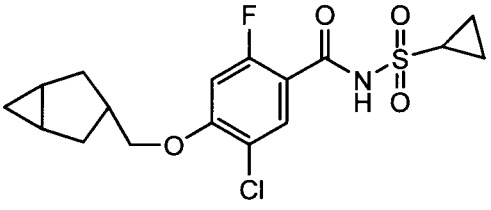
No	Structure	Name
229		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-oxa-7-azaspiro[3.5]nonan-7-ylsulfonyl)benzamide
230		5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)-4-[[1-(trifluoromethyl)cyclohexyl]methoxy]benzamide
231		N-(azetidin-1-ylsulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-benzamide
232		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[3-(hydroxymethyl)-1-adamantyl]methoxy]benzamide
233		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(3,5,7-trifluoro-1-adamantyl)methoxy]benzamide
234		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-[[1-(trifluoromethyl)cyclopentyl]methoxy]benzamide
235		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(1-methylcyclohexyl)methoxy]benzamide

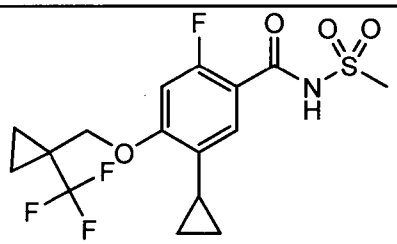
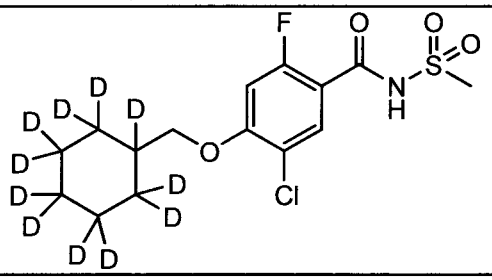
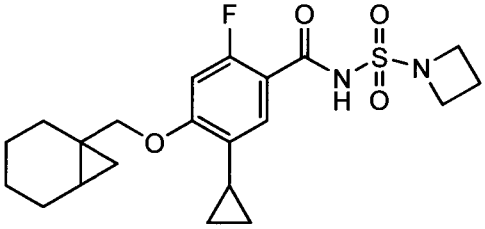
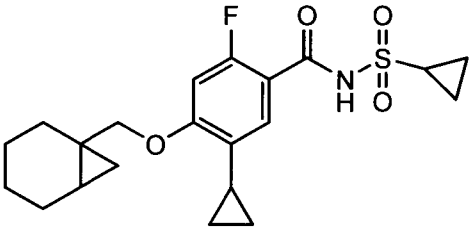
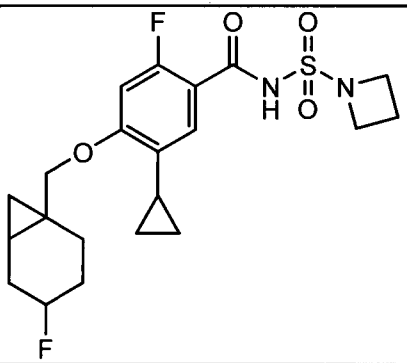
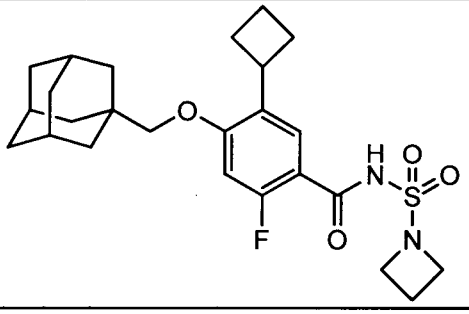
No	Structure	Name
236		[3-[[4-(azetidin-1-ylsulfonylcarbamoyl)-2-cyclopropyl-5-fluoro-phenoxy]methyl]-1-adamantyl] 2,2,2-trifluoroacetate
237		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-oxa-6-azaspiro[3.3]heptan-6-ylsulfonyl)benzamide
238		5-cyclopropyl-2-fluoro-N-(methylsulfamoyl)-4-[[1-(trifluoromethyl)cyclohexyl]methoxy]benzamide
239		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(3,3-dimethylcyclohexyl)methoxy]-2-fluoro-benzamide
240		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[3-(fluoromethyl)-1-adamantyl]methoxy]benzamide
241		5-cyclopropyl-4-[(4,4-difluorocyclohexyl)methoxy]-2-fluoro-N-(methylsulfamoyl)benzamide
242		4-(cyclopentylmethoxy)-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide

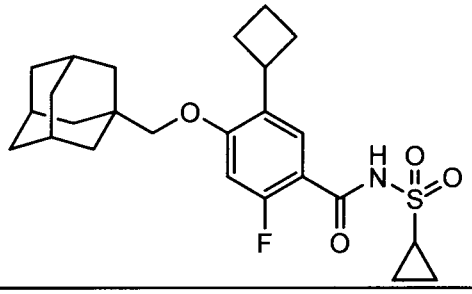
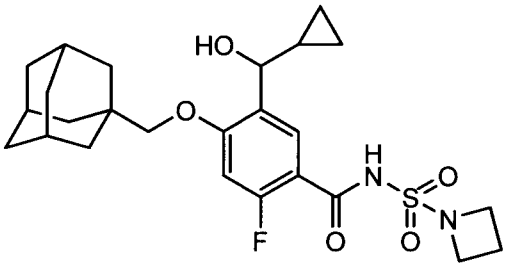
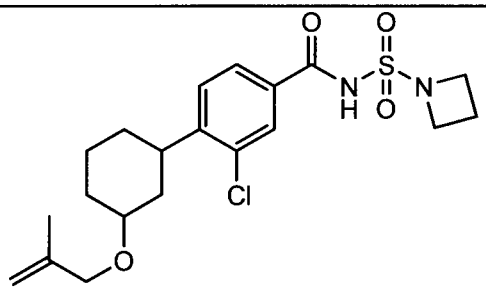
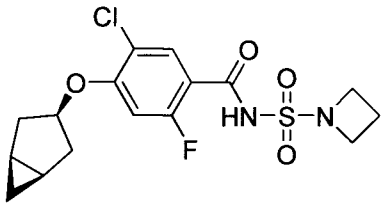
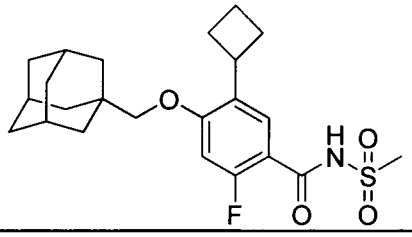
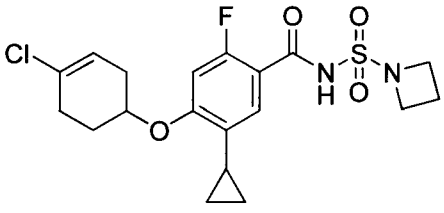
No	Structure	Name
243		4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
244		4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-(3-methoxyazetidin-1-yl)sulfonyl-benzamide
245		5-cyclopropyl-N-cyclopropylsulfonyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-benzamide
246		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-benzamide
247		5-cyclopropyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
248		5-cyclopropyl-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide

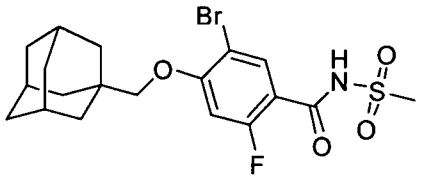
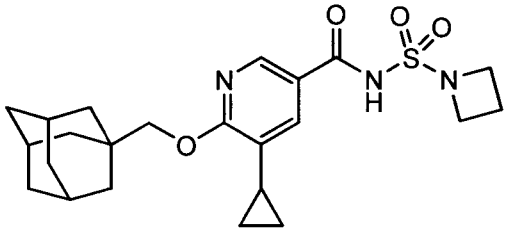
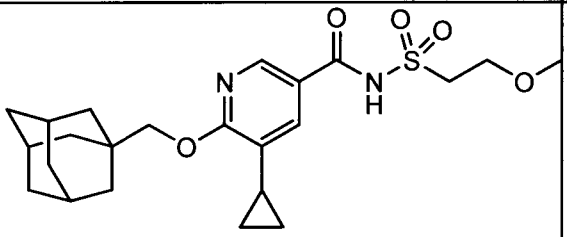
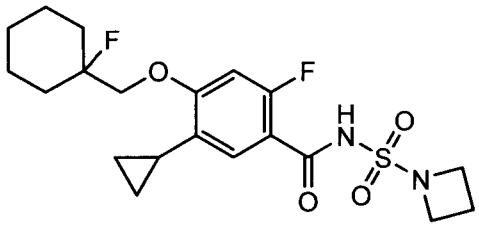
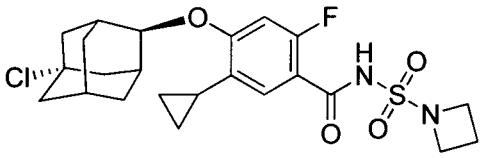
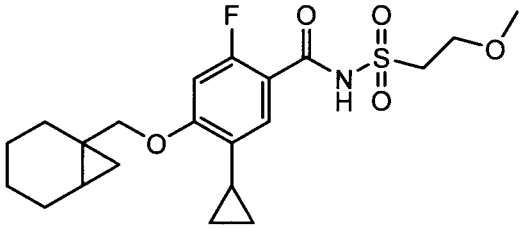
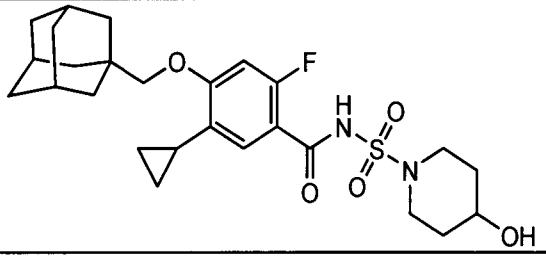
No	Structure	Name
249		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[1-(trifluoromethyl)cyclopentyl]methoxy]benzamide
250		5-cyclopropyl-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
251		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-benzamide
252		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-tetrahydrofuran-3-ylsulfonyl-benzamide
253		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-fluoro-1-methyl-ethyl)benzamide
254	 single isomer	4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-tetrahydrofuran-3-ylsulfonyl-benzamide

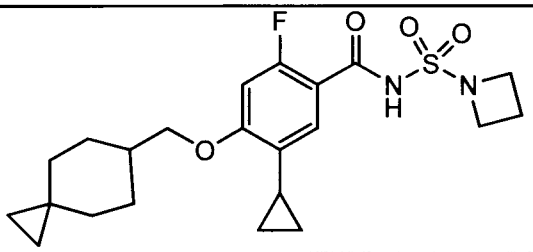
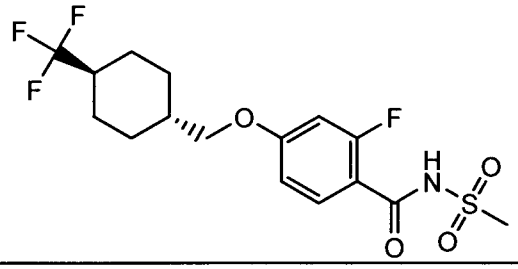
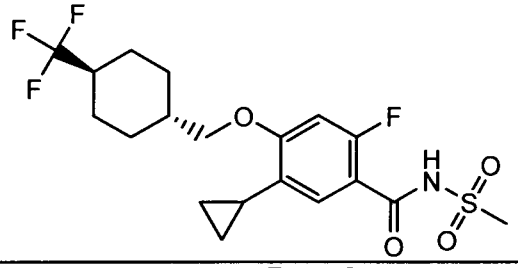
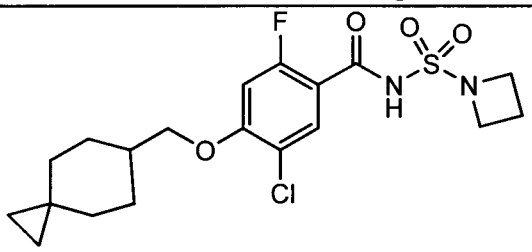
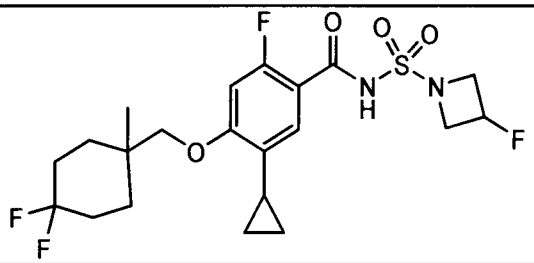
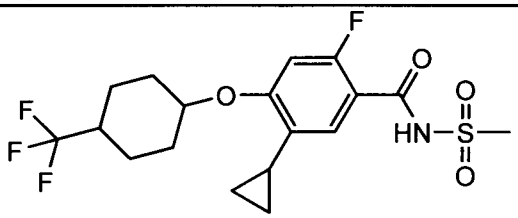
No	Structure	Name
255		5-cyclopropyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-N-(methylsulfamoyl)benzamide
256		5-cyclopropyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
257		4-(3-bicyclo[3.1.0]hexanylmethoxy)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
258		4-(3-bicyclo[3.1.0]hexanylmethoxy)-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide
259		4-[[(1R,5S)-6-bicyclo[3.1.0]hexanyl]methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
260		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(3-hydroxy-1-adamantyl)methoxy]benzamide

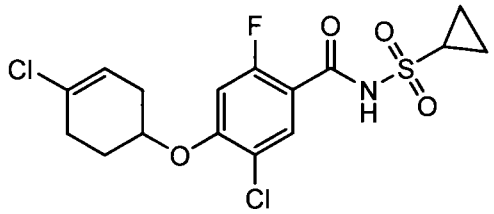
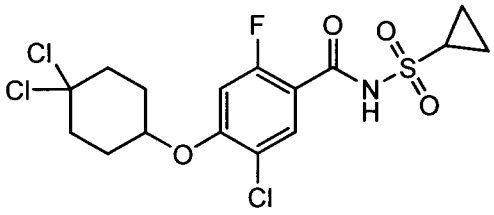
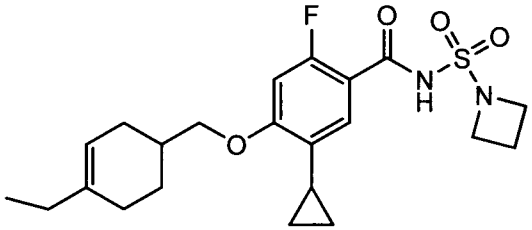
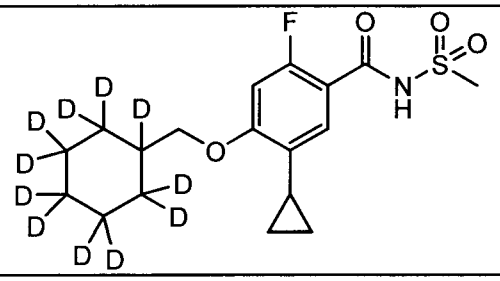
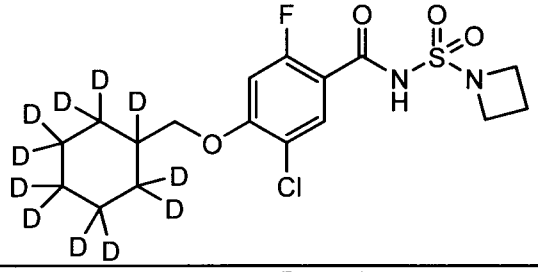
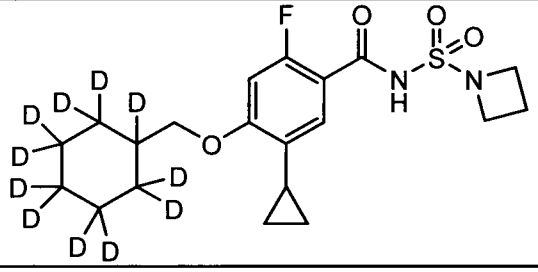
No	Structure	Name
261		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-(1-oxa-6-azaspiro[3.3]heptan-6-ylsulfonyl)benzamide
262		5-cyclopropyl-N-cyclopropylsulfonyl-4-[(4,4-difluoro-1-adamantyl)methoxy]-2-fluoro-benzamide
263	 single isomer	4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxyethyl)benzamide
264	 single isomer	4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxyethyl)benzamide
265		N-(azetidin-1-ylsulfonyl)-4-(3-bicyclo[3.1.0]hexanylmethoxy)-5-chloro-2-fluoro-benzamide
266		4-(3-bicyclo[3.1.0]hexanylmethoxy)-5-chloro-N-cyclopropylsulfonyl-2-fluoro-benzamide

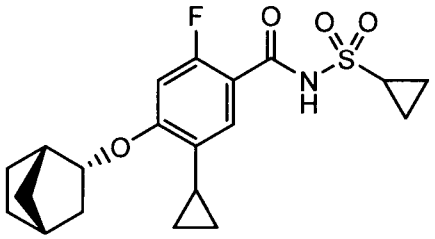
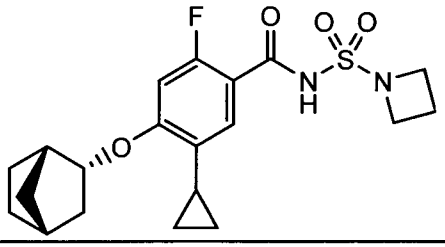
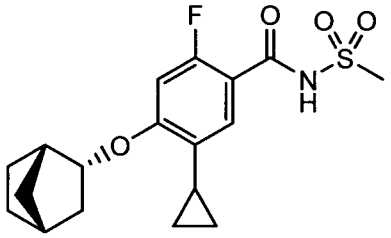
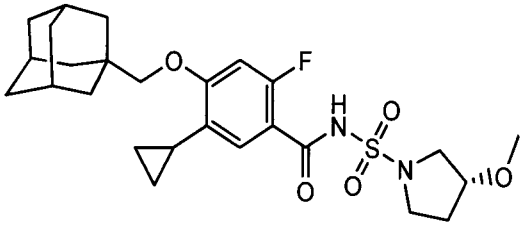
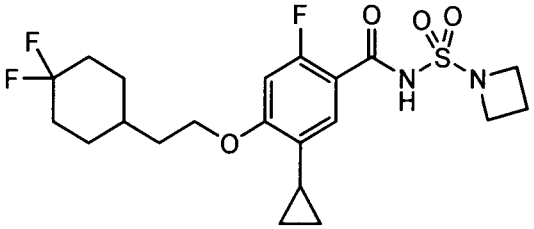
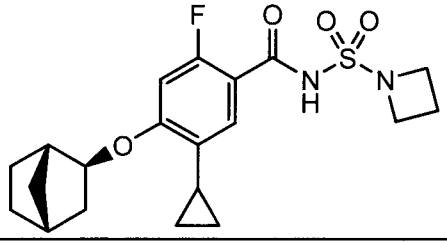
No	Structure	Name
267		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]benzamide
268		5-chloro-2-fluoro-N-methylsulfonyl-4-[(1,2,2,3,3,4,4,5,5,6,6-undecadeuteriocyclohexyl)methoxy]benzamide
269		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(norcaran-1-ylmethoxy)benzamide
270		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-(norcaran-1-ylmethoxy)benzamide
271		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(4-fluoronorcaran-1-yl)methoxy]benzamide
272		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclobutyl-2-fluoro-benzamide

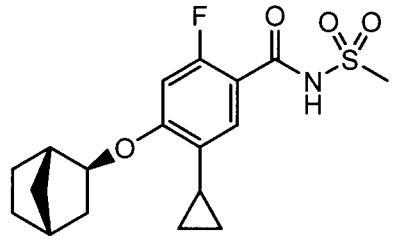
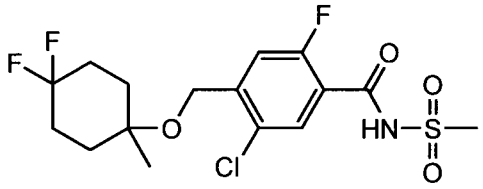
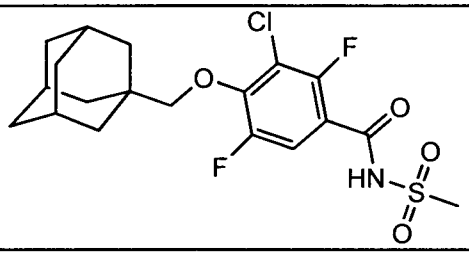
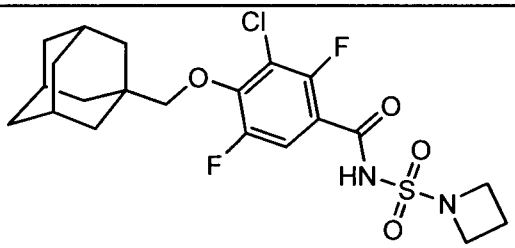
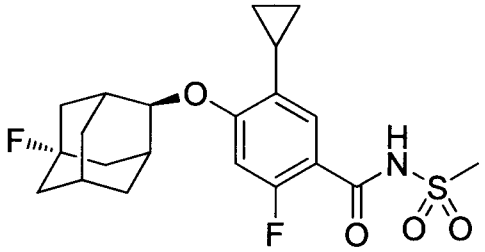
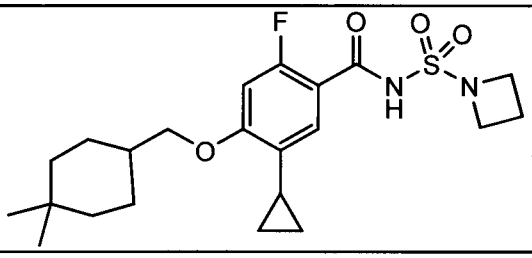
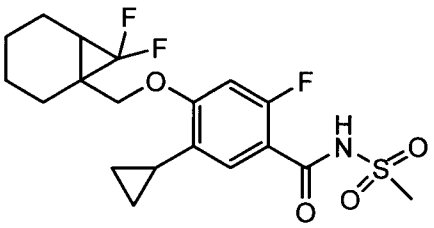
No	Structure	Name
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274		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-[cyclopropyl(hydroxy)methyl]-2-fluoro-benzamide
275		N-(azetidin-1-ylsulfonyl)-3-chloro-4-[3-(2-methylallyloxy)cyclohexyl]benzamide
276		N-(azetidin-1-ylsulfonyl)-4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluorobenzamide
277		
278		N-(azetidin-1-ylsulfonyl)-4-(4-chlorocyclohex-3-enyloxy)-5-cyclopropyl-2-fluorobenzamide

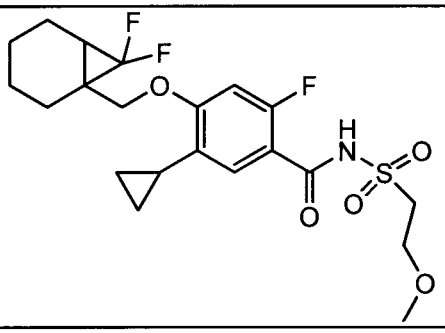
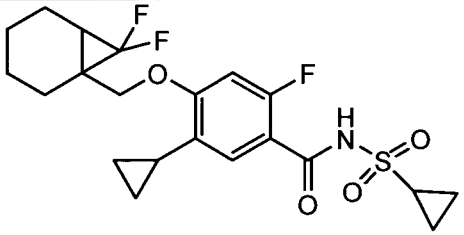
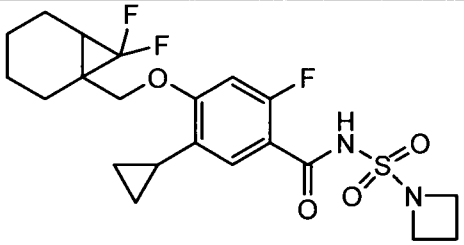
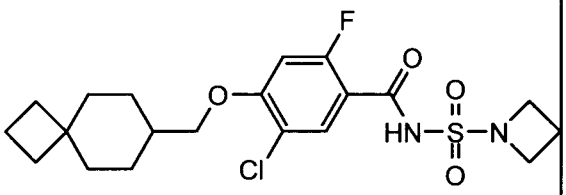
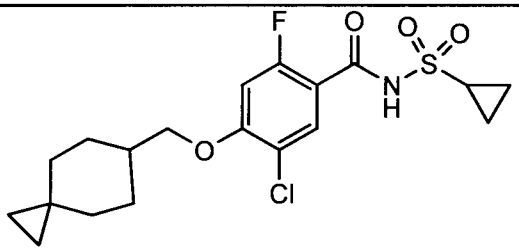
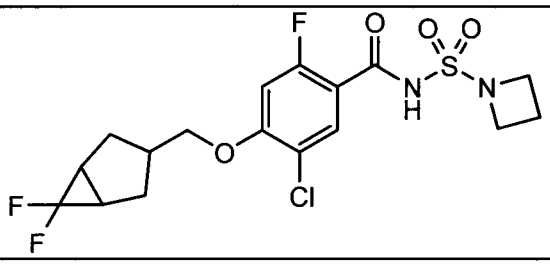
No	Structure	Name
279		
280		6-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-pyridine-3-carboxamide
281		6-(1-adamantylmethoxy)-5-cyclopropyl-N-(2-methoxyethylsulfonyl)pyridine-3-carboxamide
282		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(1-fluorocyclohexyl)methoxy]benzamide
283		trans-N-(azetidin-1-ylsulfonyl)-4-[(5-chloro-2-adamantyl)oxy]-5-cyclopropyl-2-fluoro-benzamide
284		5-cyclopropyl-2-fluoro-N-(2-methoxyethylsulfonyl)-4-(norcaran-1-ylmethoxy)benzamide
285		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-[(4-hydroxy-1-piperidyl)sulfonyl]benzamide

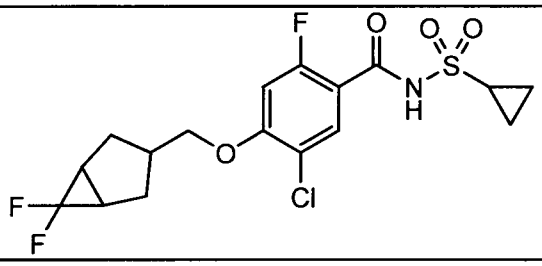
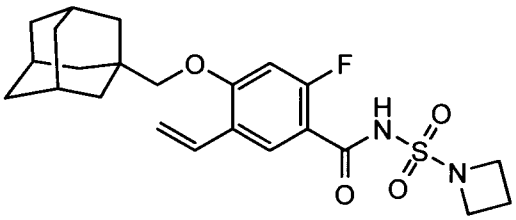
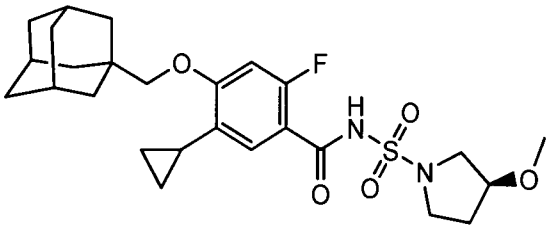
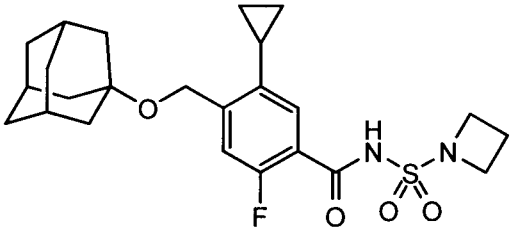
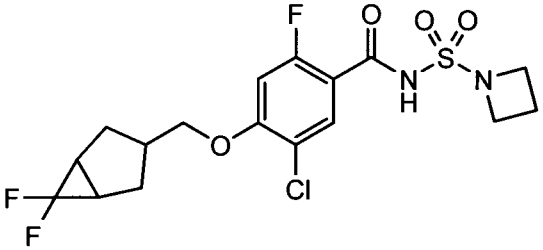
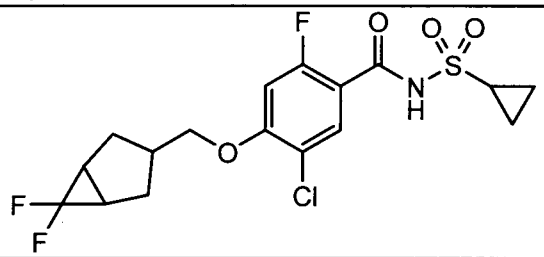
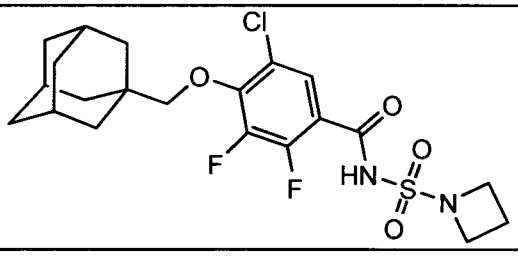
No	Structure	Name
286		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
287		2-fluoro-N-methylsulfonyl-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
288		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
289		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
290		5-cyclopropyl-4-[(4,4-difluoro-1-methyl-cyclohexyl)methoxy]-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-benzamide
291	 single isomer	5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[4-(trifluoromethyl)cyclohexoxy]benzamide

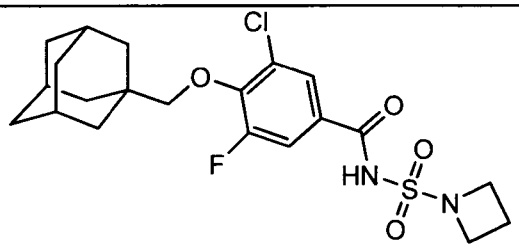
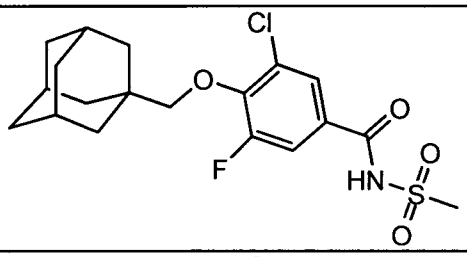
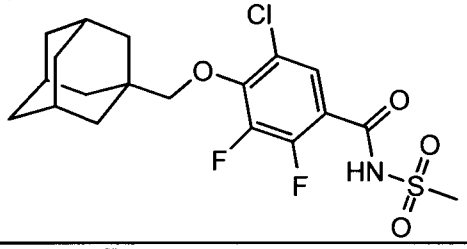
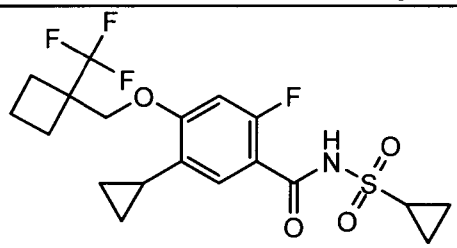
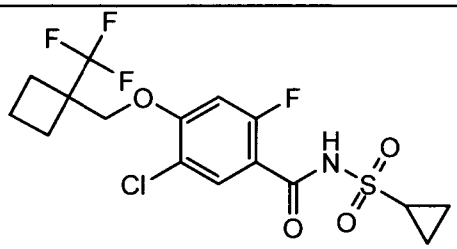
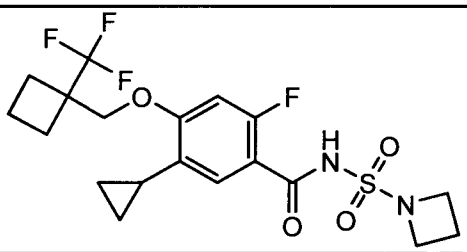
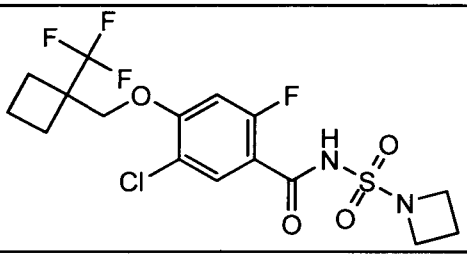
No	Structure	Name
292		5-chloro-4-(4-chlorocyclohex-3-en-1-yl)oxy-N-cyclopropylsulfonyl-2-fluoro-benzamide
293		5-chloro-N-cyclopropylsulfonyl-4-(4,4-dichlorocyclohexoxy)-2-fluoro-benzamide
294		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4-ethylcyclohex-3-en-1-yl)methoxy]-2-fluoro-benzamide
295		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[(1,2,2,3,3,4,4,5,5,6,6-undecadeuteriocyclohexyl)methoxy]benzamide
296		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-[(1,2,2,3,3,4,4,5,5,6,6-undecadeuteriocyclohexyl)methoxy]benzamide
297		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(1,2,2,3,3,4,4,5,5,6,6-undecadeuteriocyclohexyl)methoxy]benzamide

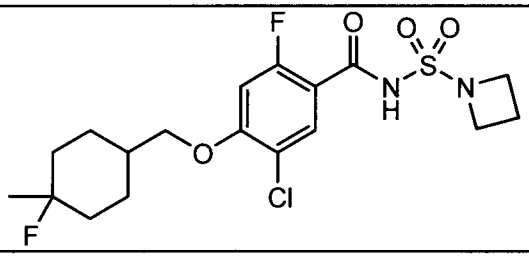
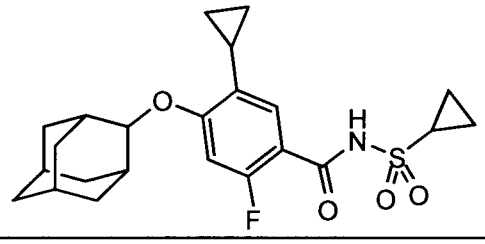
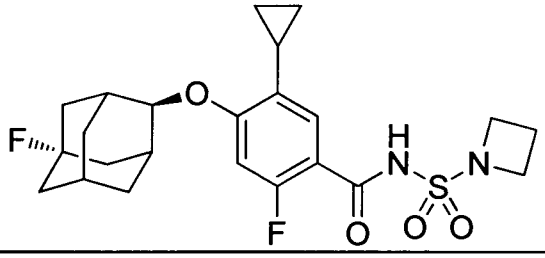
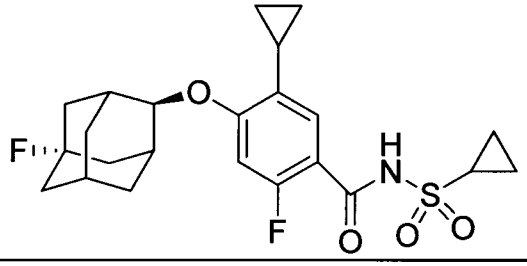
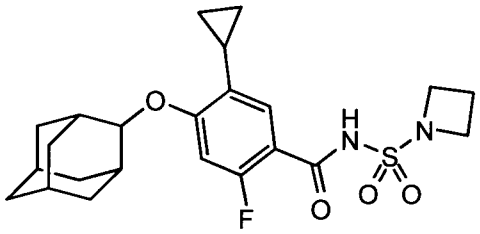
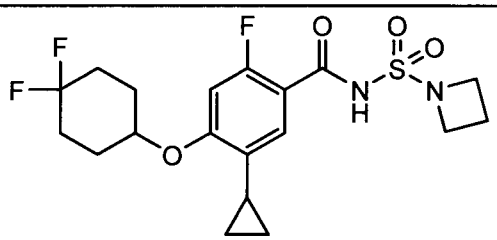
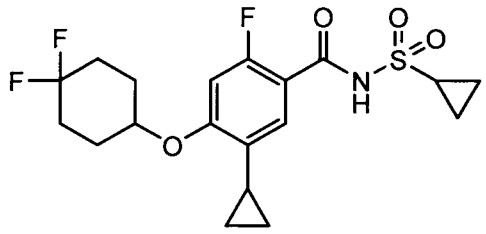
No	Structure	Name
298		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(1S,2R,4R)-norbornan-2-yl]oxy-benzamide
299		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(1S,2R,4R)-norbornan-2-yl]oxy-benzamide
300		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[(1S,2R,4R)-norbornan-2-yl]oxy-benzamide
301		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-[(3R)-3-methoxypyrrolidin-1-yl]sulfonyl-benzamide
302		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[2-(4,4-difluorocyclohexyl)ethoxy]-2-fluoro-benzamide
303		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(1S,2S,4R)-norbornan-2-yl]oxy-benzamide

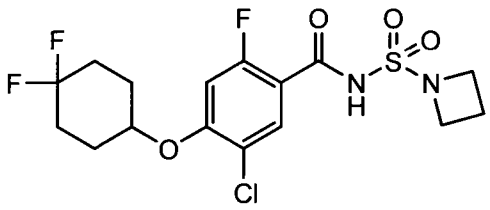
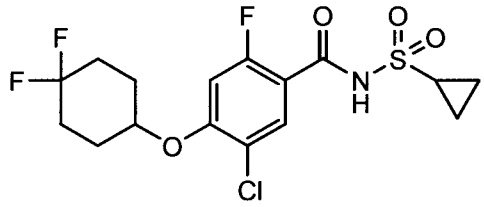
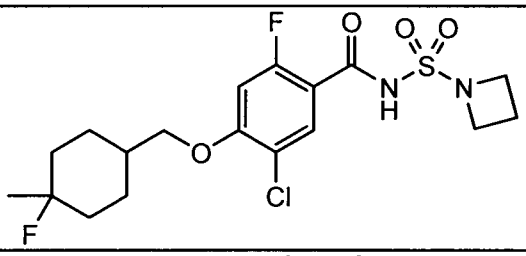
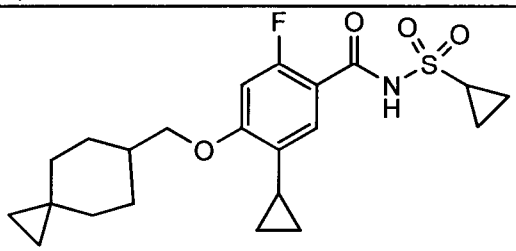
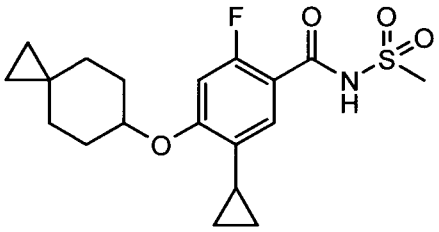
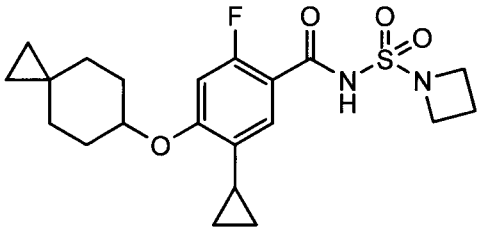
No	Structure	Name
304		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[(1S,2S,4R)-norbornan-2-yl]oxy-benzamide
305		5-chloro-4-[(4,4-difluoro-1-methyl-cyclohexoxy)methyl]-2-fluoro-N-methylsulfonyl-benzamide
306		4-(1-adamantylmethoxy)-3-chloro-2,5-difluoro-N-methylsulfonyl-benzamide
307		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-3-chloro-2,5-difluoro-benzamide
308		5-cyclopropyl-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide
309		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4,4-dimethylcyclohexyl)methoxy]-2-fluoro-benzamide
310		5-cyclopropyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide

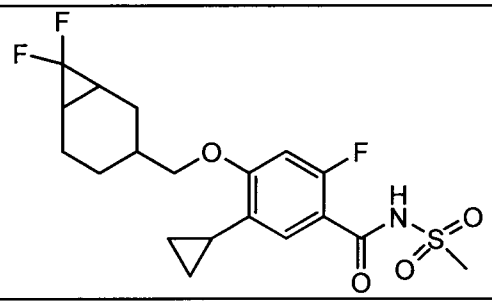
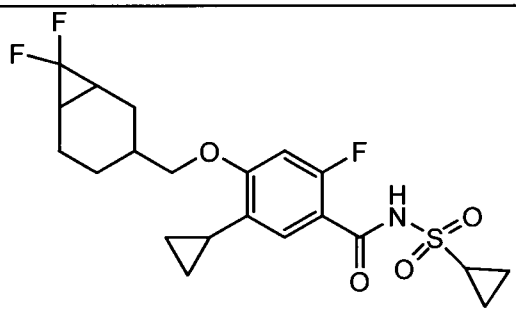
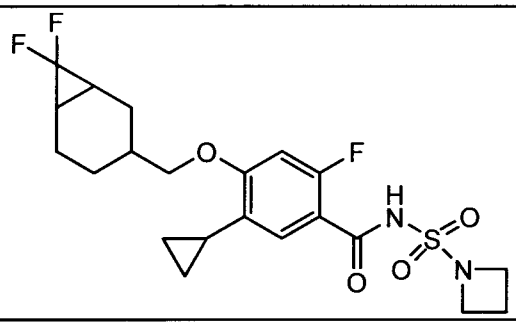
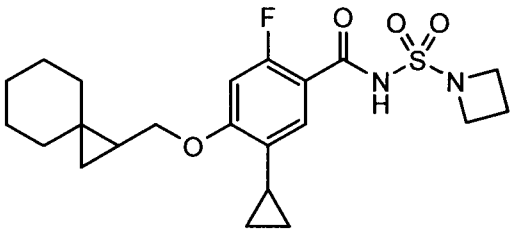
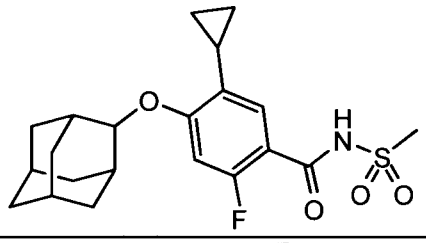
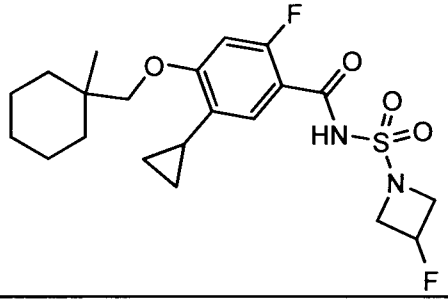
No	Structure	Name
311		5-cyclopropyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-N-(2-methoxyethylsulfonyl)benzamide
312		5-cyclopropyl-N-cyclopropylsulfonyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide
313		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide
314		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide
315		5-chloro-N-cyclopropylsulfonyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
316		N-(azetidin-1-ylsulfonyl)-5-chloro-4-[(6,6-difluoro-3-bicyclo[3.1.0]hexanyl)methoxy]-2-fluoro-benzamide

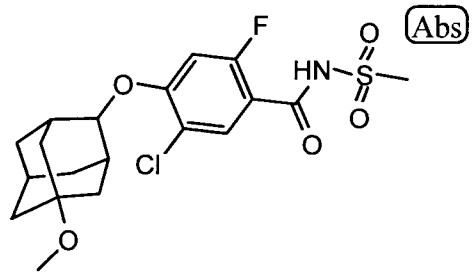
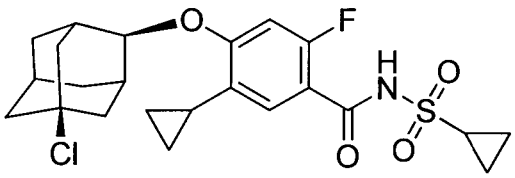
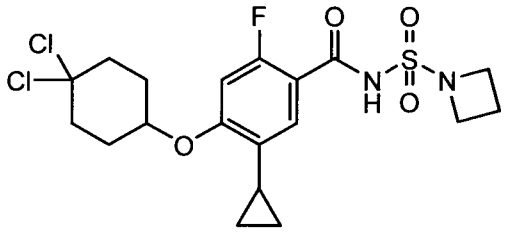
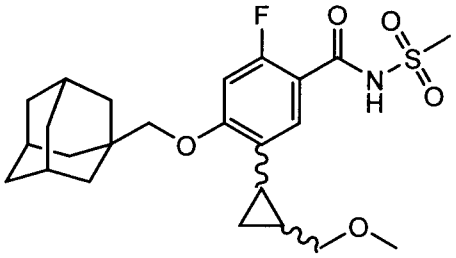
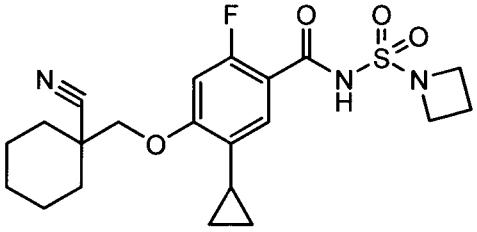
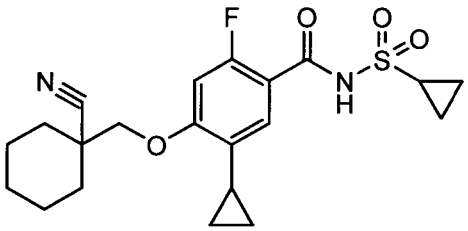
No	Structure	Name
317		5-chloro-N-cyclopropylsulfonyl-4-[(6,6-difluoro-3-bicyclo[3.1.0]hexanyl)methoxy]-2-fluoro-benzamide
318		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-vinyl-benzamide
319		4-(1-adamantylmethoxy)-5-cyclopropyl-2-fluoro-N-[(3S)-3-methoxypyrrolidin-1-yl]sulfonyl-benzamide
320		4-(1-adamantyloxymethyl)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-benzamide
321		N-(azetidin-1-ylsulfonyl)-5-chloro-4-[(6,6-difluoro-3-bicyclo[3.1.0]hexanyl)methoxy]-2-fluoro-benzamide
322		5-chloro-N-cyclopropylsulfonyl-4-[(6,6-difluoro-3-bicyclo[3.1.0]hexanyl)methoxy]-2-fluoro-benzamide
323		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-chloro-2,3-difluoro-benzamide

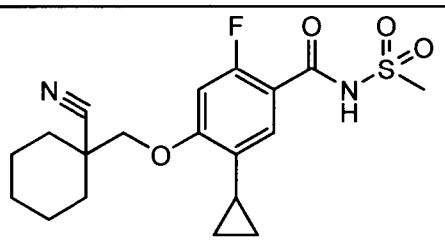
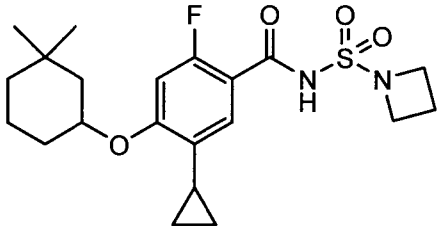
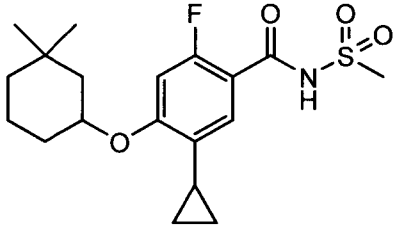
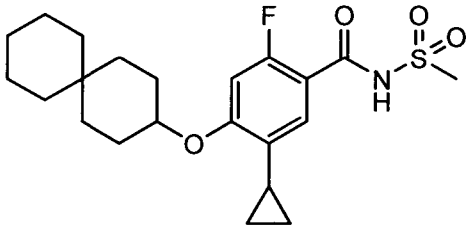
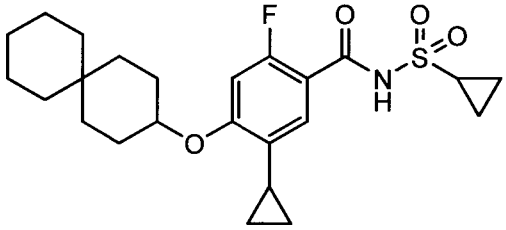
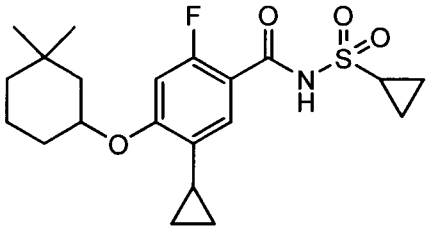
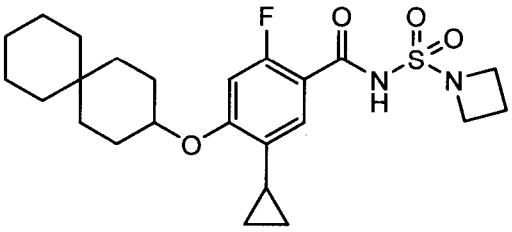
No	Structure	Name
324		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-3-chloro-5-fluoro-benzamide
325		4-(1-adamantylmethoxy)-3-chloro-5-fluoro-N-methylsulfonyl-benzamide
326		4-(1-adamantylmethoxy)-5-chloro-2,3-difluoro-N-methylsulfonyl-benzamide
327		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide
328		5-chloro-N-cyclopropylsulfonyl-2-fluoro-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide
329		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide
330		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-[[1-(trifluoromethyl)cyclobutyl]methoxy]benzamide

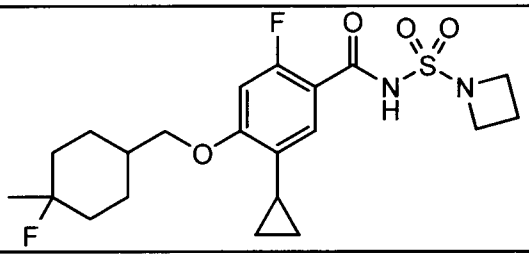
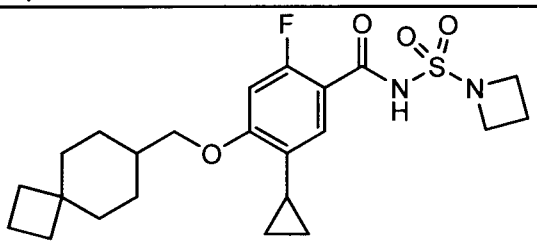
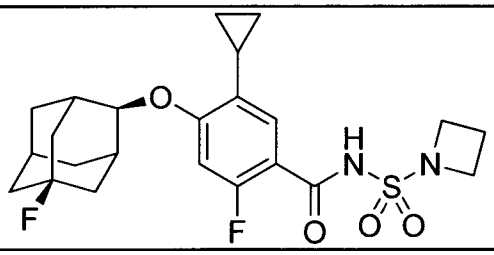
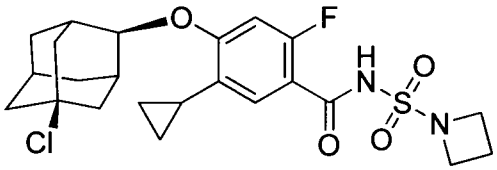
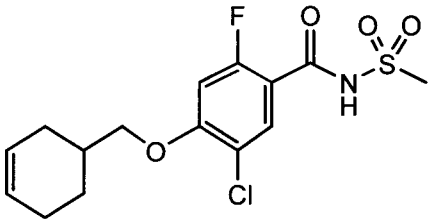
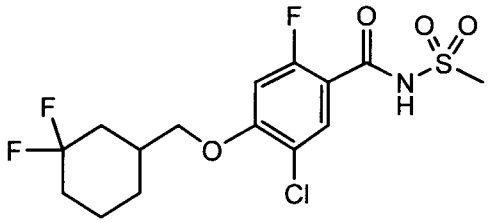
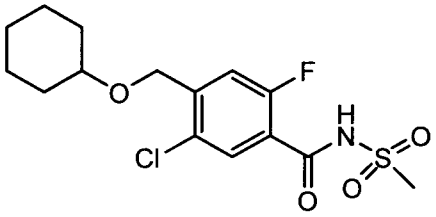
No	Structure	Name
331		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-[(4-fluoro-4-methyl-cyclohexyl)methoxy]benzamide
332		4-(2-adamantyloxy)-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide
333		*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzamide
334		5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzamide
335		4-(2-adamantyloxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-benzamide
336		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(4,4-difluorocyclohexoxy)-2-fluoro-benzamide
337		5-cyclopropyl-N-cyclopropylsulfonyl-4-(4,4-difluorocyclohexoxy)-2-fluoro-benzamide

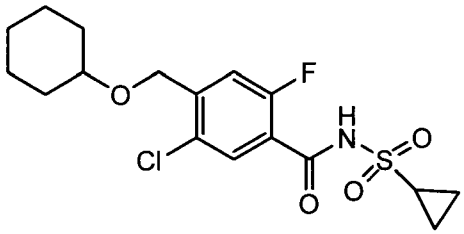
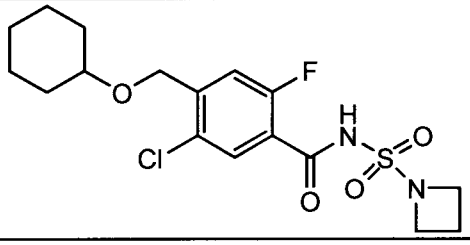
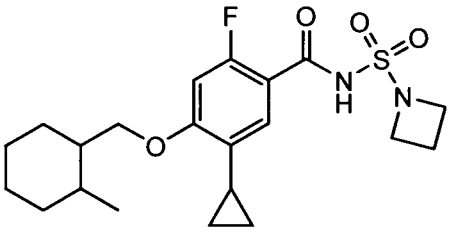
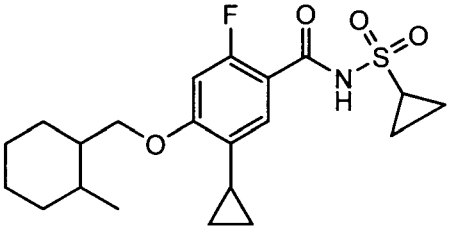
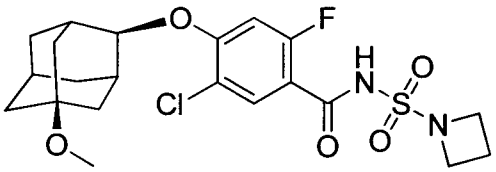
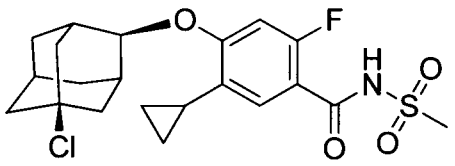
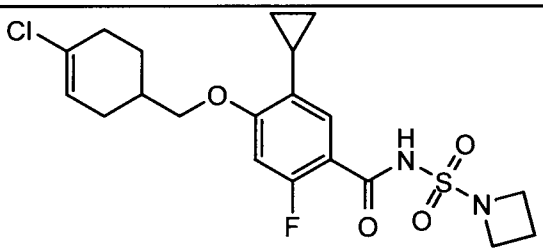
No	Structure	Name
338		N-(azetidin-1-ylsulfonyl)-5-chloro-4-(4,4-difluorocyclohexoxy)-2-fluoro-benzamide
339		5-chloro-N-cyclopropylsulfonyl-4-(4,4-difluorocyclohexoxy)-2-fluoro-benzamide
340		N-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-[(4-fluoro-4-methyl-cyclohexyl)methoxy]benzamide
341		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide
342		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-spiro[2.5]octan-6-yloxy-benzamide
343		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-spiro[2.5]octan-6-yloxy-benzamide

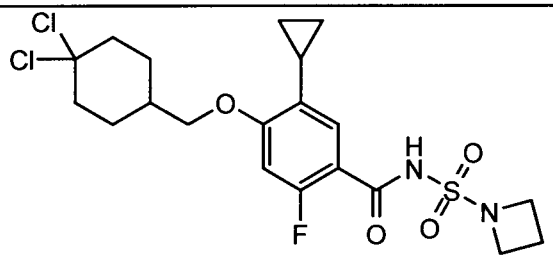
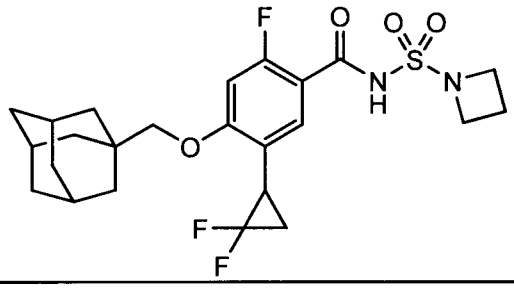
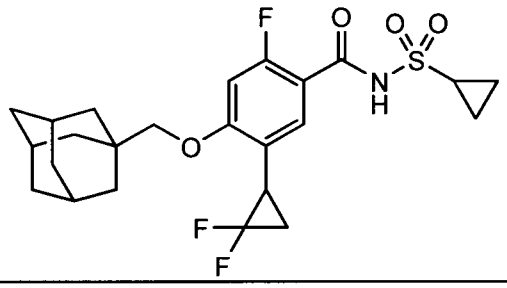
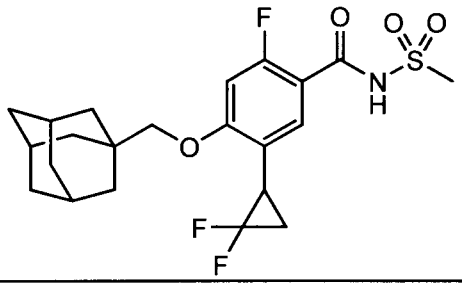
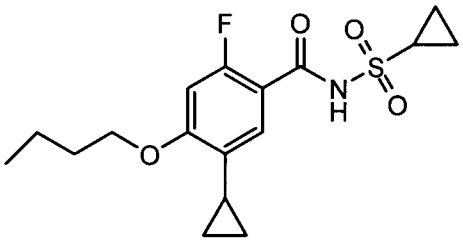
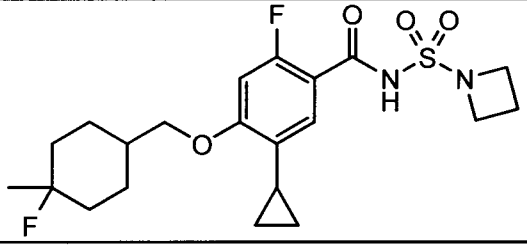
No	Structure	Name
344		5-cyclopropyl-4-[(7,7-difluoronorcaran-3-yl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
345		5-cyclopropyl-N-cyclopropylsulfonyl-4-[(7,7-difluoronorcaran-3-yl)methoxy]-2-fluoro-benzamide
346		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(7,7-difluoronorcaran-3-yl)methoxy]-2-fluoro-benzamide
347		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-2-ylmethoxy)benzamide
348		4-(2-adamantyloxy)-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
349		5-cyclopropyl-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-4-[(1-methylcyclohexyl)methoxy]benzamide

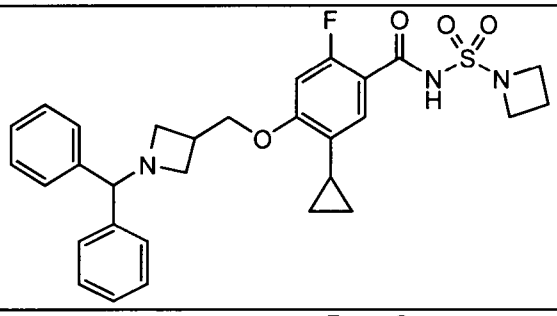
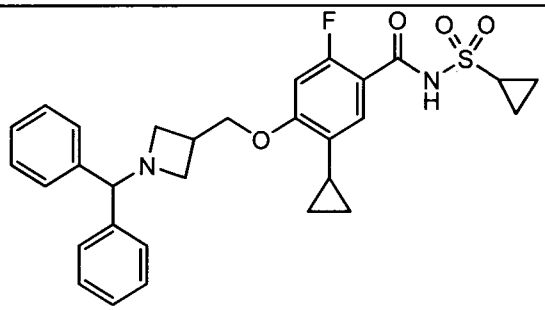
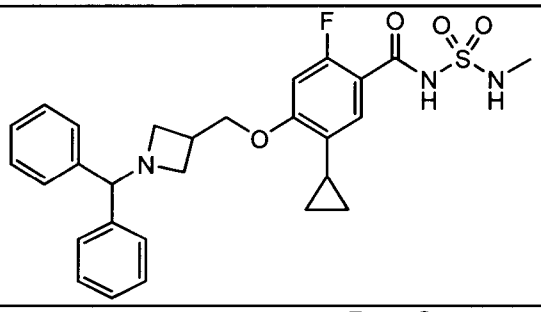
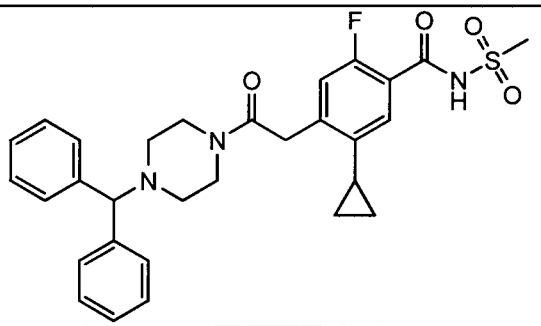
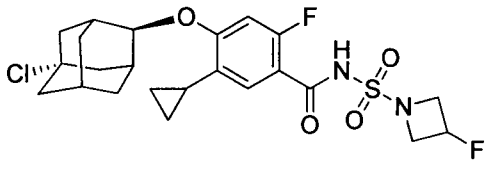
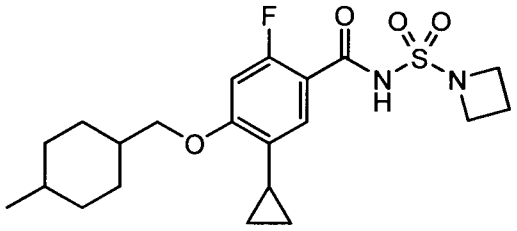
No	Structure	Name
350		5-chloro-2-fluoro-4-[(5-methoxy-2-adamantyl)oxy]-N-methylsulfonyl-benzamide
351		*cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide
352		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(4,4-dichlorocyclohexoxy)-2-fluoro-benzamide
353		trans-4-(1-adamantylmethoxy)-2-fluoro-5-[2-(methoxymethyl)cyclopropyl]-N-methylsulfonyl-benzamide
354		N-(azetidin-1-ylsulfonyl)-4-[(1-cyanocyclohexyl)methoxy]-5-cyclopropyl-2-fluoro-benzamide
355		4-[(1-cyanocyclohexyl)methoxy]-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide

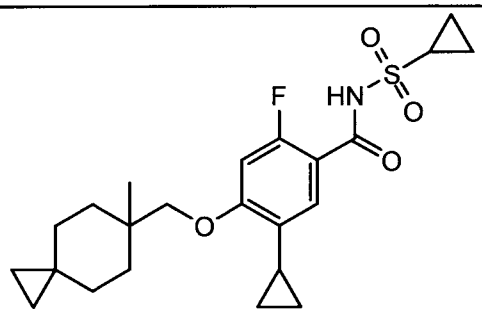
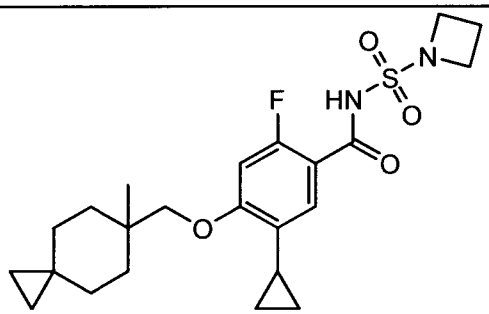
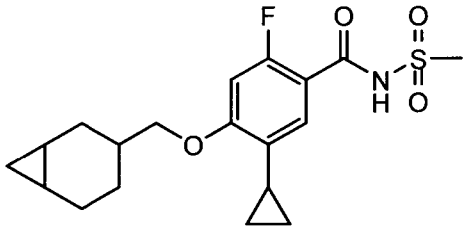
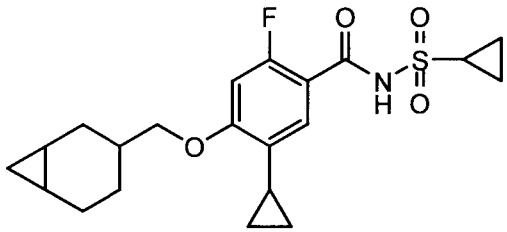
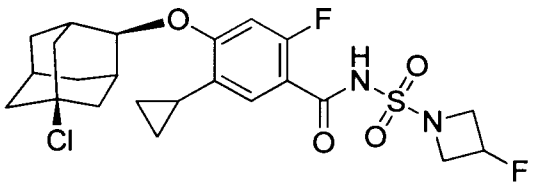
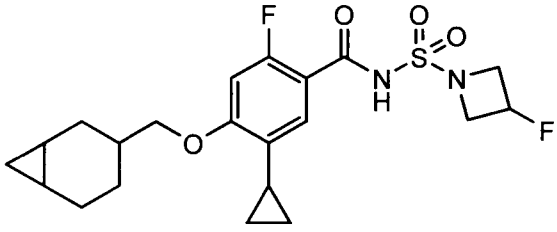
No	Structure	Name
356		4-[(1-cyanocyclohexyl)methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
357		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(3,3-dimethylcyclohexoxy)-2-fluoro-benzamide
358		5-cyclopropyl-4-(3,3-dimethylcyclohexoxy)-2-fluoro-N-methylsulfonyl-benzamide
359		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-spiro[5.5]undecan-3-yloxy-benzamide
360		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-spiro[5.5]undecan-3-yloxy-benzamide
361		5-cyclopropyl-N-cyclopropylsulfonyl-4-(3,3-dimethylcyclohexoxy)-2-fluoro-benzamide
362		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-spiro[5.5]undecan-3-yloxy-benzamide

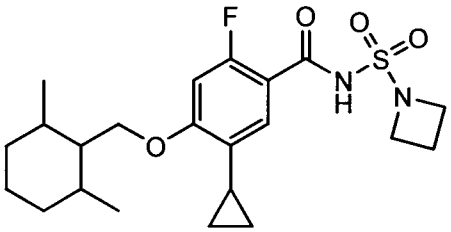
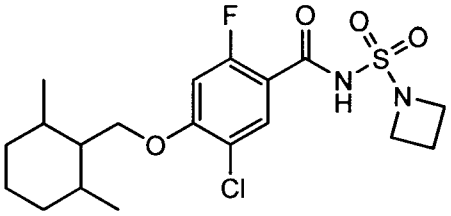
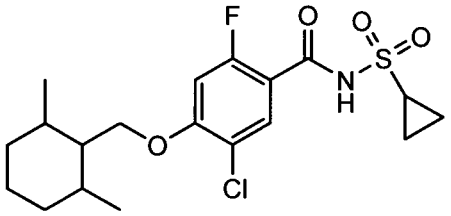
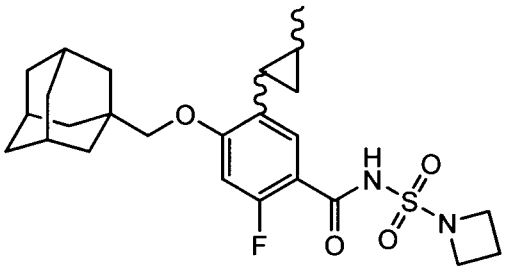
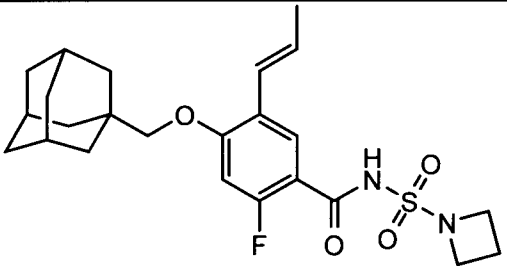
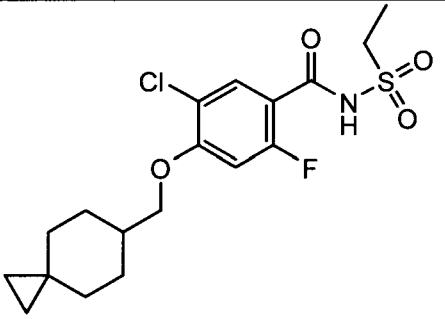
No	Structure	Name
363		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(4-fluoro-4-methyl-cyclohexyl)methoxy]benzamide
364		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide
365		*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*cis*-5-fluoroadamantan-2-yl)oxy)benzamide
366		*cis-N*-(azetidin-1-ylsulfonyl)-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzamide
367		5-chloro-4-(cyclohex-3-en-1-ylmethoxy)-2-fluoro-N-methylsulfonyl-benzamide
368		5-chloro-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
369		5-chloro-4-(cyclohexoxymethyl)-2-fluoro-N-methylsulfonyl-benzamide

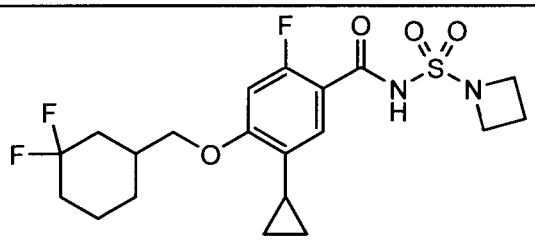
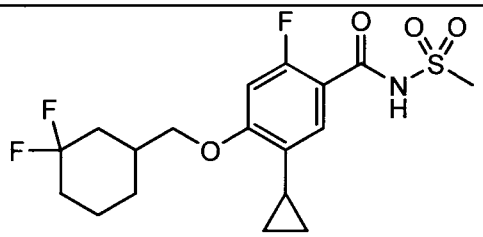
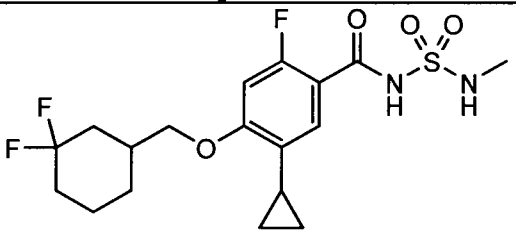
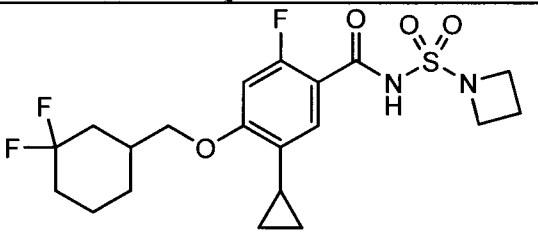
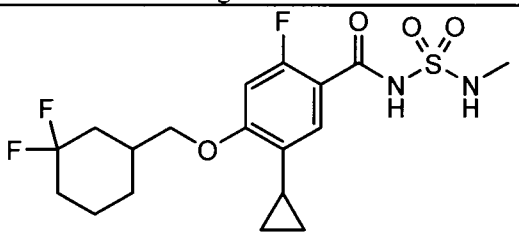
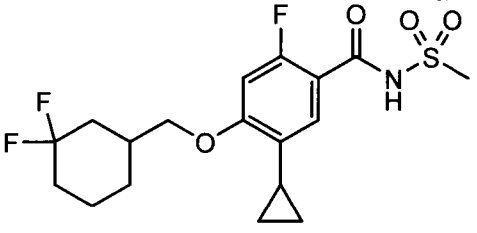
No	Structure	Name
370		5-chloro-4-(cyclohexoxymethyl)-N-cyclopropylsulfonyl-2-fluoro-benzamide
371		N-(azetidin-1-ylsulfonyl)-5-chloro-4-(cyclohexoxymethyl)-2-fluoro-benzamide
372		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(2-methylcyclohexyl)methoxy]benzamide
373		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(2-methylcyclohexyl)methoxy]benzamide
374		*N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan-2-yl)oxy)benzamide
375		*cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide
376		N-(azetidin-1-ylsulfonyl)-4-[(4-chlorocyclohex-3-en-1-yl)methoxy]-5-cyclopropyl-2-fluoro-benzamide

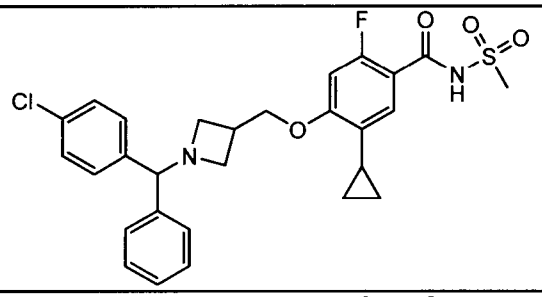
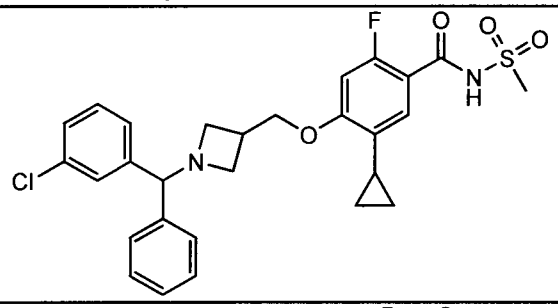
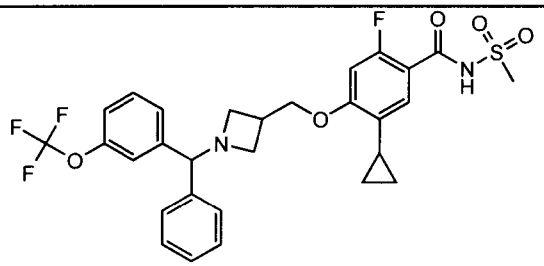
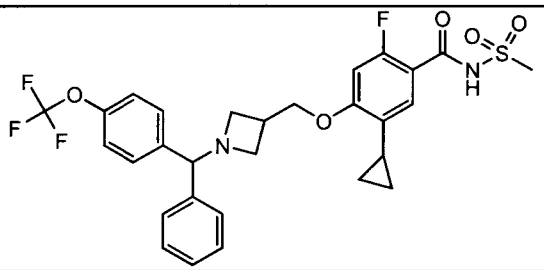
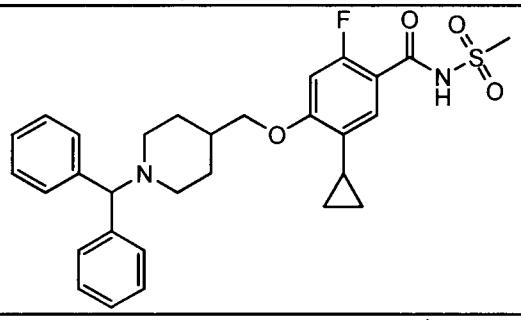
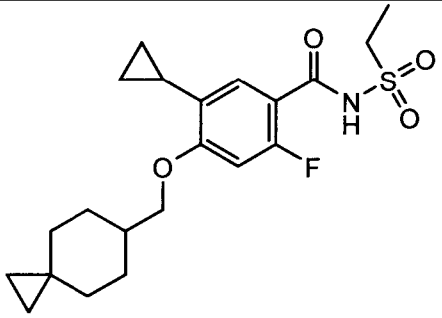
No	Structure	Name
377		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4,4-dichlorocyclohexyl)methoxy]-2-fluoro-benzamide
378		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-(2,2-difluorocyclopropyl)-2-fluoro-benzamide
379		4-(1-adamantylmethoxy)-N-cyclopropylsulfonyl-5-(2,2-difluorocyclopropyl)-2-fluoro-benzamide
380		4-(1-adamantylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluoro-N-methylsulfonyl-benzamide
381		4-butoxy-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide
382		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(4-fluoro-4-methyl-cyclohexyl)methoxy]benzamide

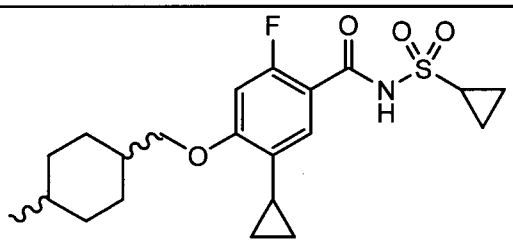
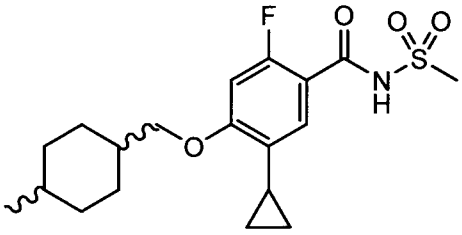
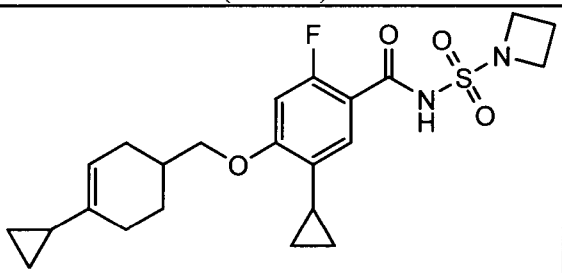
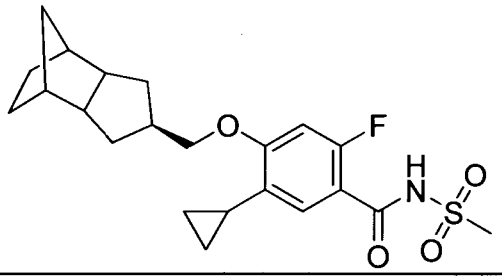
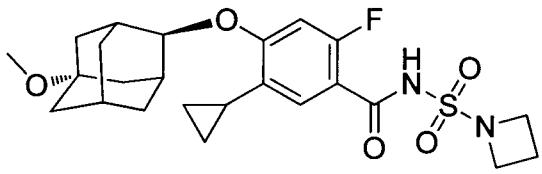
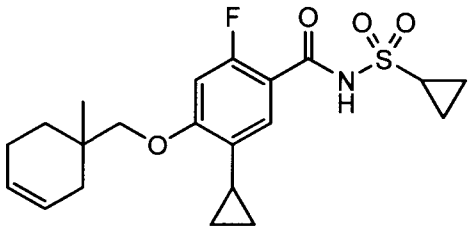
No	Structure	Name
383		N-(azetidin-1-ylsulfonyl)-4-[(1-benzhydrylazetidin-3-yl)methoxy]-5-cyclopropyl-2-fluoro-benzamide
384		4-[(1-benzhydrylazetidin-3-yl)methoxy]-5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-benzamide
385		4-[(1-benzhydrylazetidin-3-yl)methoxy]-5-cyclopropyl-2-fluoro-N-(methylsulfamoyl)benzamide
386		4-[2-(4-benzhydrylpiperazin-1-yl)-2-oxo-ethyl]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
387		*trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide
388		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(4-methylcyclohexyl)methoxy]benzamide

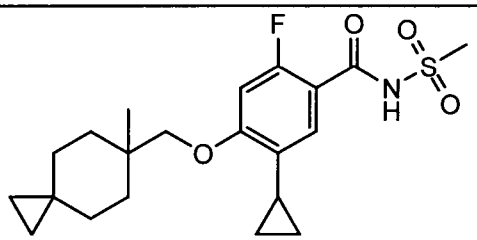
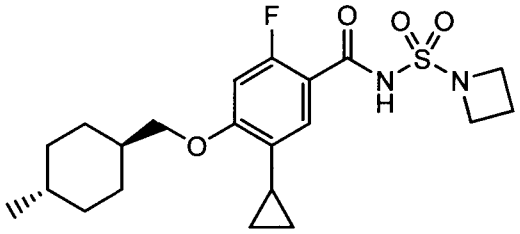
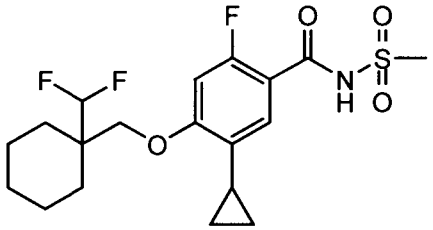
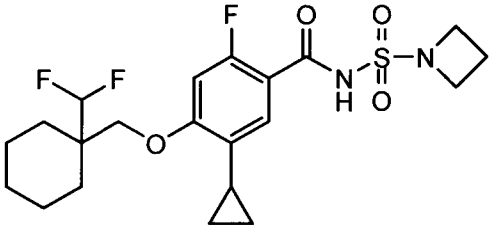
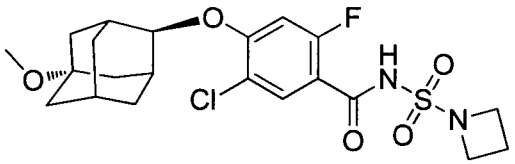
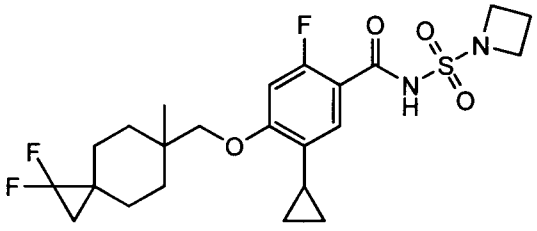
No	Structure	Name
389		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(6-methylspiro[2.5]octan-6-yl)methoxy]benzamide
390		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(6-methylspiro[2.5]octan-6-yl)methoxy]benzamide
391		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-(norcaran-3-ylmethoxy)benzamide
392		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-(norcaran-3-ylmethoxy)benzamide
393		*cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide
394		5-cyclopropyl-2-fluoro-N-(3-fluoroazetidin-1-yl)sulfonyl-4-(norcaran-3-ylmethoxy)benzamide

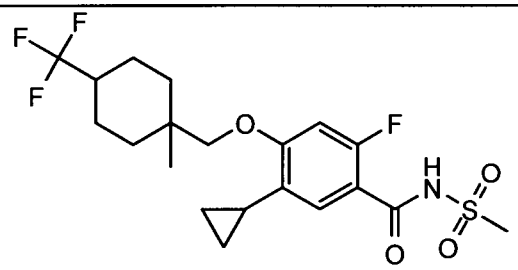
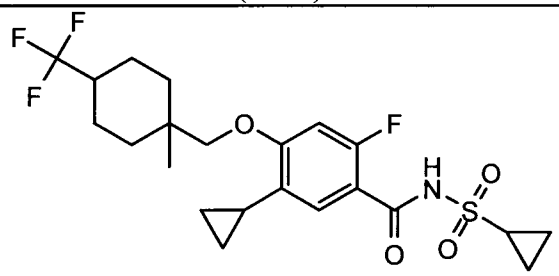
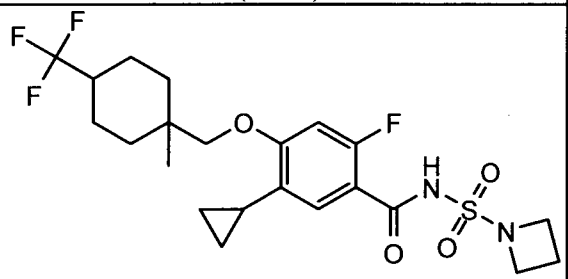
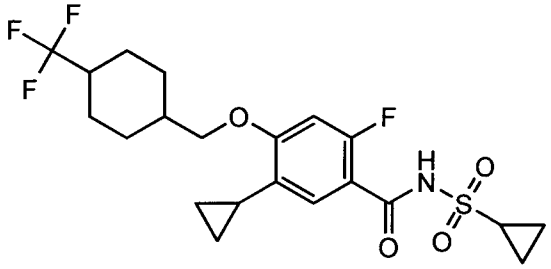
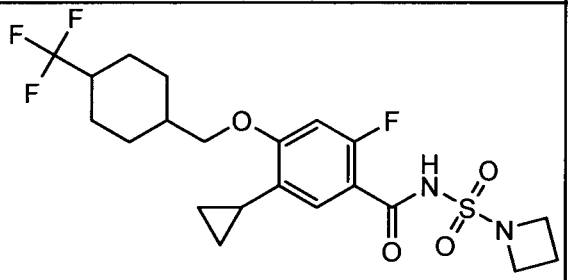
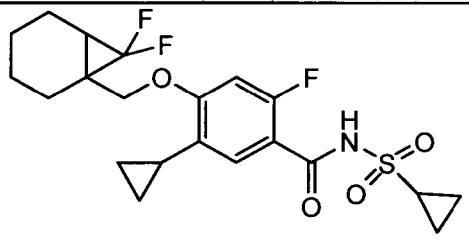
No	Structure	Name
395		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(2,6-dimethylcyclohexyl)methoxy]-2-fluoro-benzamide
396		N-(azetidin-1-ylsulfonyl)-5-chloro-4-[(2,6-dimethylcyclohexyl)methoxy]-2-fluoro-benzamide
397		5-chloro-N-cyclopropylsulfonyl-4-[(2,6-dimethylcyclohexyl)methoxy]-2-fluoro-benzamide
398	 (rel-trans)	trans-4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-(2-methylcyclopropyl)benzamide
399		4-(1-adamantylmethoxy)-N-(azetidin-1-ylsulfonyl)-2-fluoro-5-[(E)-prop-1-enyl]benzamide
400		5-chloro-N-ethylsulfonyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide

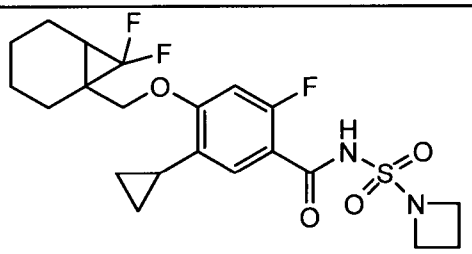
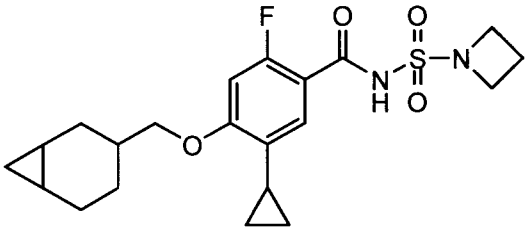
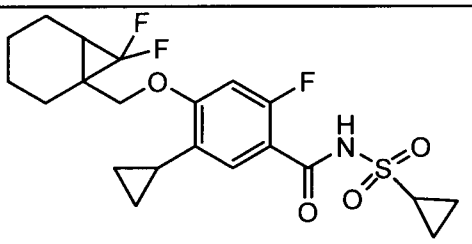
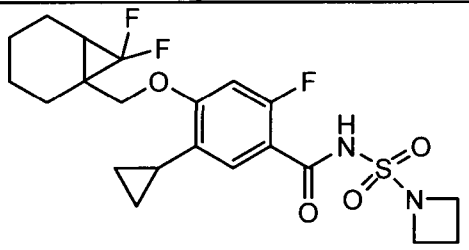
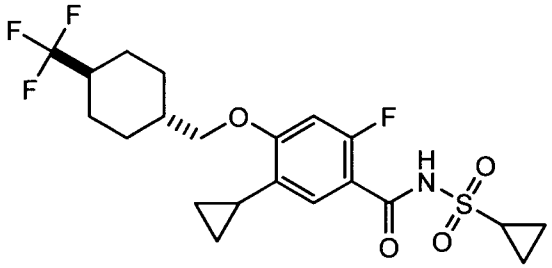
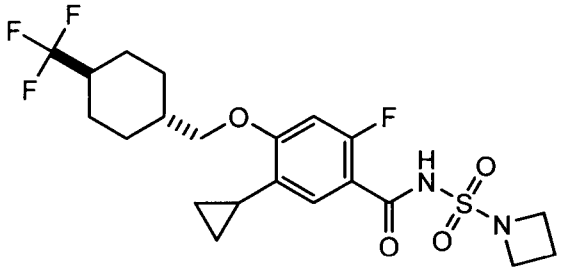
No	Structure	Name
401		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-benzamide
402	 single isomer	5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide
403	 single isomer	5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-N-(methylsulfamoyl)benzamide
404	 single isomer	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-benzamide
405	 single isomer	5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-N-(methylsulfamoyl)benzamide
406	 single isomer	5-cyclopropyl-4-[(3,3-difluorocyclohexyl)methoxy]-2-fluoro-N-methylsulfonyl-benzamide

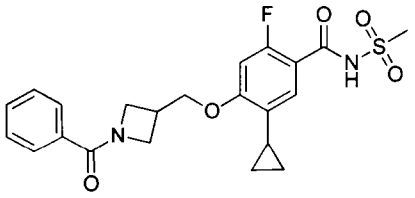
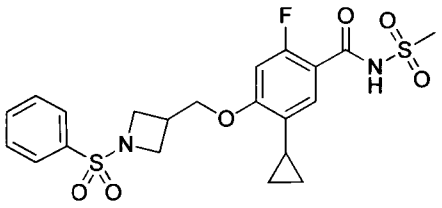
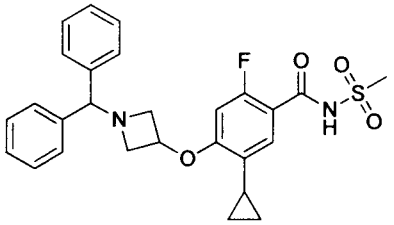
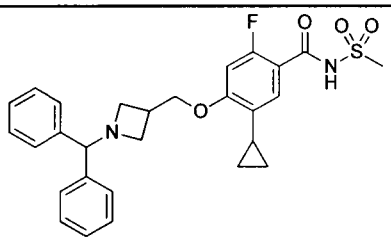
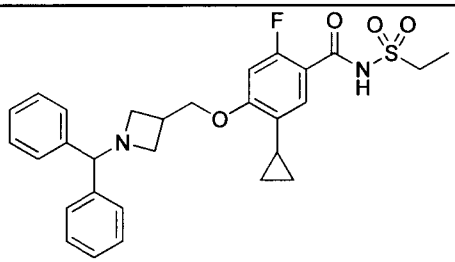
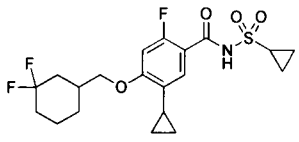
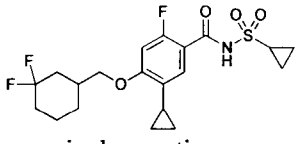
No	Structure	Name
407		4-[[1-[(4-chlorophenyl)-phenyl-methyl]azetidin-3-yl]methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
408		4-[[1-[(3-chlorophenyl)-phenyl-methyl]azetidin-3-yl]methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
409		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[1-[phenyl-[3-(trifluoromethoxy)phenyl]methyl]azetidin-3-yl]methoxy]benzamide
410		5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[1-[phenyl-[4-(trifluoromethoxy)phenyl]methyl]azetidin-3-yl]methoxy]benzamide
411		4-[(1-benzhydryl-4-piperidyl)methoxy]-5-cyclopropyl-2-fluoro-N-methylsulfonyl-benzamide
412		5-cyclopropyl-N-ethylsulfonyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide

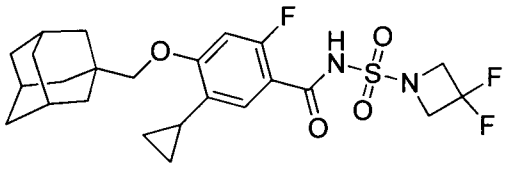
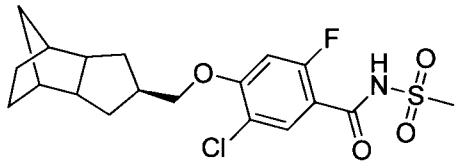
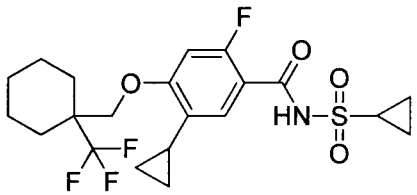
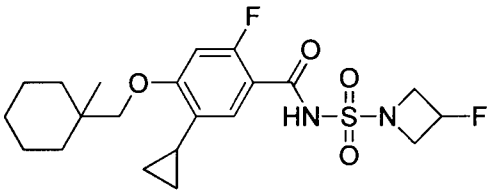
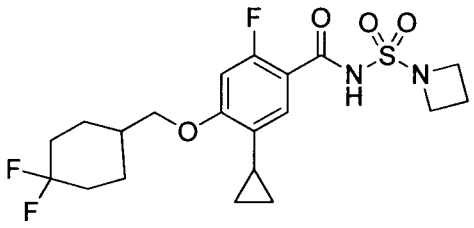
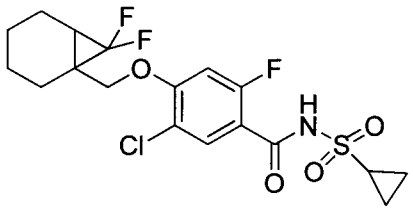
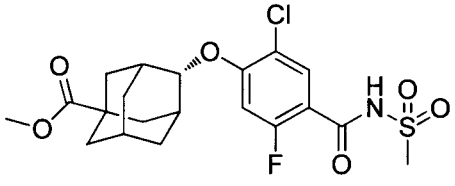
No	Structure	Name
413	 (rel-trans)	5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(4-methylcyclohexyl)methoxy]benzamide
414	 (rel-trans)	5-cyclopropyl-2-fluoro-4-[(4-methylcyclohexyl)methoxy]-N-methylsulfonyl-benzamide
415		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(4-cyclopropylcyclohex-3-en-1-yl)methoxy]-2-fluoro-benzamide
416		5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(((2s,3aR,4S,7R,7aS)-octahydro-1*H*-4,7-methanoinden-2-yl)methoxy)benzamide
417		*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*trans*-5-methoxyadamantan-2-yl)oxy)benzamide
418		5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[(1-methylcyclohex-3-en-1-yl)methoxy]benzamide

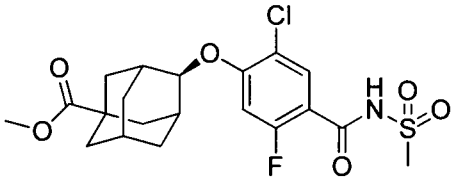
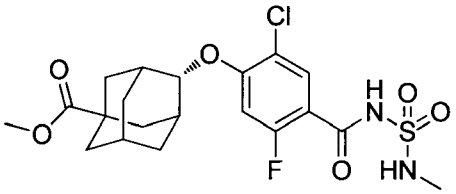
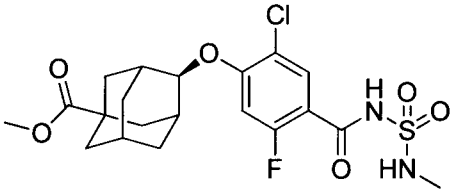
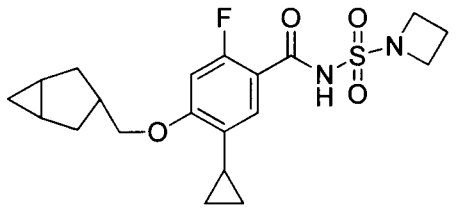
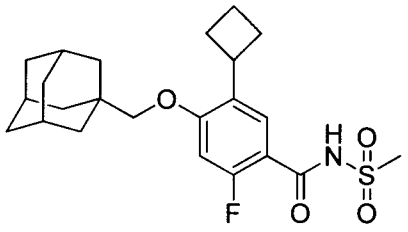
No	Structure	Name
419		5-cyclopropyl-2-fluoro-4-[(6-methylspiro[2.5]octan-6-yl)methoxy]-N-methylsulfonyl-benzamide
420	 (rel-trans)	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[(4-methylcyclohexyl)methoxy]benzamide
421		5-cyclopropyl-4-[[1-(difluoromethyl)cyclohexyl]methoxy]-2-fluoro-N-methylsulfonyl-benzamide
422		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[[1-(difluoromethyl)cyclohexyl]methoxy]-2-fluoro-benzamide
423		*N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan-2-yl)oxy)benzamide
424		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(2,2-difluoro-6-methyl-spiro[2.5]octan-6-yl)methoxy]-2-fluoro-benzamide

425	 (rel-cis)	5-cyclopropyl-2-fluoro-N-methylsulfonyl-4-[[1-methyl-4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
426	 (rel-cis)	5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[[1-methyl-4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
427	 (rel-cis)	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[1-methyl-4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
428	 (rel-cis)	5-cyclopropyl-N-cyclopropylsulfonyl-2-fluoro-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
429	 (rel-cis)	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-[[4-(trifluoromethyl)cyclohexyl]methoxy]benzamide
430	 single isomer	5-cyclopropyl-N-cyclopropylsulfonyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide

431	 single isomer	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide
432		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(norcaran-3-ylmethoxy)benzamide
433	 single isomer	5-cyclopropyl-N-cyclopropylsulfonyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide
434	 single isomer	N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-[(7,7-difluoronorcaran-1-yl)methoxy]-2-fluoro-benzamide
435		5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluoro-4-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)methoxy)benzamide
436		N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)methoxy)benzamide

437		4-((1-benzoylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide
438		5-cyclopropyl-2-fluoro-N-(methylsulfonyl)-4-((1-(phenylsulfonyl)azetidin-3-yl)methoxy)benzamide
439		4-(1-benzhydrylazetidin-3-yloxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide
440		4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide
441		4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-N-(ethylsulfonyl)-2-fluorobenzamide
442	 single enantiomer	5-cyclopropyl-N-(cyclopropylsulfonyl)-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzamide
443	 single enantiomer	5-cyclopropyl-N-(cyclopropylsulfonyl)-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzamide

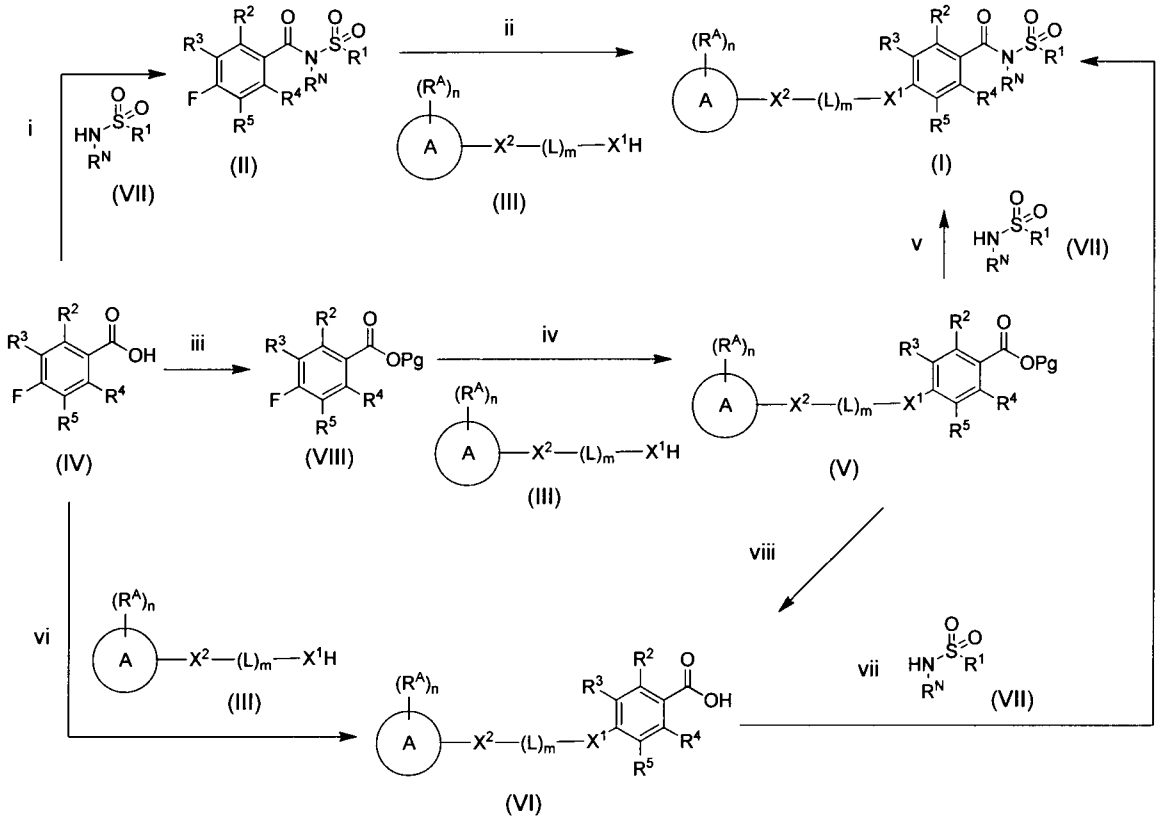
444		4-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((3,3-difluoroazetidin-1-yl)sulfonyl)-2-fluorobenzamide
445		5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((*2s,3aR,4S,7R,7aS*)-octahydro-1*H*-4,7-methanoinden-2-yl)methoxy)benzamide
446		5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide
447		5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)-4-((1-methylcyclohexyl)methoxy)benzamide
448		*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-difluorocyclohexyl)-methoxy)-2-fluorobenzamide
449		5-chloro-*N*-(cyclopropylsulfonyl)-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide
450		(1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)carbamoyl)-phenoxy)adamantane-1-carboxylate

451		(1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)-carbamoyl)-phenoxy)adamantane-1-carboxylate
452		(1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((*N*-methylsulfamoyl)-carbamoyl)phenoxy)adamantane-1-carboxylate
453		(1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((*N*-methylsulfamoyl)carbamoyl)-phenoxy)adamantane-1-carboxylate
454		*N*-(azetidin-1-ylsulfonyl)-4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide
455		4-(adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluoro-*N*-(methylsulfonyl)benzamide

[0216] SYNTHESIS OF COMPOUNDS

[0217] Compounds of formula (I), wherein X^1 is O, S, or NH, may be prepared by the process illustrated in Scheme 1.

[0218] Scheme 1



[0219] Compounds of formula (I) can be made from compounds of formula (II) by displacement with formula (III) and a base (reaction step ii in Scheme 1). Suitable conditions include potassium *tert*-butoxide in DMSO, NaH in DMF or K_2CO_3 in DMF. Formula (II) can be made according to step (i) by activation of the acid group of formula (IV) with reagents such as oxalyl chloride, carbonyl di-imidazole (CDI), propylphosphonic anhydride, a uronium based amide coupling agent or a carbodiimide reagent followed by displacement with a sulfonamide of formula (VII) in the presence of a nucleophilic base such as 4-dimethylaminopyridine. Illustrative conditions comprise *N*, *N*-dimethylaminopropyl-*N*'-ethylcarbodiimide and 4-dimethylaminopyridine with *N*, *N*-diisopropylethylamine.

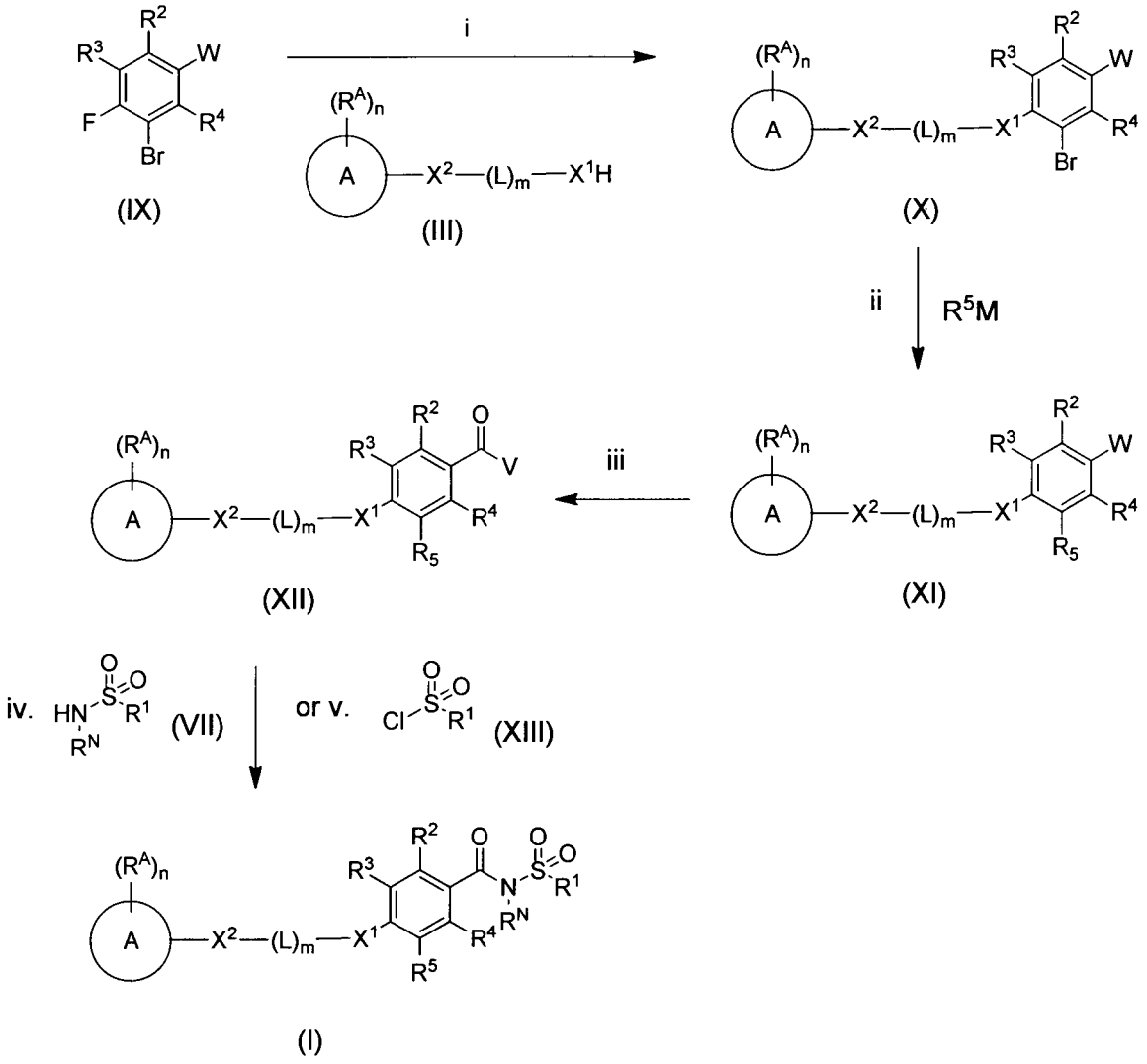
[0220] Alternatively, compounds of formula (I) can be made from compounds of formula (IV) by reversing steps (i) and (ii) as described in Scheme 1. Illustrative conditions for steps vi and vii are as previously described in steps (ii) and (i), respectively.

[0221] Compounds of formula (I) can also be made from compounds of formula (V) according to step (v) by displacement of the ester with compounds of formula (VII) and a suitable base such as potassium *tert*-butoxide, NaH or DBU. Compounds of formula (I) can also be made from compounds of formula (v)

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

[0222] Compounds of formula (I), wherein R^5 is Ar, heteroaryl, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-10} cycloalkyl or C_{2-9} heterocycloalkyl can be prepared by the process illustrated in Scheme 2. In certain embodiment, W groups in compounds of formula (IX, X and XI) are an ester or cyano group.

[0223] Scheme 2



[0224] Compounds of formula (I) can be prepared from compounds of formulae (XII)

[0225] (-V = OH) according to reaction step (iv) by activation of the acid group with reagents such as oxalyl chloride, carbonyl di-imidazole (CDI), a uronium based amide coupling agent, propylphosphonic

anhydride or a carbodiimide reagent followed by displacement with a suitable sulfonamide of formula (Vll) in the presence of a nucleophilic base such as 4-dimethylaminopyridine.

[0226] Alternatively, compounds of formula (l) can be prepared from compounds of formula (XII) (-V = NH_2) according to reaction step (v) by displacement of a sulfonyl chloride of formula (XIII) under basic reaction conditions.

[0227] Compounds of formula (Xll) can be prepared by hydrolysis of the nitrile functional group in compounds of formula (XI, W = CN) or by hydrosis of the ester functional group in compounds of formula (Xl, W = CO_2Pg) by either acidic or basic methods according to step (iii) as required.

[0228] Compounds of formula (XI) can be prepared from compounds of formula (X) by palladium-catalyzed coupling of a compound of formula (R_5M) according to step (ii).

[0229] Conveniently the coupling is effective with a boronic acid or ester of formula (R_5M). The coupling reaction can be carried out with a variety of palladium catalysts such as palladium acetate or tetrakistriphenylphosphine palladium (0) in various solvents and in the presence of bases such as sodium and potassium carbonate, cesium fluoride or potassium phosphate. Compounds of formula (X) can be prepared under similar conditions as described for the preparation of compounds of formula (V), (VI) and (I) in Scheme 1.

[0230] B. PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

[0231] In addition to one or more of the compounds provided above (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof), the invention also provides for compositions and medicaments comprising a compound of Formula I or and embodiment thereof and at least one pharmaceutically acceptable carrier, diluent or excipient. The compositions of the invention can be used to selectively inhibit NaV1.7 in patients (e.g, humans).

[0232] The term "composition," as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0233] In one embodiment, the invention provides for pharmaceutical compositions (or medicaments) comprising a compound of Formula I or an embodiment thereof, and its stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof) and a pharmaceutically acceptable carrier, diluent or excipient. In another embodiment, the invention provides for preparing compositions (or medicaments) comprising compounds of the invention. In another embodiment, the invention provides for administering compounds of Formula I or its embodiments and compositions comprising compounds of Formula I or an an embodiment thereof to a patient (e.g., a human patient) in need thereof.

[0234] Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The effective amount of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit NaV1.7 activity as required to prevent or treat the undesired disease or disorder, such as for example, pain. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

[0235] In one example, the therapeutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about e.g., 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. The daily does is, in certain embodiments, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70kg adult human, the total daily dose will generally be from about 7mg to about 1,400mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[0236] The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

[0237] The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, intracerebral, intraocular, intralesional or subcutaneous administration.

[0238] The compositions comprising compounds of Formula I or an embodiment thereof are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. A typical formulation is prepared by mixing a compound of the present invention and a diluent, carrier or excipient. Suitable diluents, carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known

additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0239] Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which a compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations can also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0240] Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). A active pharmaceutical ingredient of the invention (e.g., compound of Formula I or an embodiment thereof) can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington: The Science and Practice of Pharmacy: Remington the Science and Practice of Pharmacy (2005) 21st Edition, Lippincott Williams & Wilkins, Philidelphia, PA.

[0241] Sustained-release preparations of a compound of the invention (e.g., compound of Formula I or an embodiment thereof) can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of Formula I or an embodiment thereof, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547, 1983), non-degradable ethylene-vinyl acetate (Langer et al., J. Biomed. Mater. Res. 15:167, 1981), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid (EP 133,988A). Sustained release compositions also include liposomally entrapped compounds, which can be prepared by methods known per se (Epstein et al., Proc. Natl. Acad. Sci. U.S.A. 82:3688, 1985; Hwang et al., Proc. Natl. Acad. Sci. U.S.A. 77:4030, 1980; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324A). Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamelar type in which the lipid content is greater than about 30 mol % cholesterol, the selected proportion being adjusted for the optimal therapy.

[0242] The formulations include those suitable for the administration routes detailed herein. The formulations can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy: Remington the Science and Practice of Pharmacy (2005) 21st Edition, Lippincott Williams & Wilkins, Philidelphia, PA. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients.

[0243] In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers, diluents or excipients or finely divided solid carriers, diluents or excipients, or both, and then, if necessary, shaping the product. A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. The formulations can be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. A compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

[0244] In one example, compounds of Formula I or an embodiment thereof may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and

the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of Formula I (or an embodiment thereof) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of Formula I or an embodiment thereof are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

[0245] Formulations of a compound of the invention (e.g., compound of Formula I or an embodiment thereof) suitable for oral administration can be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of the invention.

[0246] Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets can optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0247] Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs can be prepared for oral use. Formulations of a compound of the invention (e.g., compound of Formula I or an embodiment thereof) intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets can be uncoated or can be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax can be employed.

[0248] An example of a suitable oral administration form is a tablet containing about 1 mg, 5 mg, 10 mg, 25mg, 30mg, 50mg, 80mg, 100mg, 150mg, 250mg, 300mg and 500mg of the compound of the invention compounded with about 90-30mg anhydrous lactose, about 5-40mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about 1-10mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier,

e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

[0249] For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredient can be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients can be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base can include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations can desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

[0250] The oily phase of the emulsions of this invention can be constituted from known ingredients in a known manner. While the phase can comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0251] In one aspect of topical applications, it is desired to administer an effective amount of a pharmaceutical composition according to the invention to target area, e.g., skin surfaces, mucous membranes, and the like, which are adjacent to peripheral neurons which are to be treated. This amount will generally range from about 0.0001 mg to about 1 g of a compound of the invention per application, depending upon the area to be treated, whether the use is diagnostic, prophylactic or therapeutic, the severity of the symptoms, and the nature of the topical vehicle employed. A preferred topical preparation is an ointment, wherein about 0.001 to about 50 mg of active ingredient is used per cc of ointment base. The pharmaceutical composition can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous pulsatile, or on demand delivery of the compounds of the present invention as desired.

[0252] Aqueous suspensions of a compound of the invention (e.g., compound of Formula I or an embodiment thereof) contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose,

sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0253] Formulations of a compound of the invention (e.g., compound of Formula I or an embodiment thereof) can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

[0254] The amount of active ingredient that can be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans can contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which can vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion can contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0255] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents.

[0256] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

[0257] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0258] Formulations for rectal administration can be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0259] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration can be prepared according to conventional methods and can be delivered with other therapeutic agents such as compounds heretofore used in the treatment of disorders as described below.

[0260] The formulations can be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0261] When the binding target is located in the brain, certain embodiments of the invention provide for a compound of formula I (or an embodiment thereof) to traverse the blood-brain barrier. Certain neurodegenerative diseases are associated with an increase in permeability of the blood-brain barrier, such that a compound of formula I (or an embodiment thereof) can be readily introduced to the brain. When the blood-brain barrier remains intact, several art-known approaches exist for transporting molecules across it, including, but not limited to, physical methods, lipid-based methods, and receptor and channel-based methods.

[0262] Physical methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, circumventing the blood- brain barrier entirely, or by creating openings in the blood-brain barrier.

[0263] Circumvention methods include, but are not limited to, direct injection into the brain (see, e.g., Papanastassiou et al., Gene Therapy 9:398-406, 2002), interstitial infusion/convection-enhanced delivery (see, e.g., Bobo et al., Proc. Natl. Acad. Sci. U.S.A. 91 :2076-2080, 1994), and implanting a delivery device in the brain (see, e.g., Gill et al., Nature Med. 9:589-595, 2003; and Gliadel Wafers™, Guildford.

[0264] Pharmaceutical). Methods of creating openings in the barrier include, but are not limited to, ultrasound (see, e.g., U.S. Patent Publication No. 2002/0038086), osmotic pressure (e.g., by administration

of hypertonic mannitol (Neuwelt, E. A., Implication of the Blood-Brain Barrier and its Manipulation, Volumes 1 and 2, Plenum Press, N.Y., 1989)), and permeabilization by, e.g., bradykinin or permeabilizer A-7 (see, e.g., U.S. Patent Nos. 5,112,596, 5,268,164, 5,506,206, and 5,686,416).

[0265] Lipid-based methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, encapsulating the a compound of formula I (or an embodiment thereof) in liposomes that are coupled to antibody binding fragments that bind to receptors on the vascular endothelium of the blood- brain barrier (see, e.g., U.S. Patent Application Publication No. 2002/0025313), and coating a compound of formula I (or an embodiment thereof) in low-density lipoprotein particles (see, e.g., U.S. Patent Application Publication No. 2004/0204354) or apolipoprotein E (see, e.g., U.S. Patent Application Publication No. 2004/0131692).

[0266] Receptor and channel-based methods of transporting a compound of formula I (or an embodiment thereof) across the blood-brain barrier include, but are not limited to, using glucocorticoid blockers to increase permeability of the blood-brain barrier (see, e.g., U.S. Patent Application Publication Nos. 2002/0065259, 2003/0162695, and 2005/0124533); activating potassium channels (see, e.g., U.S. Patent Application Publication No. 2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S. Patent Application Publication No. 2003/0073713); coating a compound of formula I (or an embodiment thereof) with a transferrin and modulating activity of the one or more transferrin receptors (see, e.g., U.S. Patent Application Publication No. 2003/0129186), and cationizing the antibodies (see, e.g., U.S. Patent No. 5,004,697).

[0267] For intracerebral use, in certain embodiments, the compounds can be administered continuously by infusion into the fluid reservoirs of the CNS, although bolus injection may be acceptable. The inhibitors can be administered into the ventricles of the brain or otherwise introduced into the CNS or spinal fluid. Administration can be performed by use of an indwelling catheter and a continuous administration means such as a pump, or it can be administered by implantation, e.g., intracerebral implantation of a sustained-release vehicle. More specifically, the inhibitors can be injected through chronically implanted cannulas or chronically infused with the help of osmotic minipumps. Subcutaneous pumps are available that deliver proteins through a small tubing to the cerebral ventricles. Highly sophisticated pumps can be refilled through the skin and their delivery rate can be set without surgical intervention. Examples of suitable administration protocols and delivery systems involving a subcutaneous pump device or continuous intracerebroventricular infusion through a totally implanted drug delivery system are those used for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer's disease patients and animal models for Parkinson's disease, as described by Harbaugh, J. Neural Transm. Suppl. 24:271, 1987; and DeYebenes et al., Mov. Disord. 2: 143, 1987.

[0268] A compound of formula I (or an embodiment thereof) used in the invention are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical

condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. A compound of formula I (or an embodiment thereof) need not be, but is optionally formulated with one or more agent currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of a compound of the invention present in the formulation, the type of disorder or treatment, and other factors discussed above.

[0269] These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0270] For the prevention or treatment of disease, the appropriate dosage of a compound of formula I (or an embodiment thereof) (when used alone or in combination with other agents) will depend on the type of disease to be treated, the properties of the compound, the severity and course of the disease, whether the compound is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 μg/kg to 15 mg/kg (e.g., 0.1 mg/kg-10 mg/kg) of compound can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of a compound of formula I (or an embodiment thereof) would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the patient receives from about two to about twenty, or, e.g., about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg kg of the compound. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0271] Other typical daily dosages might range from, for example, about 1 g/kg to up to 100 mg/kg or more (e.g., about 1 μg kg to 1 mg/kg, about 1 μg/kg to about 5 mg/kg, about 1 mg kg to 10 mg/kg, about 5 mg/kg to about 200 mg/kg, about 50 mg/kg to about 150 mg/mg, about 100 mg/kg to about 500 mg/kg, about 100 mg/kg to about 400 mg/kg, and about 200 mg/kg to about 400 mg/kg), depending on the factors mentioned above. Typically, the clinician will administer a compound until a dosage is reached that results in improvement in or, optimally, elimination of, one or more symptoms of the treated disease or condition. The progress of this therapy is easily monitored by conventional assays. One or more agent provided herein

may be administered together or at different times (e.g., one agent is administered prior to the administration of a second agent). One or more agent may be administered to a subject using different techniques (e.g., one agent may be administered orally, while a second agent is administered via intramuscular injection or intranasally). One or more agent may be administered such that the one or more agent has a pharmacologic effect in a subject at the same time. Alternatively, one or more agent may be administered, such that the pharmacological activity of the first administered agent is expired prior the administration of one or more secondarily administered agents (e.g., 1, 2, 3, or 4 secondarily administered agents)..

[0272] C. INDICATIONS AND METHODS OF TREATMENT

[0273] The compounds of the invention modulate, preferably inhibit, ion flux through a voltage-dependent sodium channel in a mammal, (e.g, a human). Any such modulation, whether it be partial or complete inhibition or prevention of ion flux, is sometimes referred to herein as "blocking" and corresponding compounds as "blockers" or "inhibitors". In general, the compounds of the invention modulate the activity of a sodium channel downwards by inhibiting the voltage-dependent activity of the sodium channel, and/or reduce or prevent sodium ion flux across a cell membrane by preventing sodium channel activity such as ion flux.

[0274] The compounds of the invention inhibit the ion flux through a voltage-dependent sodium channel. In one aspect, the compounds are state or frequency dependent modifers of the sodium channels, having a low affinity for the rested/closed state and a high affinity for the inactivated state. Without being bound by any particular theory, it is thought that these compounds are likely to interact with overlapping sites located in the inner cavity of the sodium conducting pore of the channel similar to that described for other state-dependent sodium channel blockers (Cestèle, S., et al., op. cit.). These compounds may also be likely to interact with sites outside of the inner cavity and have allosteric effects on sodium ion conduction through the channel pore.

[0275] Any of these consequences may ultimately be responsible for the overall therapeutic benefit provided by these compounds.

[0276] Accordingly, the compounds of the invention are sodium channel blockers and are therefore useful for treating diseases and conditions in mammals, for example humans, and other organisms, including all those diseases and conditions which are the result of aberrant voltage-dependent sodium channel biological activity or which may be ameliorated by modulation of voltage-dependent sodium channel biological activity. In particular, the compounds of the invention, i.e., the compounds of formula (I) and embodiments and (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof), are useful for treating diseases and conditions in mammals, for example humans, which are the result of aberrant voltage-dependent NaV1.7 biological activity or which may be ameliorated by the modulation, preferably the inhibition, of NaV1.7 biological activity. In certain aspects, the compounds of the invention selectively inhibit NaV1.7 over NaV1.5.

[0277] As defined herein, a sodium channel-mediated disease or condition refers to a disease or condition in a mammal, preferably a human, which is ameliorated upon modulation of the sodium channel and includes, but is not limited to, pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

[0278] In one aspect, the present invention relates to compounds, pharmaceutical compositions and methods of using the compounds and pharmaceutical compositions for the treatment of sodium channel-mediated diseases in mammals, preferably humans and preferably diseases and conditions related to pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome, by administering to a mammal, for example a human, in need of such treatment an effective amount of a sodium channel blocker modulating, especially inhibiting, agent.

[0279] A sodium channel-mediated disease or condition also includes pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, glossopharyngeal neuralgia, neuropathy secondary to metastatic infiltration, adiposis dolorosa, thalamic lesions, hypertension, autoimmune disease, asthma, drug addiction (e.g., opiate, benzodiazepine, amphetamine, cocaine, alcohol, butane inhalation), Alzheimer, dementia, age-related memory impairment, Korsakoff syndrome, restenosis, urinary dysfunction, incontinence, Parkinson's disease, cerebrovascular ischemia, neurosis, gastrointestinal disease, sickle cell anemia, transplant rejection, heart failure, myocardial infarction, reperfusion injury, intermittant claudication, angina, convulsion, respiratory disorders, cerebral or myocardial ischemias, long-QT syndrome, Catecholeminergic polymorphic ventricular tachycardia, ophthalmic diseases, spasticity, spastic paraplegia, myopathies, myasthenia gravis, paramyotonia congentia, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, alopecia, anxiety disorders, psychotic disorders, mania, paranoia, seasonal affective disorder, panic disorder, obsessive compulsive disorder (OCD), phobias, autism, Aspergers Syndrome, Retts syndrome, disintegrative disorder, attention deficit disorder, aggressivity, impulse control disorders, thrombosis, pre clampsia, congestive cardiac failure, cardiac arrest, Freidrich's ataxia, Spinocerebellear ataxia, myelopathy, radiculopathy, systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, spinocerebellar ataxia, episodic ataxia, myokymia, progressive pallidal atrophy, progressive supranuclear palsy and spasticity, traumatic brain injury, cerebral oedema, hydrocephalus injury, spinal cord injury, anorexia nervosa, bulimia, Prader-Willi syndrome, obesity, optic neuritis, cataract, retinal haemorrhage, ischaemic retinopathy, retinitis pigmentosa, acute and chronic glaucoma, macular degeneration, retinal artery occlusion, Chorea, Huntington's chorea, cerebral

edema, proctitis, post-herpetic neuralgia, eudynia, heat sensitivity, sarcoidosis, irritable bowel syndrome, Tourette syndrome, Lesch-Nyhan Syndrome, Brugado syndrome, Liddle syndrome, Crohns disease, multiple sclerosis and the pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), disseminated sclerosis, diabetic neuropathy, peripheral neuropathy, charcot marie tooth syndrome, arthritic, rheumatoid arthritis, osteoarthritis, chondrocalcinosis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, myotonic dystrophy, muscular dystrophy, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, mental handicap, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, rectal pain, cancer, epilepsy, partial and general tonic seizures, febrile seizures, absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, Lennox Gastaut, West Syndome (infantile spasms), multiresistant seizures, seizure prophylaxis (anti-epileptogenic), familial Mediterranean fever syndrome, gout, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy-arrhythmias, atrial fibrillation and ventricular fibrillation and as a general or local anaesthetic.

[0280] As used herein, the term "pain" refers to all categories of pain and is recognized to include, but is not limited to, neuropathic pain, inflammatory pain, nociceptive pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, burning mouth syndrome, somatic pain, visceral pain, myofacial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, chronic regional pain syndrome (CRPS),reflex sympathetic dystrophy, brachial plexus avulsion, neurogenic bladder, acute pain (e.g., musculoskeletal and post-operative pain), chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, non-cardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia, and combinations thereof.

[0281] Furthermore, sodium channel blockers have clinical uses in addition to pain. The present invention therefore also relates to compounds, pharmaceutical compositions and methods of using the compounds and pharmaceutical compositions for the treatment of diseases or conditions such as cancer and pruritus (itch).

[0282] Pruritus, commonly known as itch, is a common dermatological condition. While the exact causes of pruritus are complex and incompletely understood, there has long been evidence that itch involves sensory neurons, especially C fibers, similar to those that mediate pain (Schmelz, M., et al., J. Neurosci. (1997), 17: 8003-8). In particular, it is believed that sodium influx through voltage-gated sodium channels is essential for the propagation of itch sensation from the skin. Transmission of the itch impulses results in the unpleasant sensation that elicits the desire or reflex to scratch.

[0283] Multiple causes and electrical pathways for eliciting itch are known. In humans, pruritis can be elicited by histamine or PAR-2 agonists such as mucunain that activate distinct populations of C fibers (Namer, B., et al., J. Neurophysiol. (2008),100: 2062-9). A variety of neurotrophic peptides are known to mediate itch in animal models (Wang, H., and Yosipovitch, G., International Journal of Dermatology (2010), 49: 1-11). Itch can also be elicited by opioids, evidence of distinct pharmacology from that of pain responses.

[0284] There exists a complex interaction between itch and pain responses that arises in part from the overlapping sensory input from the skin (Ikoma, A., et al., Arch. Dermatol. (2003),139: 1475-8) and also from the diverse etiology of both pain and pruritis. Pain responses can exacerbate itching by enhancing central sensitization or lead to inhibition of painful scratching. Particularly severe forms of chronic itch occur when pain responses are absent, as in the case of post-herpetic itch (Oaklander, A.L. , et al., Pain (2002), 96: 9-12).

[0285] The compounds of the invention can also be useful for treating pruritus. The rationale for treating itch with inhibitors of voltage-gated sodium channels, especially NaV1.7, is as follows:

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

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

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

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

a) psoriatic pruritus, itch due to hemodyalisis, aguagenic pruritus, and itching caused by skin disorders (e.g., contact dermatitis), systemic disorders, neuropathy, psychogenic factors or a mixture thereof;

b) itch caused by allergic reactions, insect bites, hypersensitivity (e.g., dry skin, acne, eczema, psoriasis), inflammatory conditions or injury;

c) itch associated with vulvar vestibulitis; and

d) skin irritation or inflammatory effect from administration of another therapeutic such as, for example, antibiotics, antivirals and antihistamines.

[0286] The compounds of the invention are also useful in treating certain cancers, such as hormone sensitive cancers, such as prostate cancer (adenocarcinoma), breast cancer, ovarian cancer, testicular cancer and thyroid neoplasia, in a mammal, preferably a human. The voltage gated sodium channels have been demonstrated to be expressed in prostate and breast cancer cells. Up-regulation of neonatal NaV1.5 occurs as an integral part of the metastatic process in human breast cancer and could serve both as a novel marker of the metastatic phenotype and a therapeutic target (Clin. Cancer Res. (2005), Aug. 1; 11(15): 5381-9). Functional expression of voltage-gated sodium channel alpha-subunits, specifically NaV1.7, is associated with strong metastatic potential in prostate cancer (CaP) in vitro. Voltage-gated sodium channel alpha-subunits immunostaining, using antibodies specific to the sodium channel alpha subunit was evident in prostatic tissues and markedly stronger in CaP vs non-CaP patients (Prostate Cancer Prostatic Dis., 2005; 8(3):266-73). See also Diss, J.K.J., et al., Mol. Cell. Neurosci. (2008), 37:537–547 and Kis-Toth, K., et al., The Journal of Immunology (2011), 187:1273–1280.

[0287] In consideration of the above, in one embodiment, the present invention provides a method for treating a mammal for, or protecting a mammal from developing, a sodium channel-mediated disease, especially pain, comprising administering to the mammal, especially a human, in need thereof, a therapeutically effective amount of a compound of the invention or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention wherein the compound modulates the activity of one or more voltage-dependent sodium channels.

[0288] In another embodiment of the invention is a method of treating a disease or a condition in a mammal, preferably a human, wherein the disease or condition is selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, and wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0289] One embodiment of this embodiment is wherein the disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, and combinations thereof.

[0290] Another embodiment of this embodiment is wherein the disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritic, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy arrhythmias, atrial fibrillation and ventricular fibrillation.

[0291] Another embodiment of the invention is a method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0292] One embodiment of this embodiment is a method wherein the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post surgical pain, childbirth pain, labor pain, dental pain, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, trigeminal neuralgia, post herpetic neuralgia, eudynia, familial erythromelalgia, primary erythromelalgia, familial rectal pain or fibromyalgia, and combinations thereof.

[0293] Another embodiment of this embodiment is a method wherein the pain is associated with a disease or condition selected from HIV, HIV treatment induced neuropathy, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetic neuropathy, peripheral neuropathy, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, neurogenic bladder, ulcerative colitis, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, ischaemic conditions caused by stroke or neural trauma, tachy arrhythmias, atrial fibrillation and ventricular fibrillation.

[0294] Another embodiment of the invention is the method of treating pain in a mammal, preferably a human, by the inhibition of ion flux through a voltage dependent sodium channel in the mammal, wherein

the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0295] Another embodiment of the invention is the method of treating pruritus in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0296] Another embodiment of the invention is the method of treating cancer in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0297] Another embodiment of the invention is the method of decreasing ion flux through a voltage dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0298] Another embodiment of the invention is the method of selectively inhibiting a first voltage-gated sodium channel over a second voltage-gated sodium channel in a mammal, wherein the method comprises administering to the mammal an inhibitory amount of a compound of formula (I), or an embodiment of a compound of formula (I).

[0299] Another embodiment of the invention is the method of selectively inhibiting NaV1.7 in a mammal or a mammalian cell as compared to NaV1.5, wherein the method comprises administering to the mammal in need thereof an inhibitory amount of a compound of formula (I) or an embodiment of an embodiment thereof.

[0300] For each of the above embodiments described related to treating diseases and conditions in a mammal, the present invention also contemplates relatedly a compound of formula I or an embodiment thereof for the use as a medicament in the treatment of such diseases and conditions.

[0301] For each of the above embodiments described related to treating diseases and conditions in a mammal, the present invention also contemplates relatedly the use of a compound of formula I or an embodiment thereof for the manufacture of a medicament for the treatment of such diseases and conditions.

[0302] Another embodiment of the invention is a method of using the compounds of formula (I) as standards or controls in in vitro or in vivo assays in determining the efficacy of test compounds in modulating voltage-dependent sodium channels.

[0303] In another embodiment of the invention, the compounds of formula (I) are isotopically-labeled by having one or more atoms therein replaced by an atom having a different atomic mass or mass number. Such isotopically-labeled (i.e., radiolabelled) compounds of formula (I) are considered to be within the scope of this invention. Examples of isotopes that can be incorporated into the compounds of formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as, but not limited to, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These isotopically-labeled compounds would be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action on the sodium channels, or binding affinity to pharmacologically important site of action on the sodium channels, particularly NaV1.7. Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0304] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[0305] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0306] Testing Compounds

[0307] The assessment of the compounds of the invention in mediating, especially inhibiting, the sodium channel ion flux can be determined using the assays described hereinbelow. Alternatively, the assessment of the compounds in treating conditions and diseases in humans may be established in industry standard animal models for demonstrating the efficacy of compounds in treating pain. Animal models of human

neuropathic pain conditions have been developed that result in reproducible sensory deficits (allodynia, hyperalgesia, and spontaneous pain) over a sustained period of time that can be evaluated by sensory testing. By establishing the degree of mechanical, chemical, and temperature induced allodynia and hyperalgesia present, several physiopathological conditions observed in humans can be modeled allowing the evaluation of pharmacotherapies.

[0308] In rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioural signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behaviour and motor function (Mao, J. and Chen, L.L, Pain (2000), 87:7-17). Allometric scaling of the doses effective in these rat models, translates into doses similar to those shown to be efficacious in humans (Tanelian, D.L. and Brose, W.G., Anesthesiology (1991), 74(5):949-951). Furthermore, Lidoderm®, lidocaine applied in the form of a dermal patch, is currently an FDA approved treatment for post-herpetic neuralgia (Devers, A. and Glaler, B.S., Clin. J. Pain (2000), 16(3):205-8).

[0309] The present invention readily affords many different means for identification of sodium channel modulating agents that are useful as therapeutic agents. Identification of modulators of sodium channel can be assessed using a variety of in vitro and in vivo assays, e.g., measuring current, measuring membrane potential, measuring ion flux, (e.g., sodium or guanidinium), measuring sodium concentration, measuring second messengers and transcription levels, and using e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

[0310] One such protocol involves the screening of chemical agents for ability to modulate the activity of a sodium channel thereby identifying it as a modulating agent.

[0311] A typical assay described in Bean et al., J. General Physiology (1983), 83:613-642, and Leuwer, M., et al., Br. J. Pharmacol (2004), 141(1):47-54, uses patch-clamp techniques to study the behaviour of channels. Such techniques are known to those skilled in the art, and may be developed, using current technologies, into low or medium throughput assays for evaluating compounds for their ability to modulate sodium channel behaviour.

[0312] Throughput of test compounds is an important consideration in the choice of screening assay to be used. In some strategies, where hundreds of thousands of compounds are to be tested, it is not desirable to use low throughput means. In other cases, however, low throughput is satisfactory to identify important differences between a limited number of compounds. Often it will be necessary to combine assay types to identify specific sodium channel modulating compounds.

[0313] Electrophysiological assays using patch clamp techniques is accepted as a gold standard for detailed characterization of sodium channel compound interactions, and as described in Bean et al., op. cit. and Leuwer, M., et al., op. cit. There is a manual low-throughput screening (LTS) method which can compare 2-10 compounds per day; a recently developed system for automated medium-throughput

screening (MTS) at 20-50 patches (i.e. compounds) per day; and a technology from Molecular Devices Corporation (Sunnyvale, CA) which permits automated high-throughput screening (HTS) at 1000-3000 patches (i.e. compounds) per day.

[0314] One automated patch-clamp system utilizes planar electrode technology to accelerate the rate of drug discovery. Planar electrodes are capable of achieving high-resistance, cells-attached seals followed by stable, low-noise whole-cell recordings that are comparable to conventional recordings. A suitable instrument is the PatchXpress 7000A (Axon Instruments Inc, Union City, CA). A variety of cell lines and culture techniques, which include adherent cells as well as cells growing spontaneously in suspension are ranked for seal success rate and stability. Immortalized cells (e.g. HEK and CHO) stably expressing high levels of the relevant sodium ion channel can be adapted into high-density suspension cultures.

[0315] Other assays can be selected which allow the investigator to identify compounds which block specific states of the channel, such as the open state, closed state or the resting state, or which block transition from open to closed, closed to resting or resting to open. Those skilled in the art are generally familiar with such assays.

[0316] Binding assays are also available. Designs include traditional radioactive filter based binding assays or the confocal based fluorescent system available from Evotec OAI group of companies (Hamburg, Germany), both of which are HTS.

[0317] Radioactive flux assays can also be used. In this assay, channels are stimulated to open with veratridine or aconitine and held in a stabilized open state with a toxin, and channel blockers are identified by their ability to prevent ion influx. The assay can use radioactive 22[Na] and 14[C] guanidinium ions as tracers. FlashPlate & Cytostar-T plates in living cells avoids separation steps and are suitable for HTS. Scintillation plate technology has also advanced this method to HTS suitability. Because of the functional aspects of the assay, the information content is reasonably good.

[0318] Yet another format measures the redistribution of membrane potential using the FLIPR system membrane potential kit (HTS) available from Molecular Dynamics (a division of Amersham Biosciences, Piscataway, NJ). This method is limited to slow membrane potential changes. Some problems may result from the fluorescent background of compounds. Test compounds may also directly influence the fluidity of the cell membrane and lead to an increase in intracellular dye concentrations. Still, because of the functional aspects of the assay, the information content is reasonably good.

[0319] Sodium dyes can be used to measure the rate or amount of sodium ion influx through a channel. This type of assay provides a very high information content regarding potential channel blockers. The assay is functional and would measure Na+ influx directly. CoroNa Red, SBFI and/or sodium green (Molecular Probes, Inc. Eugene OR) can be used to measure Na influx; all are Na responsive dyes. They can be used in combination with the FLIPR instrument. The use of these dyes in a screen has not been previously described in the literature. Calcium dyes may also have potential in this format.

[0320] In another assay, FRET based voltage sensors are used to measure the ability of a test compound to directly block Na influx. Commercially available HTS systems include the VIPR™ II FRET system (Life Technologies, or Aurora Biosciences Corporation, San Diego, CA, a division of Vertex Pharmaceuticals, Inc.) which may be used in conjunction with FRET dyes, also available from Aurora Biosciences. This assay measures sub-second responses to voltage changes. There is no requirement for a modifier of channel function. The assay measures depolarization and hyperpolarizations, and provides ratiometric outputs for quantification. A somewhat less expensive MTS version of this assay employs the FLEXstation™ (Molecular Devices Corporation) in conjunction with FRET dyes from Aurora Biosciences. Other methods of testing the compounds disclosed herein are also readily known and available to those skilled in the art.

[0321] Modulating agents so identified are then tested in a variety of in vivo models so as to determine if they alleviate pain, especially chronic pain or other conditions such as cancer and pruritus (itch) with minimal adverse events. The assays described below in the Biological Assays Section are useful in assessing the biological activity of the instant compounds.

[0322] Typically, the efficacy of a compound of the invention is expressed by its IC50 value ("Inhibitory Concentration – 50%"), which is the measure of the amount of compound required to achieve 50% inhibition of the activity of the target sodium channel over a specific time period. For example, representative compounds of the present invention have demonstrated IC50's ranging from less than 100 nanomolar to less than 10 micromolar in the patch voltage clamp NaV1.7 electrophysiology assay described herein.

[0323] In another aspect of the invention, the compounds of the invention can be used in in vitro or in vivo studies as exemplary agents for comparative purposes to find other compounds also useful in treatment of, or protection from, the various diseases disclosed herein.

[0324] Another aspect of the invention relates to inhibiting NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 activity, preferably NaV1.7 activity, in a biological sample or a mammal, preferably a human, which method comprises administering to the mammal, preferably a human, or contacting said biological sample with a compound of formula (I) or a pharmaceutical composition comprising a compound of formula (I). 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.

[0325] Inhibition of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

[0326] The compounds of the invention (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof) and/or the pharmaceutical

compositions described herein which comprise a pharmaceutically acceptable excipient and one or more compounds of the invention, can be used in the preparation of a medicament for the treatment of sodium channel-mediated disease or condition in a mammal.

[0327] D. COMBINATION THERAPY

[0328] The compounds of the invention may be usefully combined with one or more other compounds of the invention or one or more other therapeutic agent or as any combination thereof, in the treatment of sodium channel-mediated diseases and conditions. For example, a compound of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents, including, but not limited to:

- opiates analgesics, e.g., morphine, heroin, cocaine, oxymorphine, levorphanol, levallorphan, oxycodone, codeine, dihydrocodeine, propoxyphene, nalmefene, fentanyl, hydrocodone, hydromorphone, meripidine, methadone, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;
- non-opiate analgesics, e.g., acetomeniphen, salicylates (e.g., aspirin);
- nonsteroidal antiinflammatory drugs (NSAIDs), e.g., ibuprofen, naproxen, fenoprofen, ketoprofen, celecoxib, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin and zomepirac;
- anticonvulsants, e.g., carbamazepine, oxcarbazepine, lamotrigine, valproate, topiramate, gabapentin and pregabalin;
- antidepressants such as tricyclic antidepressants, e.g., amitriptyline, clomipramine, despramine, imipramine and nortriptyline;
- COX-2 selective inhibitors, e.g., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;
- alpha-adrenergics, e.g., doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, and 4-amino-6,7-dimethoxy-2-(5- methane sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- barbiturate sedatives, e.g., amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal and thiopental;
- tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g., (αR, 9R)-7-[3,5-bis(trifluoromethyl)benzyl)]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diaz ocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethylphenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

- coal-tar analgesics, in particular paracetamol;
- serotonin reuptake inhibitors, e.g., paroxetine, sertraline, norfluoxetine (fluoxetine desmethyl metabolite), metabolite demethylsertraline, '3 fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, ericlamine, trazodone and fluoxetine;
- noradrenaline (norepinephrine) reuptake inhibitors, e.g., maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®)), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine, and venlafaxine duloxetine neuroleptics sedative/anxiolytics;
- dual serotonin-noradrenaline reuptake inhibitors, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- acetylcholinesterase inhibitors such as donepezil;
- 5-HT3 antagonists such as ondansetron;
- metabotropic glutamate receptor (mGluR) antagonists;
- local anaesthetic such as mexiletine and lidocaine;
- corticosteroid such as dexamethasone;
- antiarrhythimics, e.g., mexiletine and phenytoin;
- muscarinic antagonists, e.g.,, tolterodine, propiverine, tropsium t chloride, darifenacin, solifenacin, temiverine and ipratropium;
- cannabinoids;
- vanilloid receptor agonists (e.g., resinferatoxin) or antagonists (e.g., capsazepine);
- sedatives, e.g., glutethimide, meprobamate, methaqualone, and dichloralphenazone;
- anxiolytics such as benzodiazepines,
- antidepressants such as mirtazapine,
- topical agents (e.g., lidocaine, capsacin and resiniferotoxin);
- muscle relaxants such as benzodiazepines, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol and orphrenadine;
- anti-histamines or H1 antagonists;
- NMDA receptor antagonists;
- 5-HT receptor agonists/antagonists;
- PDEV inhibitors;
- Tramadol®;
- cholinergic (nicotinc) analgesics;
- alpha-2-delta ligands;
- prostaglandin E2 subtype antagonists;

- leukotriene B4 antagonists;
- 5-lipoxygenase inhibitors; and
- 5-HT3 antagonists.

[0329] Sodium channel-mediated diseases and conditions that may be treated and/or prevented using such combinations include but not limited to, pain, central and peripherally mediated, acute, chronic, neuropathic as well as other diseases with associated pain and other central nervous disorders such as epilepsy, anxiety, depression and bipolar disease; or cardiovascular disorders such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular disorders such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

[0330] As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention or one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include routes of administration of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

[0331] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

[0332] EXAMPLES

[0333] These examples serve to provide guidance to a skilled artisan to prepare and use the compounds, compositions and methods of the invention. While particular embodiment sof the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the inventions.

[0334] The chemical reactions in the examples described can be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-examplified compounds according to the invention can be successfully performed by modifications apparent to those skilled in the art, for example, by appropriately protecting interferring group, by utilizing other suitable reagents known in the art, for example, by appropriately protecting interferring groups by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions.

[0335] In the examples below, unless otherwise indicated all temperatures are set forth in degrees Celcius. Commerically aviable reagents were purchased from suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge and were used without further purification unless otherwise indicated. The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. ^{1}H NMR spectra were obtained in deuterated $CDCl_3$, d_6-DMSO, CH_3OD or d_6-acetone solvent solutions (reported in ppm) using or trimethylsilane (TMS) or residual non-deuterated solvent peaks as the reference standard. When peak multiplicities are reported, the following abbreviates are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, ar reported in Hz (Hertz).

[0336] All abbreviations used to describe reagents, reaction conditions or equipment are intended to be consistent with the definitions set forth in the "List of standard abbreviates and acronyms". The chemical names of discrete compounds of the invention were obtained using the structure naming feature of ChemDraw naming program.

[0337] Certain final compounds were analyzed by LC/MS methods as described hereinbelow, with UV detector monitoring at 214 nm and 254 nm, and mass spectrometry scanning 110-800 amu in ESI+ ionization mode.

[0338] LC/MS Method A: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH_3CN; gradient: 5%-95% B in 8.0 min; flow rate: 1.2 mL/min; oven temperature 40 °C.

[0339] LC/MS Method B: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (0.1% ammonia), B CH_3CN; gradient: 5%-95% B in 8.0 min; flow rate: 1.2 mL/min; oven temperature 40 °C.

[0340] LC/MS Method C: column: XBridge C18, 4.6 X 50 mm, 3.5 um; mobile phase: A water (0.1% TFA), B CH_3CN; gradient: 5%-95% B in 8.0 min; flow rate: 1.2 mL/min; oven temperature 40 °C.

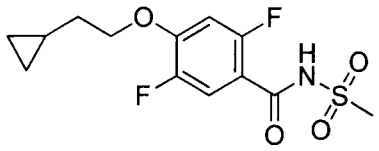
[0341] LC/MS **Method D:** column: Agilent SB C18, 2.1 X 30 mm, 1.8 μm; mobile phase: A water (0.05% TFA), B CH_3CN (0.05% TFA); gradient: 3% B (0.3 min), followed by 3-95% B (6.5 min), 95% B (1.5 min); flow rate: 0.4 mL/min; oven temperature 25 °C.

[0342] Abbreviations used herein are as follows:

EtOAc	Ethyl acetate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	DCM
DIPEA	Diisopropylethylamine
DMAP	4-dimethylaminopryidine
DME	Ethyleneglycol dimethyl ether
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
HBTU	N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uranium hexafluorophosphate
HCl	Hydrochloric acid
HPLC	High Pressure Liquid Chromatography
IMS	Industrial methylated spirits
LCMS	Liquid Chromatography Mass Spectrometry
MeCN	Acetonitrile
MeOH	Methanol
NMP	N-methyl-2-pyrrolidone
RPHPLC	Reverse phase high pressure liquid chromatography
RT	Retention time
SCX-2	Isolute ® silica-based sorbent with a chemically bonded propylsulfonic acid functional group
NH_2 cartridge	Isolute ® silica-based sorbent with a chemically bonded Aminopropyl functional group
THF	Tetrahydrofuran

[0344] EXAMPLE 1

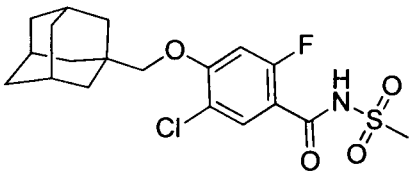
[0345] Synthesis of 4-(2-cyclopropylethoxy)-2,5-difluoro-*N*-(methylsulfonyl)benzamide.



[0346] To a mixture of 2-cyclopropylethanol (0.172 g, 2.0 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added sodium hydride (60% in mineral oil, 0.20 g, 5.0 mmol) at room temperature. The resulting mixture was stirred at 45 °C for 30 min and then cooled to room temperature. 2,4,5-Trifluoro-*N*-(methylsulfonyl)benzamide (WO 2012007883 A1) (0.51 g, 2.2 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The mixture was cooled to 0 °C and quenched with hydrochloride acid (1N, 30 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the crude product was purified by silica gel column chromatography using 10-60% ethyl acetate (containing 2% acetic acid) in hexanes as an eluent to afford the title compound as a white solid (0.12 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (brs, 1H), 7.58 (dd, J = 6.9 Hz & 11.4 Hz, 1H), 7.30 (dd, J = 6.9 Hz & 12.1 Hz, 1H), 4.19 (t, J = 6.6 Hz, 2H), 3.35 (s, 3H), 1.69-1.62 (m, 2H), 0.88-0.74 (m, 1H), 0.47-0.41 (m, 2H), 0.16-0.11 (m, 2H); MS (ES-) *m/z* 318.1 (M - 1).

[0347] EXAMPLE 2

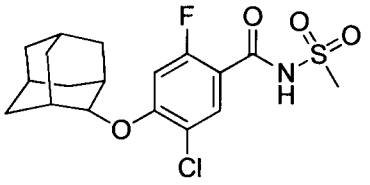
[0348] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide .



[0349] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with adamantan-1-ylmethanol and 2,4,5-trifluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2,4-difluoro-*N*- (methylsulfonyl)benzamide (WO 2012007883 A1), the title compound was obtained as a colorless solid (0.20 g, 8%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.5 Hz, 1H), 3.72 (s, 2H), 3.35 (s, 3H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2.0 Hz), 159.8 (d, $J_{C\text{-}F}$ = 255 Hz), 158.3 (d, $J_{C\text{-}F}$ = 11 Hz), 130.6 (d, $J_{C\text{-}F}$ = 4 Hz), 116.8 (d, $J_{C\text{-}F}$ = 3 Hz), 113.6 (d, $J_{C\text{-}F}$ = 14 Hz), 102.7 (d, $J_{C\text{-}F}$ = 28 Hz), 79.1, 41.2, 38.5, 36.4, 33.4, 27.3; MS(ES+) m/z 415.6, 417.6 (M + 1).

[0350] EXAMPLE 3

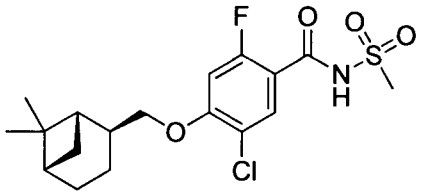
[0351] Synthesis of 4-(adamantan-2-yloxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide.



[0352] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with adamantan-2-ol and 2,4,5-trifluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2,4-difluoro-*N*- (methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.055 g, 4%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 12.6 Hz, 1H), 4.82 (br s, 1H), 3.34 (s, 3H), 2.08-2.03 (m, 4H), 1.84 (br s, 6H), 1.71 (br s, 2H), 1.55-1.51 (m, 2H); MS(ES-) m/z 400.1, 402.1 (M - 1).

[0353] EXAMPLE 4

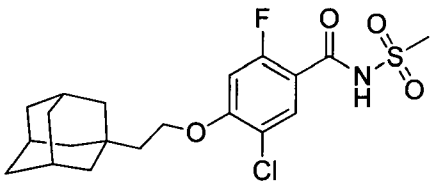
[0354] Synthesis of 5-chloro-4-(((1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide.



[0355] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with ((*1S,2S,5S*)-6,6-dimethylbicyclo[3.1.1]- heptan-2-yl)methanol and 2,4,5-trifluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)- benzamide, the title compound was obtained as a colorless solid (0.03 g, 2%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 12.5 Hz, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.35 (s, 3H), 2.47-2.37 (m, 1H), 2.10-2.03 (m, 1H), 1.94-1.65 (m, 5H), 1.48-1.37 (m, 2H), 1.12 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2 Hz), 159.8 (d, $J_{C\text{-}F}$ = 255 Hz), 158.1 (d, $J_{C\text{-}F}$ = 11 Hz), 130.7 (d, $J_{C\text{-}F}$ = 3 Hz), 116.6 (d, $J_{C\text{-}F}$ = 3 Hz), 113.7 (d, $J_{C\text{-}F}$ = 14 Hz), 102.5 (d, $J_{C\text{-}F}$ = 28 Hz), 73.1, 41.9, 41.2, 40.1, 38.8, 34.1, 26.5, 23.5, 23.1, 20.0, 17.4; MS(ES-) m/z 402.1, 404.1 (M - 1).

[0356] EXAMPLE 5

[0357] Synthesis of 4-(2-(adamantan-1-yl)ethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide

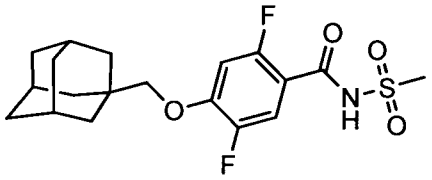


[0358] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with 2-(adamantan-1-yl)ethanol and 2,4,5-trifluoro-*N*- (methylsulfonyl)benzamide

with 5-chloro-2,4-difluoro-*N*- (methylsulfonyl)- benzamide, the title compound was obtained as a colorless solid (0.04 g, 5%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.6 Hz, 1H), 4.15 (t, J = 6.9 Hz, 2H), 3.31 (s, 3H), 1.89 (br s, 3H), 1.66-1.51 (m, 14H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J_{C-F} = 2 Hz), 159.9 (d, J_{C-F} = 254 Hz), 158.1 (d, J_{C-F} = 12 Hz), 130.7 (d, J_{C-F} = 4 Hz), 116.5 (d, J_{C-F} = 3 Hz), 113.6 (d, J_{C-F} = 14 Hz), 102.5 (d, J_{C-F} = 28 Hz), 66.1, 42.1, 41.8, 41.2, 36.4, 31.3, 27.9; MS(ES-) m/z 428.1, 430.1 (M - 1).

[0359] EXAMPLE 6

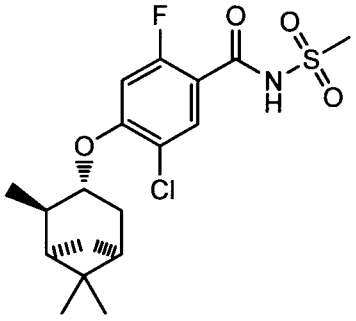
[0360] Synthesis of 4-((adamantan-1-ylmethoxy)-2,5-difluoro-*N*- (methylsulfonyl)benzamide



[0361] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with adamantan-1-ylmethanol, the title compound was obtained as a colorless solid (0.145 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (s, 1H), 7.53 (dd, J = 6.8, 11.3 Hz, 1H), 7.23 (dd, J = 6.8, 12.3 Hz, 1H), 3.68 (s, 2H), 3.31 (s, 3H), 1.95 (s, 3H), 1.71-1.58 (m, 12H); MS(ES-) m/z 398.1 (M - 1).

[0362] EXAMPLE 7

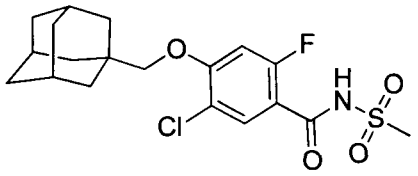
[0363] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)oxy)benzamide



[0364] Following the procedure as described in Example 1 and making variations as required to replace 2-cyclopropylethanol with (1R,2R,3R,5S)-2,6,6-trimethylbicyclo- [3.1.1]heptan-3-ol and 2,4,5-trifluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)- benzamide, the title compound was obtained as a colorless solid (0.06 g, 5%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.33 (d, J_{C-F} = 12.6 Hz, 1H), 4.79-4.74 (m, 1H), 3.31 (s, 3H), 2.71-2.64 (m, 1H), 2.37-2.26 (m, 2H), 1.91-1.80 (m, 2H), 1.59-1.52 (m, 1H), 1.19 (s, 3H), 1.10-1.06 (m, 4H), 0.95 (s, 3H); MS(ES-) m/z 402.1, 404.1 (M - 1).

[0365] EXAMPLE 8

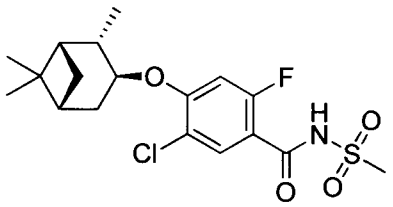
[0366] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide



[0367] To a mixture of adamantan-1-ylmethanol (1.00 g, 6.0 mmol) in anhydrous dimethyl sulfoxide (40 mL) was added potassium t-butoxide (1.68 g, 15.0 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 min followed by the addition of 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide (1.62 g, 6.0 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was cooled to 0 °C and quenched with hydrochloride acid (1N, 30 mL) followed by extraction with ethyl acetate (200 mL). The organic layer was washed with water (2 x 40 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the crude product was purified by silica gel column chromatography using 10-60% ethyl acetate (containing 0.2% acetic acid) in hexanes as an eluent to afford the title compound as a white solid (1.17 g, 46%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.77 (d, J= 7.5 Hz 1H), 7.23 (d, J= 12.5 Hz, 1H), 3.72 (s, 2H), 3.35 (s, 3H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2.2 Hz), 159.8 (d, $J_{C\text{-}F}$ = 255 Hz), 158.3 (d, $J_{C\text{-}F}$ = 11 Hz), 130.6 (d, $J_{C\text{-}F}$ = 4 Hz), 116.8 (d, $J_{C\text{-}F}$ = 3 Hz), 113.6 (d, $J_{C\text{-}F}$ = 14 Hz), 102.7 (d, $J_{C\text{-}F}$ = 28 Hz), 79.1, 41.2, 38.5, 36.4, 33.4, 27.3; MS(ES-) m/z 414.1, 416.1 (M - 1).

[0368] EXAMPLE 9

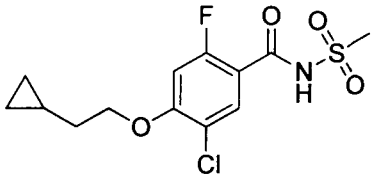
[0369] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)oxy)benzamide



[0370] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (*1S,2S,3S,5R*)-2,6,6- trimethylbicyclo[3.1.1]heptan-3-ol, the title compound was obtained as a colorless solid (0.27 g, 45%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.26 (d, J= 12.6 Hz, 1H), 4.81-4.78 (m, 1H), 3.35 (s, 3H), 2.75-2.67 (m, 1H), 2.40-2.30 (m, 2H), 1.94-1.85 (m, 2H), 1.61-1.56 (m, 1H), 1.22 (s, 3H), 1.14-1.09 (m, 4H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2 Hz), 159.8 (d, $J_{C\text{-}F}$ = 254 Hz), 157.3 (d, $J_{C\text{-}F}$ = 11 Hz), 130.8 (d, $J_{C\text{-}F}$ = 3 Hz), 117.5 (d, $J_{C\text{-}F}$ = 3 Hz), 113.7 (d, $J_{C\text{-}F}$ = 14 Hz), 104.0 (d, $J_{C\text{-}F}$ = 27 Hz), 78.6, 46.5, 43.7, 41.2, 40.5, 37.7, 34.6, 32.1, 27.1, 23.5, 20.5; MS(ES-) m/z 402.1, 404.1 (M - 1).

[0371] EXAMPLE 10

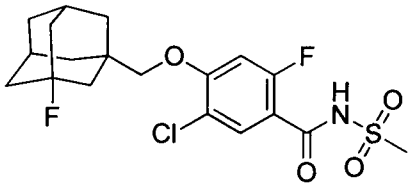
[0372] Synthesis of 5-chloro-4-(2-cyclopropylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0373] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 2-cyclopropylethanol, the title compound was obtained as a colorless solid (0.26 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (s,1H), 7.78 (d, J = 7.5 Hz 1H), 7.26 (d, J = 12.5 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 3.35 (s, 3H), 1.70-1.63 (m, 2H), 0.87-0.79 (m, 1H), 0.47-0.41 (m, 2H), 0.17-0.12 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2 Hz), 159.9 (d, J_{C-F} = 254 Hz), 158.1 (d, J_{C-F} = 11 Hz), 130.8 (d, J_{C-F} = 3 Hz), 116.6 (d, J_{C-F} = 3 Hz), 113.7 (d, J_{C-F} = 14 Hz), 102.5 (d, J_{C-F} = 27 Hz), 70.3, 41.7, 33.5, 8.0, 4.5; MS(ES-) m/z 334.1, 336.1 (M - 1).

[0374] EXAMPLE 11

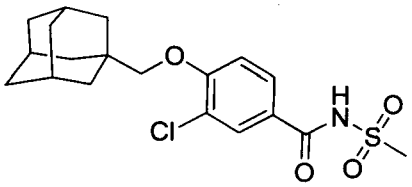
[0375] Synthesis of 5-chloro-2-fluoro-4-((3-fluoroadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide



[0376] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 3-fluoroadamantan-1-ylmethanol, the title compound was obtained as a colorless solid (0.37 g, 58%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 3.85 (s, 2H), 3.35 (s, 3H), 2.30 (s, 2H), 1.82-1.76 (m, 6H), 1.61-1.52 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3 (d, J = 2 Hz), 159.8 (d, J_{C-F} = 254 Hz), 158.1 (d, J_{C-F} = 11 Hz), 130.7 (d, J_{C-F} = 3 Hz), 116.8 (d, J_{C-F} = 3 Hz), 113.8 (d, J_{C-F} = 14 Hz), 102.6 (d, J_{C-F} = 28 Hz), 92.5 (d, J_{C-F} = 183 Hz), 77.6 (d, J_{C-F} = 1 Hz), 43.7 (d, J_{C-F} = 18 Hz), 41.8 (d, J_{C-F} = 17 Hz), 41.2, 38.3 (d, J_{C-F} = 10 Hz), 37.0 (d, J_{C-F} = 2 Hz), 34.6 (d, J_{C-F} = 2 Hz), 30.3 (d, J_{C-F} = 10 Hz); MS(ES-) m/z 432.1, 434.1 (M - 1).

[0377] EXAMPLE 12

[0378] Synthesis of 4-(adamantan-1-ylmethoxy)-3-chloro-*N*-(methylsulfonyl)benzamide

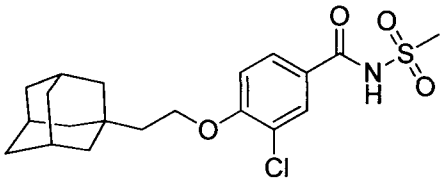


[0379] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with

3-chloro-4-fluoro-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.34 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.04-7.94 (m, 2H), 7.25 (d, J = 8.5 Hz, 1H), 3.72 (s, 2H), 3.36 (s, 3H), 1.99 (br, 3H), 1.71-1.66 (m, 12H);MS(ES-) m/z 396.1, 398.1 (M - 1).

[0380] EXAMPLE 13

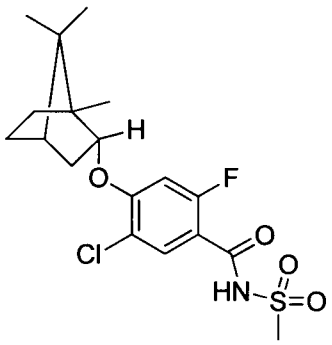
[0381] Synthesis of 4-(2-(adamantan-1-yl)ethoxy)-3-chloro-*N*-(methylsulfonyl)benzamide



[0382] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 2-(adamantan-1-yl)ethanol and 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 3-chloro-4-fluoro-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.43 g, 71%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.93 (dd, J = 8.7 Hz, 2.2 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 4.20 (t, J = 6.9 Hz, 2H), 3.36 (s, 3H), 1.93 (br s, 3H), 1.70-1.55 (m, 14H); MS(ES+) m/z 411.8, 413.8 (M + 1).

[0383] EXAMPLE 14

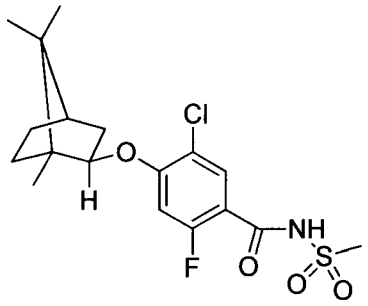
[0384] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide.



[0385] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with [(1S)-*endo*]-(-)-borneol, the title compound was obtained as a colorless solid (0.18 g, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.15-8.04 (m, 1H), 6.63-6.50 (m, 1H), 4.44-4.32 (m, 1H), 3.43 (s, 3H), 2.50-2.23 (m, 2H), 1.88-1.74 (m, 2H), 1.49-1.36 (m, 1H), 1.35-1.21 (m, 1H), 1.15-1.05 (m, 1H), 1.01-0.89 (m, 9H); MS(ES-) m/z 402.1 (M -1), 404.1 (M - 1).

[0386] EXAMPLE 15

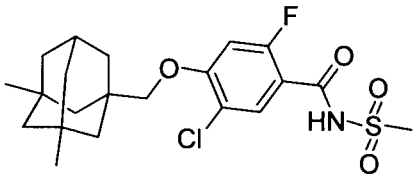
[0387] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((*exo*-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide.



[0388] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with is isoborneol, the title compound was obtained as a colorless solid (0.18 g, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.33-8.20 (m, 1H), 6.87-6.74 (m, 1H), 4.28-4.06 (m, 1H), 3.38 (s, 3H), 2.06-1.62 (m, 5H), 1.29-1.06 (m, 8H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (d, J_{C-F} = 248.69 Hz), 160.3 (d, J_{C-F} = 3.43 Hz), 159.0 (d, J_{C-F} = 12.21 Hz), 132.7 (d, J_{C-F} = 3.20 Hz), 120.8 (d, J_{C-F} = 2.62 Hz), 109.9 (d, J_{C-F} = 11.91 Hz), 101.3 (d, J_{C-F} = 30.39 Hz), 87.1, 49.7, 47.2, 45.3, 42.0, 39.0, 33.8, 27.2, 20.2, 20.1, 11.7; MS(ES-) m/z 402.1 (M -1), 404.1 (M - 1).

[0389] EXAMPLE 16

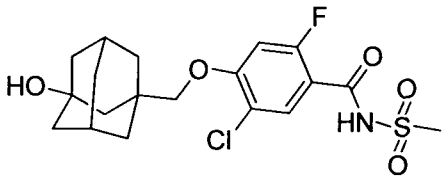
[0390] Synthesis of 5-chloro-4-((-3, 5-dimethyladamantan-1-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide.



[0391] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with is 3,5-dimethyl-1-adamantanemethanol, the title compound was obtained as a colorless solid (0.37 g, 41%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.76 (d, J = 7.2 Hz 1H), 7.21 (d, J = 12.0 Hz, 1H), 3.75 (s, 2H), 3.35 (s, 3H), 1.47 (s, 1H), 1.33-1.07 (m, 12H), 0.81 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2 (d, J = 1.8 Hz), 160.3 (d, $^1J_{C-F}$ = 255.7 Hz), 158.8 (d, J_{C-F} = 11.1 Hz), 131.1 (d, J_{C-F} = 3.1 Hz), 117.3 (d, J_{C-F} = 2.9 Hz), 114.0 (d, J_{C-F} = 13.7 Hz), 102.9 (d, $^2J_{C-F}$ = 27.5 Hz), 79.1, 51.1, 45.4, 43.2, 41.7, 37.7, 35.7, 31.0, 30.9, 29.1; MS(ES-) m/z 442.1, 444.1 (M - 1).

[0392] EXAMPLE 17

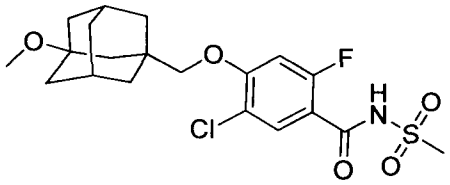
[0393] Synthesis of 5-chloro-2-fluoro-4-((3-hydroxyadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide.



[0394] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 3-(hydroxymethyl)-1-adamantol, the title compound was obtained as a colorless solid (0.25 g, 29%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.76 (d, J = 6.6 Hz, 1H), 7.23 (d, J = 12.3 Hz, 1H), 4.36 (br s, 1H), 3.78 (s, 2H), 3.35 (s, 3H), 2.14 (br s, 2H), 1.68-1.39 (m, 12H); MS(ES-) m/z: 430.1, 432.1 (M - 1).

[0395] EXAMPLE 18

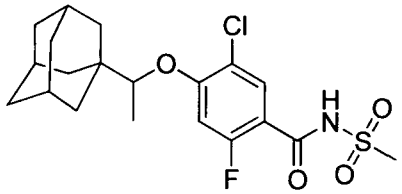
[0396] Synthesis of 5-chloro-2-fluoro-4-((3-methoxyadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide.



[0397] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 3-methoxy adamantan-1-ylmethanol, the title compound was obtained as a colorless solid (0.28 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 3.81 (s, 2H), 3.35 (s, 3H), 3.12 (s, 3H), 2.21 (s, 2H), 1.70-1.55 (m, 12H); MS(ES+) m/z 414.0, 416.0 (M – OCH_3).

[0398] EXAMPLE 19

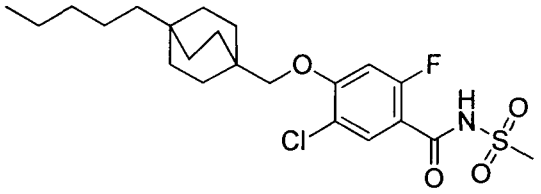
[0399] Synthesis of 4-(1-(adamantan-1-yl)ethoxy)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide



[0400] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 1-(adamantan-1-yl)ethanol, the title compound was obtained as a colorless solid (0.22 g, 44%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.77-7.74 (m, 1H), 7.30 (d, J = 12.7 Hz, 1H), 4.24 (q, J = 6.2 Hz, 1H), 3.34 (s, 3H), 1.97 (brs, 3H), 1.72-1.56 (m, 12H), 1.16 (d, 6.2 Hz, 3H); MS(ES-) m/z 428.1, 430.1 (M - 1).

[0401] EXAMPLE 20

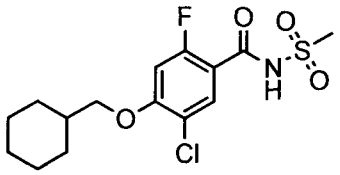
[0402] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4-pentylbicyclo-[2.2.2]octan-1-yl)methoxy)benzamide.



[0403] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (4-pentylbicyclo[2.2.2]- octan-1-yl)methanol (*Jpn. Kokai Tokkyo Koho*, 2010083938, 15 Apr 2010), the title compound was obtained as a colorless solid (0.17 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 3.76 (s, 2H), 3.35 (s, 3H), 1.51-1.06 (m, 20H), 0.85 (t, J = 6.9 Hz, 3H); MS(ES-) m/z 458.2, 460.1 (M - 1).

[0404] EXAMPLE 21

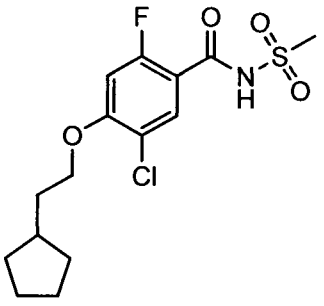
[0405] Synthesis of 5-chloro-4-(cyclohexylmethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide.



[0406] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with cyclohexylmethanol, the title compound was obtained as a colorless solid (0.091 g, 25%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.6 Hz, 1H), 3.93 (d, J = 5.9 Hz, 2H), 3.31 (s, 3H), 1.79-1.60 (m, 6H), 1.29-0.97 (m, 5H); MS(ES-) m/z 362.1, 364.1 (M - 1).

[0407] EXAMPLE 22

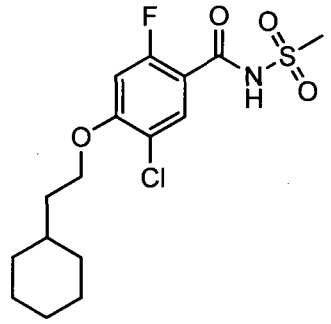
[0408] Synthesis of 5-chloro-4-(2-cyclopentylethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide.



[0409] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 2-cyclopentylethanol, the title compound was obtained as a colorless solid (0.107 g, 29%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 12.5 Hz, 1H), 4.12 (t, J = 6.5 Hz, 2H), 3.31 (s, 3H), 1.95-1.83 (m, 1H), 1.80-1.71 (m, 4H), 1.59-1.42 (m, 4H), 1.18-1.07 (m, 2H); MS(ES-) m/z 362.1, 364.1 (M - 1).

[0410] EXAMPLE 23

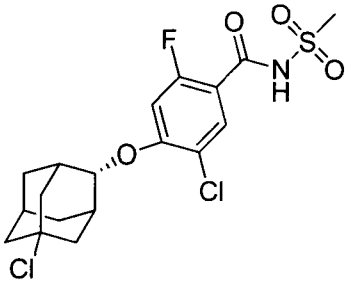
[0411] Synthesis of 5-chloro-4-(2-cyclohexylethoxy)-2-fluoro-*N*- (methylsulfonyl)benzamide.

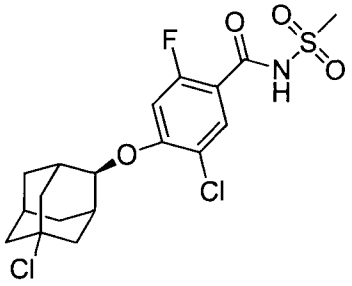


[0412] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 2-cyclohexylethanol, the title compound was obtained as a colorless solid (0.05 g, 14%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 12.4Hz, 1H), 4.17 (t, J = 6.6 Hz, 2H), 3.29 (s, 3H), 1.76-1.41 (m, 8H), 1.27-0.90 (m, 5H); MS(ES-) m/z 376.1, 378.1 (M - 1).

[0413] EXAMPLE 24/25

[0414] Synthesis of 5-chloro-4-(((1*R*,2s,3*S*,5s,7s)-5-chloroadamantan-2-yl)oxy)2-fluoro-*N*-(methylsulfonyl)benzamide and 5-chloro-4-(((1*R*,2r,3*S*,5s,7s)-5-chloroadamantan-2-yl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide.



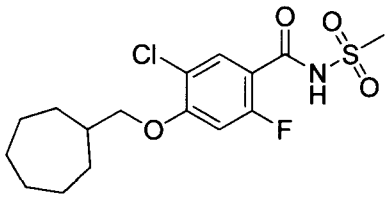


[0415] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 5-chloroadamantan-2-ol (*J. Am. Chem. Soc.* **1986**, 108, 1598), the crude product was purified by silica gel column chromatography using 10-60% ethyl acetate (containing 0.2% acetic acid) in hexanes as an eluent to provide pure separated diastereomers of 5-chloro-4-(((1*R*,2s,3*S*,5s,7s)-5-chloroadamantan-2- yl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide and 5-chloro-4-(((1*R*,2r,3*S*,5s,7s)-5-chloroadamantan-2-yl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide. Data for first eluting diasteromeomer: a colorless solid (0.22 g, 19%), (Example 24): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 12.6 Hz, 1H), 4.17 (m, 1H), 3.31 (s, 3H), 2.29-2.10 (m, 9H), 1.93 (d, J = 12.5 Hz, 2H), 1.47 (d, J = 12.5 Hz, 2H); MS(ES-) m/z 434.0, 436.0, (M - 1). Data for the second eluting diasteromer was also obtained as a colorless solid (0.15 g, 12%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 12.6 Hz, 1H), 4.71 (m, 1H), 3.31 (s,

3H), 2.37-2.28 (m, 4H), 2.06 (brs, 3H), 1.97-1.93 (m, 2H) , 1.74 (brs, 4H); MS(ES-) m/z 434.1, 436.1, (M - 1).

[0416] EXAMPLE 26

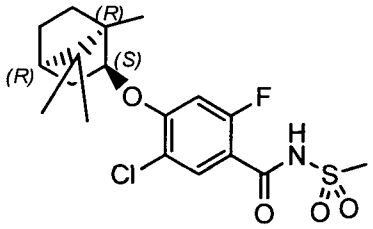
[0417] Synthesis of 5-chloro-4-(2-cycloheptylethoxy)-2-fluoro-*N*- (methylsulfonyl)benzamide



[0418] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with cycloheptylmethanol, the title compound was obtained as a colorless solid (0.12 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.5 Hz, 1H), 3.91 (d, J = 6.5 Hz, 2H), 3.31 (s, 3H), 1.98-1.21 (m, 13H); MS(ES-) m/z 376.1, 378.1 (M - 1).

[0419] EXAMPLE 27

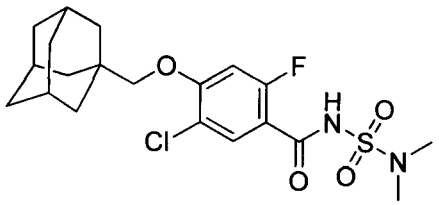
[0420] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide



[0421] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (+)-Borneol, the title compound was obtained as a colorless solid (0.25 g, 33%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.13-8.06 (m, 1H), 6.64-6.47 (m, 1H), 4.46-4.30 (m, 1H), 3.43 (s, 3H), 2.52-2.21 (m, 2H), 1.89-1.70 (m, 2H), 1.49-1.19 (m, 2H), 1.16-1.05 (m, 1H), 1.03-0.79 (m, 9H); MS(ES-) m/z 402.1 (M -1), 404.1 (M - 1).

[0422] EXAMPLE 28

[0423] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide

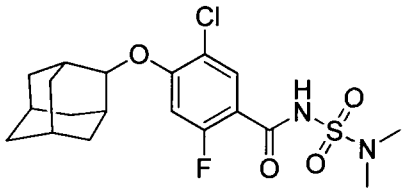


[0424] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2,4-difluorobenzamide (as prepared in Example 31), the title compound was obtained as a colorless solid (0.25 g, 38%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H),

7.72 (d, J = 7.45 Hz 1H), 7.22 (d, J = 12.3 Hz, 1H), 3.72 (s, 2H), 2.87 (s, 6H), 1.99 (br, 3H), 1.75-1.64 (m, 12H); MS(ES-) m/z 443.1, 445.1 (M - 1).

[0425] EXAMPLE 29

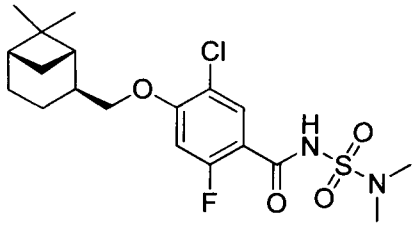
[0426] Synthesis of 4-(adamantan-2-yloxy)-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)- 2-fluorobenzamide



[0427] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with adamantan-2-ol and 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*- dimethylsulfamoyl)-2,4-difluorobenzamide (as prepared in Example 31), the title compound was obtained as a colorless solid (0.21 g, 38%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 12.5 Hz, 1H), 4.81 (s, 1H), 2.87 (s, 6H), 2.08-2.03 (m, 4H), 1.84-1.71 (m, 8H), 1.54-1.50 (m, 2H); MS(ES-) m/z 429.2, 431.2 (M - 1).

[0428] EXAMPLE 30

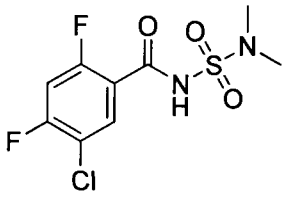
[0429] Synthesis of 5-chloro-4-(((1*S*,2*S*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-methoxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluorobenzamide.



[0430] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with ((1*S*,2*S*,5*S*)-6,6- dimethylbicyclo[3.1.1]heptan-2-yl)methanol and 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)- benzamide with 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2,4-difluorobenzamide (as prepared in Example 31), the title compound was obtained as a colorless solid (0.25 g, 45%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.3 Hz, 1H), 3.95 (d, J = 6.8 Hz, 2H), 2.87 (s, 6H), 2.50-2.40 (m, 1H), 2.10-1.65 (m, 6H), 1.48-1.37 (m, 2H), 1.21 (s, 3H), 0.85 (s, 3H); MS(ES-) m/z 431.2, 433.2 (M - 1).

[0431] EXAMPLE 31

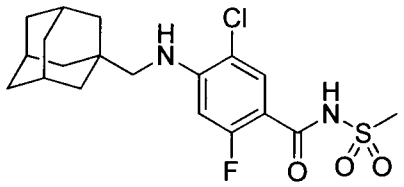
[0432] Synthesis of 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2,4-difluorobenzamide.



[0433] To a mixture of 5-chloro-2,4-difluorobenzoic acid (3.48 g, 18.1 mmol) in anhydrous dichloromethane (100 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.20 g, 27.1 mmol), *N,N*-dimethylpyridin-4-amine (5.04 g, 41.3 mmol), and *N,N*-dimethylsulfamide (3.37 g, 27.1 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 h. The mixture was then cooled to 0 °C and quenched with hydrochloride acid (1N, 100 mL) followed by extraction with dichloromethane (2 x 200 mL). The organic layer was washed with ammonium chloride solution (3 x 30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* and the crude product was crystallized from ethyl acetate and hexanes to afford the title compound as a white solid (1.20 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.98-7.93 (m, 1H), 7.74-7.68 (m, 1H), 2.89 (s, 6H); MS (ES-) m/z 297.1, 299.1 (M - 1).

[0434] EXAMPLE 32

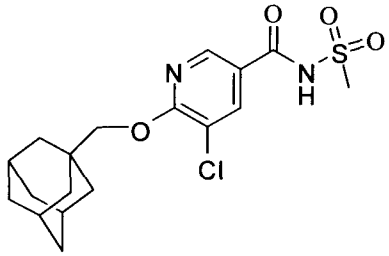
[0435] Synthesis of 4-((-adamantan-1-ylmethyl)amino)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide.



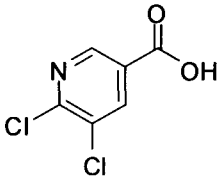
[0436] A stirred mixture of 1-(aminomethyl)adamantane (0.31 g, 1.85 mmol), 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide (0.5 g, 1.85 mmol) and potassium carbonate (0.64 g, 4.63 mmol) in *N,N*-dimethylformamide (18 mL) and tetrahydrofuran (10 mL) was heated at 65 °C for 48 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was diluted with saturated aqueous ammonium chloride (50 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a 0 to 10% gradient of methanol in dichloromethane to afford the title compound as a pale yellow solid (0.064 g, 8%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55-8.08 (m, 2H), 7.51-7.40 (m, 1H), 6.58-6.43 (m, 1H), 3.44 (s, 3H), 2.84-2.75 (m, 2H), 2.02 (br s, 3H), 1.81-1.46 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 162.5 (d, $^1J_{C\text{-}F}$ = 255.0 Hz), 153.1 (d, $J_{C\text{-}F}$ = 11.8 Hz), 130.9 (d, $J_{C\text{-}F}$ = 3.2 Hz), 106.8, 106.2 (d, $J_{C\text{-}F}$ = 19.5 Hz), 99.6 (d, $^2J_{C\text{-}F}$ = 25.3 Hz), 55.7, 42.1, 40.6, 36.9, 33.8, 28.2; MS (ES+) *m/z* 414.8, 416.8 (M + 1).

[0437] EXAMPLE 33

[0438] Synthesis of 6-(Adamantan-1-ylmethoxy)-5-chloro-N-methanesulfonylpyridine- 3-carboxamide



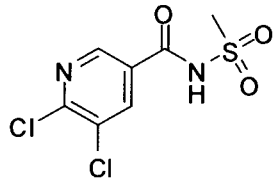
[0439] Step 1 Preparation of 5,6-dichloronicotinic acid.



[0440] A mixture of ethyl 5,6-dichloronicotinate (1.0 g, 4.5 mmol) and aqueous NaOH (2 N, 6.75 mL, 13.5 mmol) in a mixed solvents of THF/MeOH/water (50 mL, 4/1/1) was stirred at room temperature for 0.5 h. After concentration, the mixture was acidified with 2 N HCl to pH around 2. The resulting mixture was extracted with ether (30 mL x 3). The organic layer was washed with water (50 mL x 3), dried over Na_2SO_4, and concentrated to afford 5,6-dichloronicotinic acid (800 mg, 91% yield) as a white solid. LCMS (ESI) m/z: 192.0 $[M+H]^+$.

[0441] Step 2

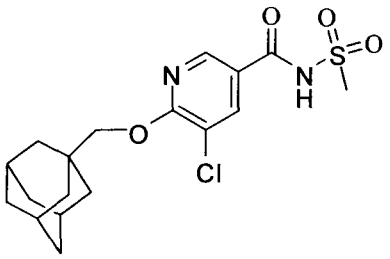
[0442] Preparation of 5,6-Dichloro-N-(methylsulfonyl)nicotinamide



[0443] A mixture of 5,6-dichloronicotinic acid (800 mg , 4.16 mmol), methanesulfonamide (779 mg, 8.40 mmol), EDCI (1.56 g, 8.20 mmol), and DMAP (1.00 g, 8.20 mmol) in DCM (10 mL) was stirred at room temperature for 16 h. The reaction was quenched with water (5 mL) and the resulting mixture was concentrated. The residue was adjusted to pH around 5 by 1M HCl, extracted with DCM (30 mL x 3), dried over Na_2SO_4. The organic layer was concentrated to afford 5,6-dichloro-*N*-(methylsulfonyl)nicotinamide (700 mg, 62% yield). LCMS (ESI) m/z: 269.0 $[M+H]^+$.

[0444] Step 3

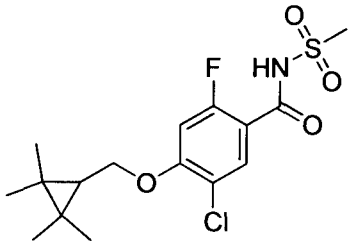
[0445] 6-(Adamantan-1-ylmethoxy)-5-chloro-N-methanesulfonylpyridine-3- carboxamide



[0446] To a solution of 5,6-dichloro-N-(methylsulfonyl)nicotinamide (60 mg, 0.22 mmol) and 1-(hydroxymethyl) adamantine (182 mg, 1.10 mmol) in DMF (3 mL) at 0 °C was added NaH (60%, 52 mg, 1.3 mmol). The mixture was then stirred at 45 °C for 72 h. Sat. NH_4Cl (5 mL) was added to quench the reaction and the resulting mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layer was dried and concentrated in vacuo. The residue was purified by prep-HPLC (Gilson GX 281, Shim-pack PRC-ODS 250 mm x 20 mm x 2, gradient: CH_3CN / 10 mm/L NH_4HCO_3, 17 min) to afford 6-(adamantan-1-ylmethoxy)-5-chloro-N-methanesulfonyl pyridine-3-carboxamide (20 mg, 22% yield). LCMS (ESI) Method B: RT = 4.45 min, m/z: 423.0 $[M+Na]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.63 (s, 1H), 8.32 (s, 1H), 4.02 (s, 2H), 3.27 (s, 3H), 1.98 (s, 3H), 1.73-1.63 (m, 12H).

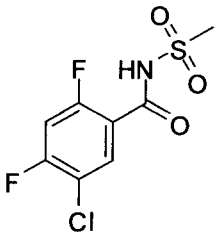
[0447] EXAMPLE 34

[0448] Synthesis of 5-Chloro-2-fluoro-N-(methylsulfonyl)-4-((2,2,3,3-tetramethylcyclopropyl)-methoxy)benzamide



[0449] Step 1

[0450] Preparation of 5-Chloro-2,4-difluoro-N-(methylsulfonyl)benzamide.

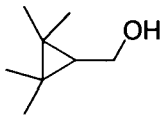


[0451] To a mixture of 5-chloro-2,4-dilfluorobenzoic acid (0.291 g, 1.51 mmol), EDCI (0.438 g, 2.29 mmol), and 4-dimethylaminopyridine (0.420 g, 3.44 mmol) in THF (5 mL) was methanesulfonamide (0.222 g, 2.33 mmol). After being stirred at room temperature for 18 h, the mixture was diluted with DCM (10 mL) and washed with 2 N HCl (15 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated

in vacuo to to afford 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (0.388 g, 95% yield) as a white solid. LCMS (ESI) m/z: 268 $[M-H]^+$. The compound can also be prepared as described in International Patent Application Publication Number WO/2012/007883.

[0452] Step 2

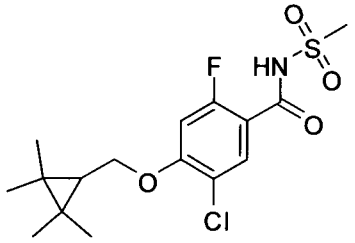
[0453] Preparation of (2,2,3,3-Tetramethylcyclopropyl)methanol:



[0454] To a stirred solution of 2,2,3,3-tetramethylcyclopetanecarboxylic acid (500 mg, 3.50 mmol) in THF (25 mL) at 0 °C was added 2.0 M borane dimethylsulfide complex in THF (1.8 mL, 3.5 mmol). The mixture was then warmed to 50 °C and stirred for 3 h. After cooling to room temperature, methanol (10 mL) was carefully added. The resulting mixture was then concentrated and filtered. The filtrate was concentrated to afford (2,2,3,3-tetramethyl- cyclopropyl)methanol (250 mg, 56% yield) as oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (d, J = 8.0 Hz, 2H), 1.10 (s, 6H), 1.02 (s, 6H), 0.54 (t, J = 8.0 Hz, 1H).

[0455] Step 3

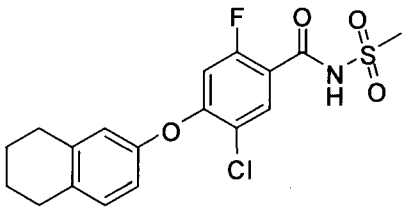
[0456] Preparation of 5-Chloro-2-fluoro-*N*-(methylsulfonyl)-4-((2,2,3,3-tetramethylcyclopropyl)-methoxy)benzamide

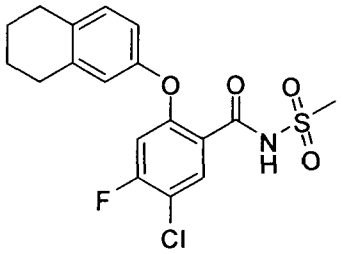


[0457] To a stirred solution of (2,2,3,3-tetramethylcyclopropyl)methanol (80 mg, 0.62 mmol) in dry DMF (10 mL) at 0 °C was added NaH (25 mg, 0.62 mmol). After being stirred for 30 min, 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (54 mg, 0.21 mmol) was added. After being stirred at room temperature for 18 h, the mixture was diluted with water (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 ml x 2). The combined organic layers was dried over Na_2SO_4 and concentrated. The residue was purified by prep-HPLC (Gilson GX 281, Shim-pack PRC-ODS 250 mm x 20 mm x 2, gradient: CH_3CN / 10 mm/L NH_4HCO_3, 17 min) to afford 5-chloro-2-fluoro-N-(methylsulfonyl)-4-((2,2,3,3-tetramethylcyclopropyl)- methoxy)benzamide (20 mg, 25% yield) as a white solid. LCMS (ESI) Method A: RT = 5.11 min, m/z: 268 $[M-109]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 (d, J = 9.0 Hz 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.04 (brs, 1H), 3.99 (d, J = 7.5 Hz, 2H), 2.80 (s, 3H), 1.06 (s, 6H), 0.99 (s, 6H), 0.65 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, MeOH-d_4): δ 159.4 (d, J = 3.5 Hz), 133.9 (d, J = 2.1 Hz), 114.1, 104.2, 103.9, 71.4, 41.7, 32.5, 24.2, 23.7, 17.4.

[0458] EXAMPLE 35

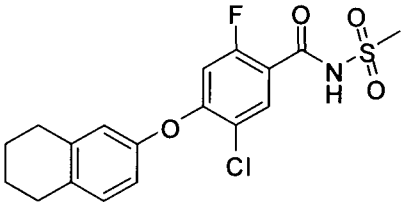
[0459] Synthesis of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yloxy)benzamide and 5-chloro-4-fluoro-N-(methylsulfonyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)benzamide.

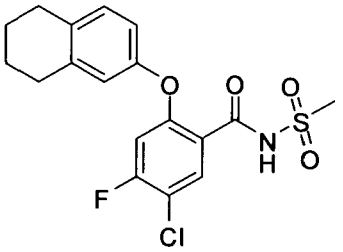




[0460] Step 1

[0461] Preparation of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yloxy)benzamide and 5-chloro-4-fluoro-N-(methylsulfonyl)- 2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)benzamide





[0462] To a solution of 5,6,7,8-tetrahydronaphthalen-2-ol (66 mg, 0.44 mmol) in DMF (3 mL) was added NaH (19 mg, 0.48 mmol). After being stirred at room temperature for 0.5 h, 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (100 mg, 0.37 mmol) was added and the mixture was stirred at room temperature for 16 h. Sat. NH_4Cl (10 mL) was added to quench the reaction and the resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by prep-HPLC (Gilson GX 281, Shim-pack PRC-ODS 250 mm x 20 mm x 2, gradient: CH_3CN / 10 mm/L NH_4HCO_3, 17 min) to afford 5-chloro-2-fluoro-N- (methylsulfonyl)-4-(5,6,7,8- tetrahydronaphthalen-2-yloxy)benzamide (44 mg, 30% yield) and 5-chloro-4-fluoro-N- (methylsulfonyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)- benzamide (21 mg, 14% yield).

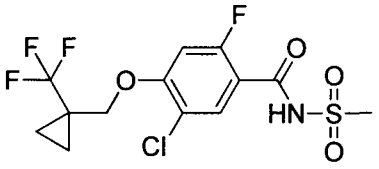
[0463] 5-Chloro-2-fluoro-N-(methylsulfonyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yloxy) benzamide. LCMS (ESI) Method B: RT = 3.92 min, m/z: 398.1 $[M+H]^+$. ^1H NMR (500 MHz, MeOH-d_4): δ 7.57 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.66-6.57 (m, 3H), 2.73 (s, 3H), 2.63 (br s, 4H), 1.68 (br s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.5 (d, J = 2.1 Hz), 160.2, 158.2, 155.1(d, J = 8.9 Hz), 152.5, 138.9, 133.3, 132.0 (d, J = 3.6 Hz), 130.6, 118.8, 118.1 (d, J = 3.4 Hz), 116.2, 107.0 (d, J = 2.8 Hz), 40.7, 28.8, 28.1, 22.6, 22.4.

[0464] 5-Chloro-4-fluoro-N-(methylsulfonyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yloxy) benzamide. LCMS (ESI) Method B: RT = 4.06 min, m/z: 398.0 $[M+H]^+$. ^1H NMR (500 MHz, MeOH-d_4): δ 7.90 (d, J =

7.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.82-6.79 (m, 2H), 6.55 (d, J = 11.5 Hz, 1H), 3.21 (s, 3H), 2.79 (br s, 4H), 1.84 (br s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.4, 159.1, 157.1 (d, J = 3.1 Hz), 154.6 (d, J = 9.1 Hz), 153.5, 138.4, 132.5, 131.3, 130.2, 118.8, 116.3, 113.1 (d, J = 18.3 Hz), 107.6 (d, J = 22.1 Hz), 40.4, 28.8, 28.1, 22.7, 22.4.

[0465] EXAMPLE 36

[0466] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((1-(trifluoromethyl)cyclopropyl)-methoxy)benzamide

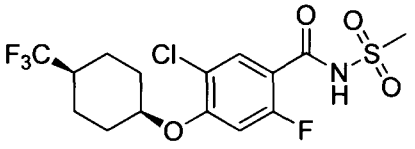


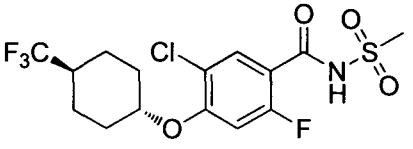
[0467] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (1-(trifluoromethyl)- cyclopropyl)methanol, the title compound was obtained as a colorless solid (0.28 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.3 Hz, 1H), 4.31 (s, 1H), 1.18-0.98 (m, 4H); MS (ES-) m/z: 388.0.1, 390.0 (M - 1).

[0468] EXAMPLE 37

Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1s,4s)-4-(trifluoromethyl)cyclohexyl)-oxy)benzamide and

5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1r,4r)-4-(trifluoromethyl)cyclohexyl)- oxy)benzamide

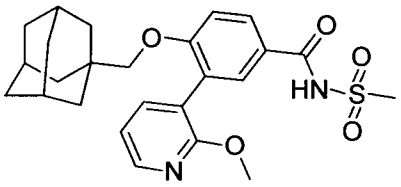




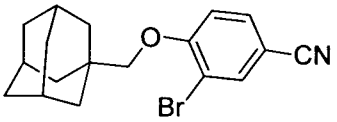
[0469] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 4-(trifluoromethyl)- cyclohexanol, two steroisomers were obtained by column chromatography, eluting with 15-30% gradient of ethyl acetate (containing 0.2% acetic acid) in hexanes. The first fraction, 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1s,4s)-4-(trifluoromethyl)cyclohexyl)oxy)- benzamide, colorless solid (0.07 g, 5%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 8.11(d, J = 8.1 Hz, 1H), 6.71 (d, J = 13.8 Hz, 1H), 4.35-4.22 (m, 1H), 3.42 (s, 3H), 2.31-2.03 (m, 4H), 1 .69-1 .42 (m, 5H); MS (ES -) m/z: 416.1, 418. 1 (M - 1). The second fraction, 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((1r,4r)-4-(trifluoromethyl)-cyclohexyl)-oxy)benzamide, colorless solid (0.59 g, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s,1H), 8.12 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 13.8 Hz, 1H), 4.71 (dd, J = 2.4, 2.7 Hz, 1H), 3.42 (s, 3H), 2.22-2.03 (m, 3H), 1.87-1.56 (m, 6H); MS (ES-) m/z: 416.1, 418.1 (M - 1).

[0470] EXAMPLE 38

[0471] Synthesis of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)-*N*-(methylsulfonyl)benzamide

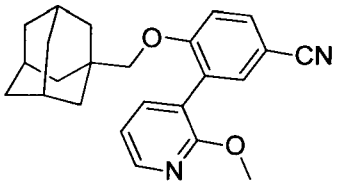


[0472] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile



[0473] To a mixture of adamantan-1-ylmethanol (12.47 g, 75.00 mmol) in anhydrous tetrahydrofuran (100 mL) was added sodium hydride (60% w/w in mineral oil, 3.30 g, 82.50 mmol) at 0 °C. The resulting mixture was stirred at ambient temperature for 2 h, followed by the addition of 4-fluoro-3-bromobenzonitrile (15.00 g, 75.00 mmol). Stirring was continued at ambient temperature for 17 h, cooled to 0 °C and quenched with saturated ammonium chloride solution (20 mL). The volatiles were removed by evaporation *in vacuo*. The residue was washed with water and diethyl ether to give the title compound as a pale yellow solid (21.00 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.78 (m, 1H), 7.56-7.51 (m, 1H), 6.88-6.84 (m, 1H), 3.57 (s, 3H), 2.02 (br s, 3H), 1.73-1.55 (m, 12H).

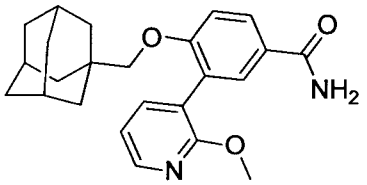
[0474] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile



[0475] A reaction mixture of 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile (1.04 g, 3.00 mmol), potassium carbonate (1.00 g, 7.20 mmol) and (2-methoxypyridin-3-yl)boronic acid (0.92 g, 6.00 mmol) in dioxane (30 mL) was degassed three times with nitrogen, then tetrakis(triphenylphosphine)palladium(0) (0.18 g, 0.15 mmol) was added and the reaction mixture was degassed three further times with nitrogen. The resulting mixture was heated at 90 °C for 19 h, and then the reaction was cooled to ambient temperature, (2-methoxypyridin-3-yr)boronic acid (0.46 g, 3.00 mmol) and tetrakis(triphenylphosphfne)-pailadium(0) (0.09 g, 0.08 mmol) were added and the reaction was degassed three times with nitrogen and heated at 90 °C for further 7 h. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate (200 mL) and washed with water and brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (15% ethyl acetate in

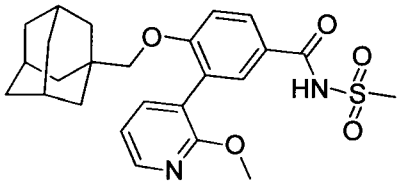
hexanes) afforded the title compound as a colorless solid (1.11 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.16 (m, 1H), 7.62-7.48 (m, 3H), 6.96-6.91 (m, 2H), 3.87 (s, 3H), 3.48 (s, 2H), 1.89 (br s, 3H), 1.68-1.35 (m, 12H); MS (ES+) m/z: 375.2, (M + 1).

[0476] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide



[0477] To a solution of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile (1.15 g, 3.07mmol) in dimethylsulfoxide (25 mL) and methylene chloride (25 mL) was added potassium carbonate (0.85 g, 6.15 mmol) followed by addition of 35% hydrogen peroxide aqueous solution (5.30 mL, 61.60 mmol) dropwise. The mixture was stirred at ambient temperature for 4 h, the volatiles were removed by evaporation *in vacuo.* The residue was diluted with water (100 mL). The precipitate was collected by filtration and washed with water to give the title compound as a colorless solid (0.97g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.15 (m, 1H), 7.84-7.79 (m, 1H), 7.71-7.69 (m, 1H), 7.54-7.50 (m, 1H), 6.95-6.91 (m, 2H), 5.85 (br s, 2H), 3.87 (s, 3H), 3.49 (s, 2H), 1.89 (br s, 3H), 1.68-1.37 (m, 12H); MS (ES+) m/z: 393.2 (M + 1).

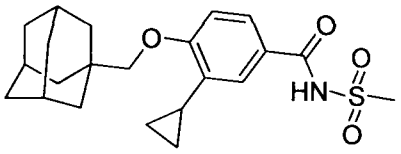
[0478] Step 4. Preparation of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)-*N*-(methylsulfonyl)benzamide



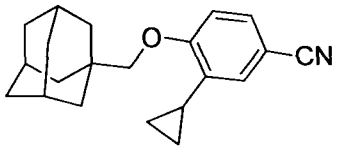
[0479] To a solution of 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide (0.39 g, 1.00 mmol) in tetrahydrofuran (30 mL) was added sodium hydride (0.09 g, 2.25 mmol). The reaction mixture was stirred at ambient temperature for 2 h, methanesulfonyl chloride (0.12 mL, 1.54 mmol) was added; stirring was continued for 46 h at ambient temperature and quenched by addition of 5% hydrochloric acid (1.0 mL). Diluted with ethyl acetate (100 mL) and washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo.* Purification of the residue by column chromatography using 10% to 50% gradient ethyl acetate in hexanes to afford the title compound as a colorless solid (0.13 g, 27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.21-8.17 (m, 1H), 7.88-7.83 (m, 1H), 7.78-7.65 (m,1H), 7.55-7.50 (m, 1H), 7.00-6.93 (m, 2H), 3.88 (s, 3H), 3.53 (s, 2H), 3.40 (s, 3H), 1.90 (br s, 3H), 1.69-1.31 (m, 12H); MS (ES-) m/z: 469.1 (M - 1).

[0480] EXAMPLE 39

[0481] Synthesis of 4-(adamantan-1-ylmethoxy)-3-cyclopropyl-*N*-(methylsulfonyl)benzamide

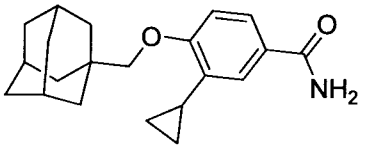


[0482] Step 1. preparation of 4-(adamantan-1-ylmethoxy)-3-cyclopropylbenzonitrile



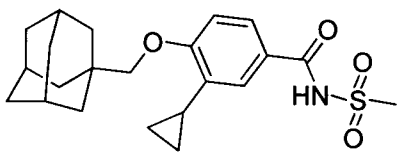
[0483] A solution of 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile (6.93 g, 20.00 mmol), cyclopropylboronic acid (2.58 g, 30.00 mmol) and potassium phosphate (19.10 g, 90.00 mmol) in toluene (100 mL) and water (5 mL) was bubbled with a nitrogen atmosphere for 10 min, tricyclohexylphosphine tetrafluoroborate (0.74 g, 2.00 mmol) and palladium acetate (0.23 g, 1.00 mmol) was added to this reaction mixture. The reaction mixture was heated to 100 °C for 18 h and then cooled to ambient temperature. Water (50 mL) was added and the mixture, extracted with ethyl acetate (100 mL x 3), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was titrated in methanol (50 mL), the solid was filtered and dried to give the title compound as a colorless solid (5.70 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 1H), 7.11-7.10 (m, 1H), 6.82-6.78 (m, 1H), 3.52 (s, 2H), 2.16-1.98 (m, 4H), 1.00-1.64 (m, 12H), 0.99-0.91 (m, 2H), 0.66-0.59 (m, 2H); MS (ES+) m/z: 308.2 (M + 1).

[0484] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-3-cyclopropylbenzamide



[0485] Following the procedure as described in Example 38 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile with 4-(adamantan-1-ylmethoxy)-3-cyclopropylbenzonitrile, the title compound was obtained as a colorless solid (0.48 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.53 (m, 1H), 7.37-7.35 (m, 1H), 6.81-6.76 (m,1H), 5.69 (br s, 2H), 3.55 (s, 2H), 2.19-2.09 (m, 1H), 2.04 (br s, 3H), 1.90-1.67 (m, 12H), 0.98-0.91 (m, 2H), 0.73-0.66 (m, 2H); MS (ES+) m/z: 326.2 (M + 1).

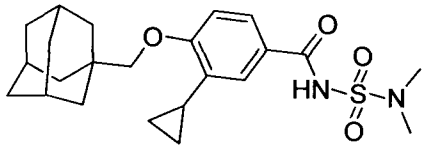
[0486] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-3-cyclopropyl-*N*- (methylsulfonyl)benzamide



[0487] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3- (2-methoxypyridin-3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-3-cyclopropyl- benzamide, the title compound was obtained as a colorless solid (0.36 g, 18%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.62-7.57 (m, 1H), 7.36-7.34 (m, 1H), 6.85-6.80 (m, 1H), 2.58 (s, 2H), 3.41 (s, 3H), 2.19-2.09 (m, 1H), 2.02 (br s, 3H), 1.79-1.52 (m, 12H), 0.99-0.91 (m, 2H), 0.71-0.64 (m, 2H); MS (ES-) m/z: 402.3 (M - 1).

[0488] EXAMPLE 40

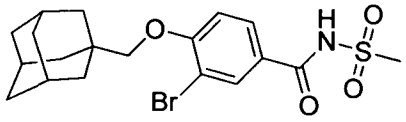
[0489] Synthesis of 4-(adamantan-1-ylmethoxy)-3-cyclopropyl-*N*- (*N,N*-dimethylsulfamoyl)benzamide



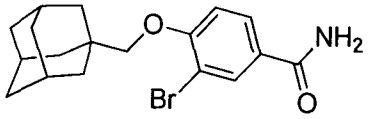
[0490] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin- 3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-3-cyclopropylbenzamide and methanesulfonyl chloride with dimethylsulfamoyl chloride, the title compound was obtained as a colorless solid (0.19 g, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.64-7.56 (m, 1H), 7.41-7.35 (m, 1H), 6.85-6.77 (m, 1H), 3.57 (s, 2H), 3.01 (s, 6H), 2.19-2.08 (m, 1H), 2.02 (br s, 3H), 1.79-1.58 (m, 12H), 0.99-0.91 (m, 2H), 0.71-0.64 (m, 2H); MS (ES-) m/z: 431.2 (M - 1).

[0491] EXAMPLE 41

[0492] Synthesis of 4-(adamantan-1-ylmethoxy)-3-bromo-*N*-(methylsulfonyl)benzamide

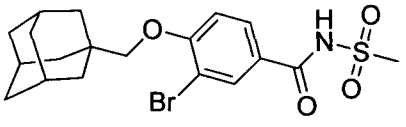


[0493] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-3-bromobenzamide



[0494] Following the procedure as described in Example 38 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile with 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile, the title compound was obtained as a colorless solid (1.80 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99-7.97 (m, 1H), 7.74-7.69 (m, 1H), 6.87-6.83 (m, 1H), 5.86 (br s, 2H), 3.57 (s, 2H), 2.02 (br s, 3H), 1.79-1.58 (m, 12H); MS (ES+) m/z: 364.1, 366.1 (M +1).

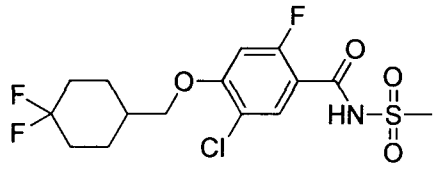
[0495] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-3-bromo-*N*-(methylsulfonyl)benzamide



[0496] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-3-bromobenzamide, the title compound was obtained as a colorless solid (0.17 g, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.09-8.06 (m, 1H), 7.80-7.72 (m, 1H), 6.93-6.87 (m, 1H), 3.61 (s, 2H), 3.43 (s, 3H), 2.04 (br s, 3H), 1.81-1.53 (m, 12H); MS(ES-) m/z: 442.2, 440.2 (M - 1).

[0497] EXAMPLE 42

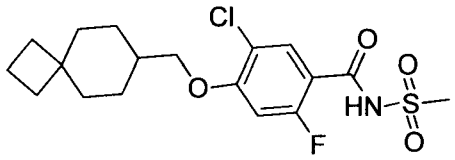
[0498] Synthesis of 5-chloro-4-((4,4-difluorocyclohexyl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0499] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (4,4-difluorocyclohexyl)- methanol, the title compound was obtained as a colorless solid (0.31 g, 15%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 13.5 Hz, 1H), 3.92 (d, J = 6.3 Hz, 2H), 3.42 (s, 3H), 2.25-2.11 (m, 2H), 2.04-1.93 (m, 3H), 1.91-1.69 (m, 2H), 1.54-1.40 (m, 2H); MS (ES-) m/z: 398.1, 400.1 (M - 1).

[0500] EXAMPLE 43

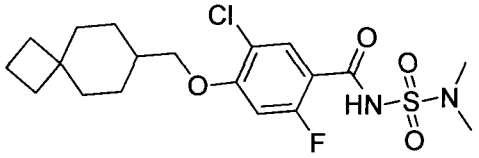
[0501] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[3.5]nonan-7- ylmethoxy)benzamide



[0502] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with spiro[3.5]nonan- 7-ylmethanol, the title compound was obtained as a colorless solid (0.15 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 13.8 Hz, 1H), 3.84 (d, J = 6.0 Hz, 2H), 3.42 (s, 3H), 1.85-1.65 (m, 11H), 1.36-1.11(m, 4H); MS (ES-) m/z: 402.1, 404.1 (M - 1).

[0503] EXAMPLE 44

[0504] Synthesis of 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluoro-4- (spiro[3.5]nonan-7-ylmethoxy)-benzamide

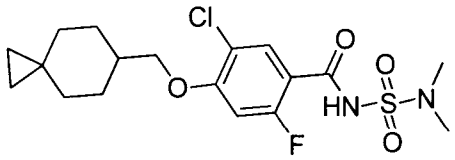


[0505] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-

(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with spiro[3.5]nonan-7-ylmethanol, the title compound was obtained as a colorless solid (0.26 g, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 13.5 Hz, 1H), 3.82 (d, J = 6.3 Hz, 2H), 3.01 (s, 6H), 1.89-1.65 (m, 11H), 1.35-1.04 (m, 4H); MS (ES-) m/z: 431.2, 433.2 (M - 1).

[0506] EXAMPLE 45

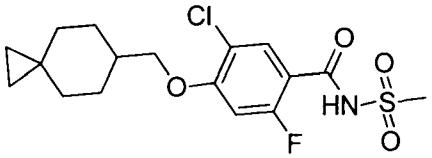
[0507] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



[0508] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with spiro[2.5]octan-6-ylmethanol, the title compound was obtained as a colorless solid (0.17 g, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65-8.59 (m, 1H), 8.06 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 13.8 Hz, 1H), 3.88 (d, J = 6.3 Hz, 2H), 3.01 (s, 6H), 1.95-1.72 (m, 5H), 1.34-1.21 (m, 2H), 0.96-0.90 (m, 2H), 0.33-0.26 (m, 2H), 0.22-0.16 (m, 2H); MS (ES-) m/z: 417.2, 419.2 (M - 1).

[0509] EXAMPLE 46

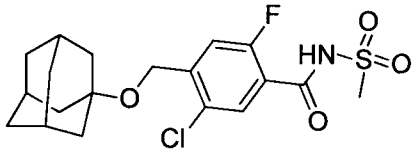
[0510] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]octan- 6-ylmethoxy)benzamide



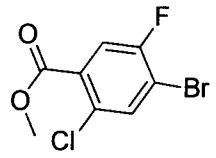
[0511] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with spiro[2.5]octan-6-ylmethanol, the title compound was obtained as a colorless solid (0.21 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 8.07 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 13.8 Hz, 1H), 3.89 (d, J = 6.3 Hz, 2H), 3.40 (s, 3H), 1.96-1.71 (m, 5H), 1.33-1.19 (m, 2H), 0.99-0.86 (m, 2H), 0.33-0.26 (m, 2H), 0.23-0.15 (m, 2H); MS (ES-) m/z: 388.2, 390.2 (M - 1).

[0512] EXAMPLE 47

[0513] Synthesis of 4-((adamantan-1-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide

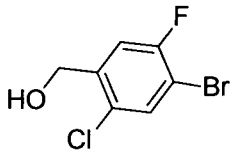


[0514] Step 1. Preparation of methyl 4-bromo-2-chloro-5-fluorobenzoate



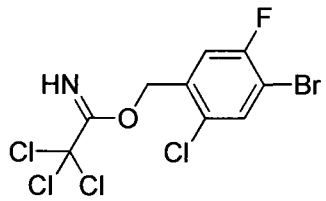
[0515] To a solution of 4-bromo-2-chloro-5-fluorobenzoic acid (25.40 g, 100.00 mmol) in methanol (300 mL) was added thionyl chloride (0.8 mL, 11.00 mmol) over 5 min at 0 °C. The reaction mixture was heated to reflux for 8 h and then neutralized by slow addition of sodium bicarbonate (5.0 g) at 0 °C. The solid was filtered out and washed with ethyl acetate (50 mL), the combined filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow solid (24.7 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.60 (m, 2H), 3.91 (s, 3H).

[0516] Step 2. Preparation of (4-bromo-2-chloro-5-fluorophenyl)methanol



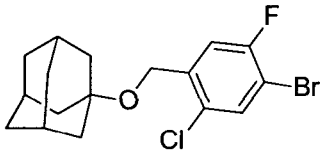
[0517] To a solution of methyl 4-bromo-2-chloro-5-fluorobenzoate (18.00 g, 67.28 mmol) in tetrahydrofuran (100 mL) was added methanol (3.0 mL, 74.15 mmol), followed by the addition of lithium borohydride solution (4.0 M in tetrahydrofuran, 33.7 mL, 134.80 mmol) at 0 °C over 30 min. The reaction mixture was stirred for further 10 min at 0 °C, and then at ambient temperature for 20 h; 5% sodium hydroxide solution (100 mL) was added to the reaction mixture slowly at 0 °C. After stirring for 30 min. the reaction mixture was extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine, and concentrated *in vacuo* to afford the title compound as a pale yellow solid (16.00 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 6.0 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 4.69 (s, 2H), 2.08 (s, 1H).

[0518] Step 3. Preparation of 4-bromo-2-chloro-5-fluorobenzyl 2,2,2-trichloroacetimidate



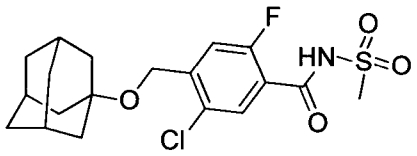
[0519] To a solution of (4-bromo-2-chloro-5-fluorophenyl)methanol (3.95 g, 16.49 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.5 mL, 3.34 mmol) in methylene chloride (30 mL) was added trichloroacetonitrile (, 2.50 mL, 24.93 mmol) over 5 min at 0 °C, stirring was continued for 4 h at 0 °C. After concentrated *in vacuo*, the residue was purified by column chromatography eluting with 5% ethyl acetate in hexanes to give 4-bromo-2- chloro-5-fluorobenzyl 2,2,2-trichloroacetimidate as a colorless solid (5.80 g, 91%): δ 8.49 (s, 1H), 7.59 (d, J = 6.3 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 5.37 (s, 2H).

[0520] Step 4. Preparation of 1-((4-bromo-2-chloro-5-fluorobenzyl)oxy)adamantane



[0521] To a solution of 4-bromo-2-chloro-5-fluorobenzyl 2,2,2-trichloroacetimidate (3.95 g, 16.49 mmol) and 1-adamantanol (0.65 g, 4.26 mmol) in methylene chloride (15 mL) and cyclohexane (30 mL) was added trifluoromethanesulfonic acid (0.04 mL, 0.45 mmol) at 0 °C. The reaction mixture was stirred for 56 h at ambient temperature and quenched by addition of saturated sodium bicarbonate solution (10 mL), and then diluted with methylene chloride (100 mL). The organic layer was separated and washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) and recrystalization from methanol afforded 1-((4-bromo-2-chloro-5-fluorobenzyl)- oxy)adamantane as a colorless solid (0.70 g, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 6.3 Hz, 1H), 7.37 (d, J = 9.3 Hz, 1H), 4.48 (s, 2H), 2.16 (br s, 3H), 1.82-1.80 (m, 6H), 1.70-1.55 (m, 6H).

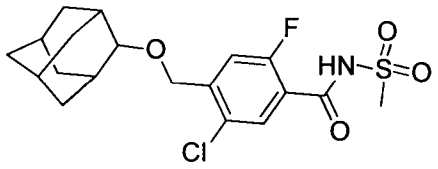
[0522] Step 5. Preparation of 4-((adamantan-1-yloxy)methyl)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide



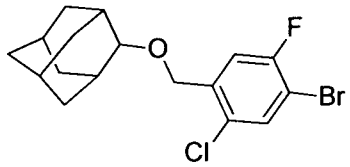
[0523] A mixture of 1-((4-bromo-2-chloro-5-fluorobenzyl)oxy)adamantane (0.37 g, 1.00 mmol), methanesulfonamide (0.29 g, 3.00 mmol), molybdenumhexacarbonyl (0.27 g, 1.00 mmol) and triethylamine (0.6 mL, 4.30 mmol) in dioxane was purged with nitrogen for 5 min, xantphos (0.10 g, 0.18 mmol) and palladium acetate (0.02 g, 2.00 mmol) were added to the reaction mixture. The reaction mixture was heated at 100 °C for 1 h under microwave irradiation (300 psi) and then cooled to ambient temperature, diluted with methylene chloride (100 mL) and saturated ammonium chloride (20 mL). The organic layer was washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% gradient ethyl acetate in hexanes) afforded the title compound as a colorless solid (0.12 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 8.01 (d, J = 6.9 Hz, 1H), 7.49 (d, J = 12.9 Hz, 1H), 4.57 (s, 2H), 3.41 (s, 3H), 2.18 (br s, 3H), 1.84-1.81 (m, 6H), 1.70-1.54 (m, 6H); MS (ES-) m/z: 414.1, 416.1 (M - 1).

[0524] EXAMPLE 48

[0525] Synthesis of 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide

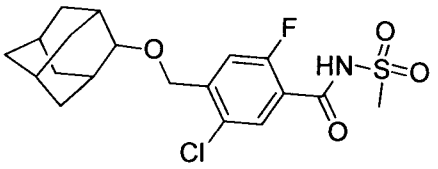


[0526] Step 1. Preparation of 2-((4-bromo-2-chloro-5-fluorobenzyl)oxy)adamantane



[0527] Following the procedure as described in Example 47 step 4 and making variations as required to replace 1-adamantanol with 2-adamantanol, the title compound was obtained as a colorless solid (1.07 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 6.0 Hz, 1H), 7.40 (d, J = 9.3 Hz, 1H), 4.49 (s, 2H), 3.57 (br s, 1H), 2.55-1.49 (m, 14H); MS (ES+) m/z: 373.0, 375.0 (M + 1).

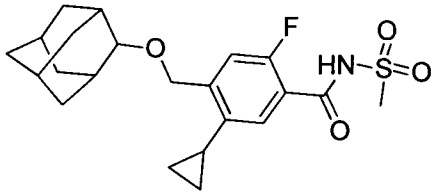
Step 2. Preparation of 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)- benzamide



[0528] Following the procedure as described in preparation of Example 47 step 5 and making variation as required to replace 1-((4-bromo-2-chloro-5- fluorobenzyl)oxy)adamantane with 2-((4-bromo-2-chloro-5-fluorobenzyl)oxy)adamantane, the title compound was obtained as a colorless solid (0.68 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 8.02 (d, J = 6.9 Hz, 1H), 7.52 (d, J = 12.9 Hz, 1H), 4.58 (s, 2H), 3.60 (br s, 1H), 3.41 (s, 3H), 2.11-1.50 (m, 14H); MS (ES-) m/z: 414.2, 416.2 (M - 1).

[0529] EXAMPLE 49

[0530] Synthesis of 4-((adamantan-2-yloxy)methyl)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide

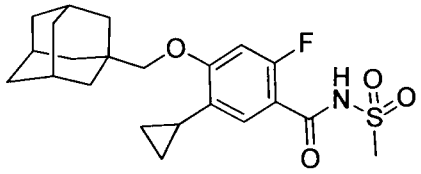


[0531] To a solution of 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)-benzamide (0.30 g, 0.72 mmol), cyclopropylboronic acid (0.40 g, 4.65 mmol) and potassium phosphate (2.55 g, 12.00 mmol) in toluene (10 mL) and water (0.5 mL) was bubbled with a nitrogen atmosphere for 10 min, tricyclohexylphosphine tetrafluoroborate (0.17 g, 0.48 mmol) and palladium acetate (0.05 g, 0.22

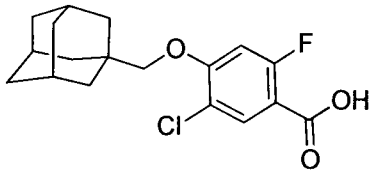
mmol) was added to this reaction mixture. The reaction mixture was heated to 100 °C for 18 h under a nitrogen atmosphere and then cooled to ambient temperature. 5% aqueous hydrochloric acid (20 mL) was added and the mixture was extracted with ethyl acetate (100 mL x 3), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% gradient ethyl acetate in hexanes) afforded the title compound as a colorless solid (0.19 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 13.5 Hz, 1H), 4.71(s, 2H), 3.60 (br s, 1H), 3.41 (s, 3H), 2.16-2.03 (m, 4H), 1.90-1.51 (m, 11H), 0.97-0.90 (m, 2H), 0.68-0.62 (m, 2H); MS (ES-) m/z: 420.35 (M - 1).

[0532] EXAMPLE 50

[0533] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*- (methylsulfonyl)benzamide

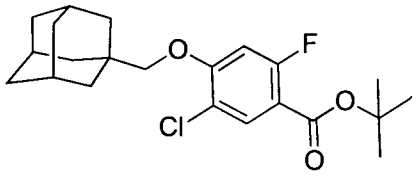


[0534] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid



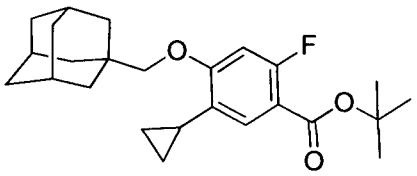
[0535] To a solution of 1-adamantane methanol (28.50 g, 171.40 mmol) in anhydrous dimethylsulfoxide (300 ml) in a 2 L two necked flask fitted with a mechanic stirrer was added potassium *tert*-butoxide (48.10 g, 428.50 mmol) and the suspension was stirred at ambient temperature for 30 minutes. 5-chloro-2,4-difluorobenzoic acid (33.00 g, 171.40 mmol) was added to the reaction mixture in 5 minutes. During this period, the mixture became hot (do not use ice bath) and yellow gummy solid was formed. Stirring was continued for 2 h. The reaction mixture was acidified to pH = 1 with cold aqueous hydrochloric acid solution (1N), followed by addition of 25% aqueous ammonium chloride solution (400 mL). The solid was filtered and washed with water and a mixture of hexanes/diethyl ether (3/1, v/v); dried to give crude product (~75% *p*-substituted and ~25% *o*-substituted by 1H NMR; 95% *p*-substituted by HPLC at 254 nm) as off-white solid (32 g, 55%), which was used for next step without further purification. Additional 15 g of light yellow solid (87% by HPLC) was obtained from the filtrate. The pure product can be obtained by recrystallization from 2-propanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 12.7 Hz, 1H), 3.71 (s, 2H), 1.99 (s, 3H), 1.74-1.63 (m, 12H);

[0536] Step 2. Preparation of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoate



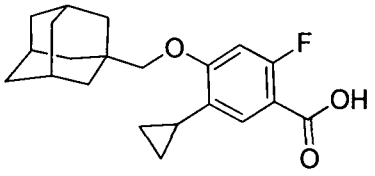
[0537] To a suspension of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid (30.00 g, 88.54 mmol) and *N,N*-dimethylpyridin-4-amine (0.50g, 4.16 mmol) in *tert*-butanol (200 mL) was added di-*tert*-butyldicarbonate (40.60 g, 186.02 mmol). The reaction mixture was heated at 50 °C for 6 h. Additional di-*tert*-butyldicarbonate (20.30 g, 93.01 mmol) was added; stirring was continued for 17 h at 50 °C and concentrated *in vacuo*. The residue was titrated in methanol (100 mL), the solid was collected by filtration and dried to give the title compound as a colorless solid (25.00 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 12.3 Hz, 1H), 3.53 (s, 2H), 2.01 (s, 3H), 1.78-1.61 (m, 12H), 1.55 (s, 9H).

[0538] Step 3. Preparation of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoate



[0539] To a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoate (15.80 g, 40.00 mmol), cyclopropylboronic acid (5.16 g, 60.00 mmol) and potassium phosphate (38.20 g, 180.00 mmol) in toluene (160 mL) and water (8 mL) was bubbled with a nitrogen atmosphere for 10 min, tricyclohexylphosphine tetrafluoroborate (1.47 g, 3.99 mmol) and palladium acetate (0.45 g, 2.00 mmol) was added to this reaction mixture. The reaction mixture was heated to 100 °C for 18 h and then cooled to ambient temperature. Water (100 mL) was added and the mixture was extracted with ethyl acetate (100 mL x 3), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded the title compound as a colorless solid (13.8 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 12.9 Hz, 1H), 3.49 (s, 2H), 2.05-1.95 (m, 4H), 1.78-1.61 (m, 12H), 1.55 (s, 9H), 0.91-0.84 (m, 2H), 0.64-0.58 (m, 2H).

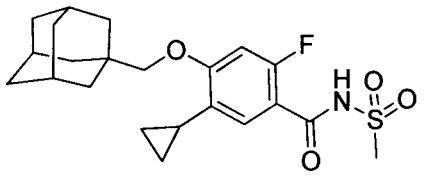
[0540] Step 4. Preparation of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid



[0541] To a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoate (13.80 g, 34.45 mmol) in dichloromethane (50 mL), was added trifluoroacetic acid (25 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*. The residue was titrated in

methanol (50 mL), the solid was collected by filtration and dried to give the title compound as a colorless solid (10.10 g, 85%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 13.2 Hz, 1H), 3.59 (s, 2H), 2.04-1.92 (m, 4H), 1.71-1.58 (m, 12H), 0.91-0.83 (m, 2H), 0.59-0.52 (m, 2H).

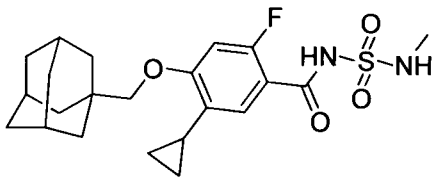
[0542] Step 5. Preparation of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*- (methylsulfonyl)-benzamide



[0543] To a stirred solution of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid (0.52 g, 1.50 mmol) in dichloromethane (40 mL) and tetrahydrofuran (40 mL) were added *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.43 g, 2.24 mmol), and 4-(dimethylamino)pyridine (0.42 g, 3.43 mmol). The reaction mixture was stirred at ambient temperature for 10 min, methanesulfonamide (0.22 g, 2.28 mmol) was added and stirring continued at ambient temperature for 36 h. 5% aqueous hydrochloric acid (10 mL) were added and then diluted with ethyl acetate (200 mL), washed with water and brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% gradient ethyl acetate in hexanes) afforded the title compound as a colorless solid (0.45 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 16.2 Hz, 1H), 7.58 (d, J = 9.3 Hz, 1H), 6.56 (d, J = 14.7 Hz, 1H), 3.56 (s, 2H), 3.41 (s, 3H), 2.09-2.00 (m, 4H), 1.81-1.58(m, 12H), 0.99-0.91 (m, 2H), 0.70-0.62 (m, 2H); MS (ES-) m/z: 420.2 (M - 1).

[0544] EXAMPLE 51

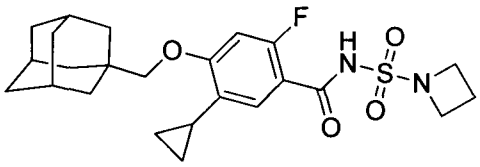
[0545] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[0546] Following the procedure as described in preparation of Example 50 step 5 and making variation as required to replace methanesulfonamide with (methylsulfamoyl)amine, the title compound was obtained as a colorless solid (0.17 g, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 15.9Hz, 1H), 7.56 (d, J = 9.0Hz, 1H), 6.56 (d, J = 14.4Hz, 1H), 5.35-5.22 (m, 1H), 3.55 (s, 2H), 2.76 (d, J = 5.4Hz,, 3H), 2.09-1.99 (m, 4H), 1.81-1.59(m, 12H), 0.99-0.91 (m, 2H), 0.70-0.62 (m, 2H); MS (ES-) m/z: 435.3 (M - 1).

[0547] EXAMPLE 52

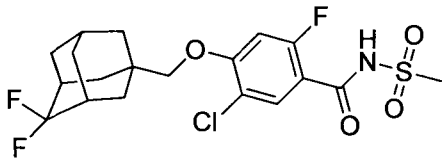
[0548] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide



[0549] Following the procedure as described in preparation of Example 50 step 5 and making variation as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.17 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.58 (d, J = 9.0Hz, 1H), 6.54 (d, J = 14.4Hz, 1H), 4.22 (t, J = 7.8Hz, 4H), 3.54 (s, 2H), 3.00-2.19 (m, 2H), 2.08-1.97 (m, 4H), 1.79-1.57(m, 12H), 0.96-0.89 (m, 2H), 0.68-0.62 (m, 2H); MS (ES-) m/z: 461.3 (M - 1).

[0550] EXAMPLE 53

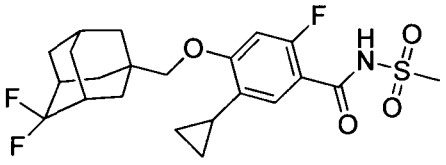
[0551] Synthesis of 5-chloro-4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0552] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 4,4-difluoro-1-(hydroxymethyl)adamantane, the title compound was obtained as a colorless solid (0.47 g, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 8.06 (d, J = 8.4Hz, 1H), 6. 65 (d, J = 13.8Hz, 1H), 3.61 (s, 2H), 3.39 (s, 3H), 2.28 (br s, 2H), 2.05-1.87 (m, 5H), 1.78-1.66 (m, 6H); MS (ES-) m/z: 450.2, 452.2 (M - 1).

[0553] EXAMPLE 54

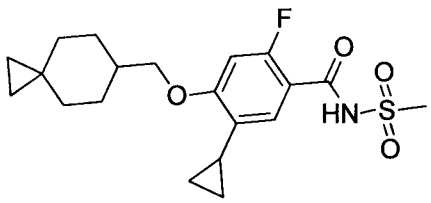
[0554] Synthesis of 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide

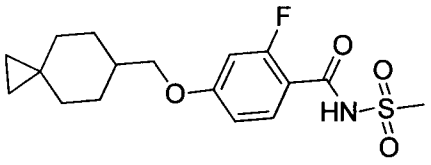


[0555] Following the procedure as described in Example 49 and making variation as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide with 5-chloro-4-((4,4-difluoroadamantan-1-yl)methoxy)-2- fluoro-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.32 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 7.59 (d, J = 9.0Hz, 1H), 6.53 (d, J = 14.1Hz, 1H), 3.59 (s, 2H), 3.39 (s, 3H), 2.28 (br s, 2H), 2.08-1.92 (m, 6H), 1.53-1.51 (m, 6H), 0.97-0.89 (m, 2H), 0.66-0.60 (m, 2H); MS (ES-) m/z: 456.2 (M - 1).

[0556] EXAMPLE 55

[0557] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]octan-6-ylmethoxy)benzamide and 2-fluoro-*N*-(methylsulfonyl)-4- (spiro[2.5]octan-6-ylmethoxy)benzamide

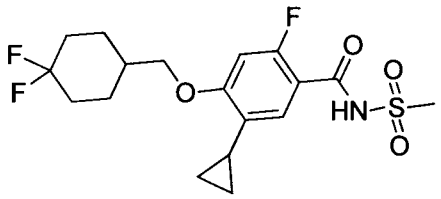




[0558] Following the procedure as described in Example 49 and making variation as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro- *N*-(methylsulfonyl)benzamide with 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]- octan-6-ylmethoxy)benzamide, two compounds were obtained by column chromatography, eluting with 10-30% gradient of ethyl acetate (containing 0.2% acetic acid) in hexanes. The first fraction, 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]octan-6- ylmethoxy)benzamide, colorless solid (0.25 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 7.54 (d, J = 9.3 Hz, 1H), 6.56 (d, J = 14.4 Hz, 1H), 3.85 (d, J = 6.0 Hz, 2H), 3.39 (s, 3H), 2.08-1.72 (m, 6H), 1.36-1.22 (m, 2H), 0.96-0.88 (m, 4H), 0.67-0.62 (m, 2H), 0.33-0.15 (m, 4H); MS (ES-) m/z: 394.3 (M - 1). The second fraction, 2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]octan-6-ylmethoxy)benzamide, colorless solid (0.1 g, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 8.05-7.98 (m, 1H), 6.84-6.79 (m, 1H), 6.68-6.61 (m, 1H), 3.84 (d, J = 6.0 Hz, 2H), 3.40 (s, 3H), 1.91-1.69 (m, 5H), 1.30-1.16 (m, 2H), 0.97-0.89 (m, 2H), 0.33-0.15 (m, 4H); MS (ES-) m/z: 354.3 (M - 1).

[0559] EXAMPLE 56

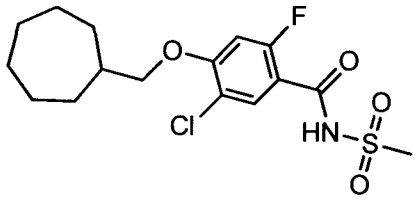
[0560] Synthesis of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0561] Following the procedure as described in Example 49 and making variation as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide with 5-chloro-4-((4,4-difluorocyclohexyl)methoxy)-2- fluoro-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.04 g, 13%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 15.0 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 6.55 (d, J = 14.4 Hz, 1H), 3.88 (d, J = 9.0 Hz, 2H), 3.39 (s, 3H), 2.25-2.11 (m, 2H), 2.04-1.66 (m, 6H), 1.54-1.41 (m, 2H), 0.97-0.89 (m, 2H), 0.67-0.61 (m, 2H); MS (ES-) m/z: 404.1 (M - 1).

[0562] EXAMPLE 57

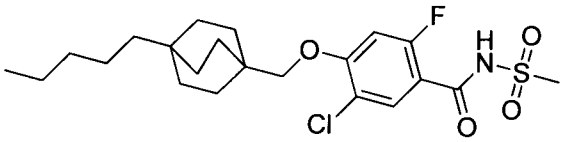
[0563] Synthesis of 5-chloro-4-(2-cycloheptylethoxy)-2-fluoro-N-(methylsulfonyl)benzamide



[0564] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with cycloheptylmethanol, the title compound was obtained as a colorless solid (0.12 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.5 Hz, 1H), 3.91 (d, J = 6.5 Hz, 2H), 3.31 (s, 3H), 1.98-1.21 (m, 13H); MS (ES-) m/z 376.1, 378.1 (M - 1).

[0565] EXAMPLE 58

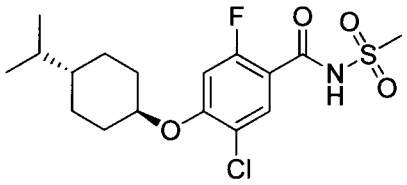
[0566] Synthesis of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-((4-pentylbicyclo[2.2.2]octan-1-yl)methoxy)benzamide



[0567] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (4-pentylbicyclo[2.2.2]octan-1-yl)- methanol, the title compound was obtained as a colorless solid (0.17 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 3.76 (s, 2H), 3.35 (s, 3H), 1.51-1.06 (m, 20H), 0.85 (t, J = 6.9 Hz, 3H); MS (ES-) m/z 458.2, 460.1 (M - 1).

[0568] EXAMPLE 59

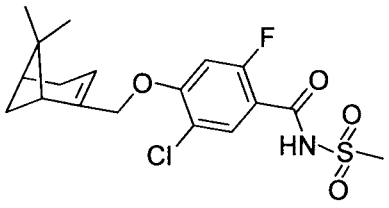
[0569] Synthesis of *trans*-5-chloro-2-fluoro-4-((4-isopropylcyclohexyl)oxy)-*N*-(methylsulfonyl)benzamide



[0570] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with *trans*-4-isopropylcyclohexanol, the title compound was obtained as a colorless solid (0.14 g, 36%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 12.8 Hz, 1H), 4.49 (m, 1H), 3.35 (s, 3H), 2.11-2.08 (m, 2H), 1.75-1.71 (m, 2H), 1.48-1.13 (m, 6H), 0.86 (d, J = 6.8 Hz, 6H); MS (ES-) m/z 390.1, 392.1 (M - 1).

[0571] EXAMPLE 60

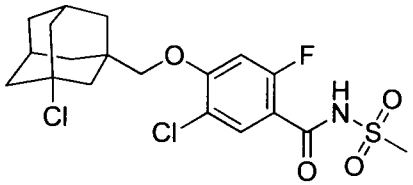
[0572] Synthesis of 5-chloro-4-(((*1R,5S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0573] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with ((*1R,5S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methanol, the title compound was obtained as a colorless solid (0.15 g, 37%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 12.5 Hz, 1H), 5.71-5.70 (m ,1H), 4.64 (s, 2H), 3.35 (s, 3H), 2.43-2.33 (m, 5H), 1.27 (s, 3H), 1.10-1.08 (m, 1H), 0.76 (m, 3H); MS (ES-) m/z 400.1, 402.3 (M - 1).

[0574] EXAMPLE 61

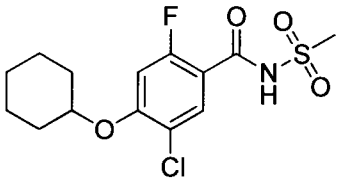
[0575] Synthesis of 5-chloro-4-((3-chloroadamantan-1-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0576] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 3-chloroadamantan-1-yl methanol, the title compound was obtained as a colorless solid (0.26 g, 29%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 3.82 (s, 2H), 3.35 (s, 3H), 2.22-2.04 (m, 8H), 1.65-1.54 (m, 6H); MS (ES-) m/z 448.0, 450.0 (M - 1).

[0577] EXAMPLE 62

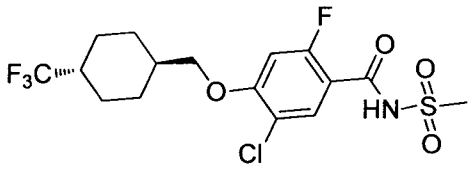
[0578] Synthesis of 5-chloro-4-(cyclohexyloxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0579] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with cyclohexanol, the title compound was obtained as a colorless solid (0.03 g, 9%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 12.7 Hz, 1H), 4.64-4.57 (m, 1H), 3.95-3.88 (m, 2H), 3.31 (s, 3H), 1.88-1.82 (m, 2H), 1.69-1.64 (m, 2H), 1.54-1.27 (m, 6H); MS (ES-) m/z 348.1, 350.1 (M - 1).

[0580] EXAMPLE 63

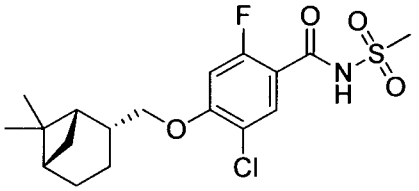
[0581] Synthesis of *trans*-5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0582] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with *trans*-4-(trifluoromethyl)cyclohexyl)- methanol, the title compound was obtained as a colorless solid (0.178 g, 41%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 3.99 (d, J = 6.1 Hz, 2H), 3.35 (s, 3H), 2.29-2.18 (m, 1H), 1.94-1.81 (m, 5H), 1.36-1.09 (m, 4H); MS (ES-) m/z 430.1, 432.1 (M - 1).

[0583] EXAMPLE 64

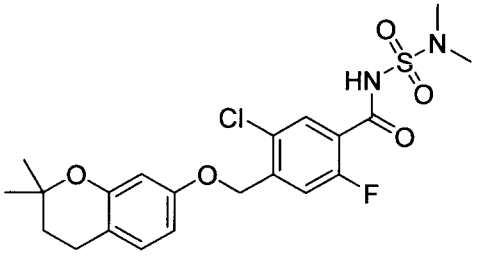
[0584] Synthesis of 5-chloro-4-(((*1S,2R,5S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



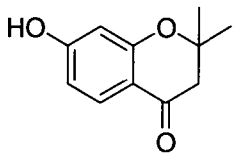
[0585] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with *((1S,2R,5S)*-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methanol, the title compound was obtained as a colorless solid (0.08 g, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 12.5 Hz, 1H), 4.12-4.00 (m, 2H), 3.35 (s, 3H), 2.57-2.04 (m, 1H), 2.10-1.85 (m, 5H), 1.61-1.48 (m, 1H), 1.18 (s, 3H), 1.00 (m, 3H), 0.99-0.95 (m, 1H); MS (ES-) m/z 402.1, 404.1 (M - 1).

[0586] EXAMPLE 65

[0587] Synthesis of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-N-(N,N-dimethylsulfamoyl)-2-fluorobenzamide

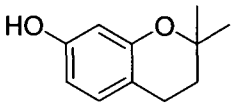


[0588] Step 1. Preparation of 7-hydroxy-2,2-dimethylchroman-4-one



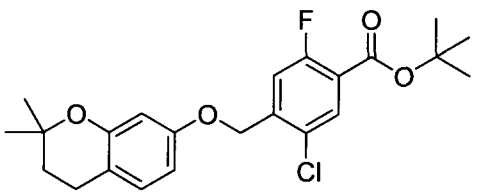
[0589] To a solution of 2,4-dihydroxy acetophenone (6.00 g, 39.4 mmol) and pyrrolidine (15.0 mL, 181 mmol) in toluene (200 mL), acetone (22.9 g, 394 mmol) was added. After heated to reflux for 16 hrs, the solvents were removed and the residue was added HCl (2.0 N, 100 mL) and brine (200 mL) then the mixture was extracted with EtOAc (150 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by SGC (eluting with petroleum ether/ethyl acetate = 6/1) to give target compound (2.56 g, 33%) as a brown yellow solid. LCMS (ESI) m/z: 191.1 $[M-H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 1H), 6.49 (dd, J = 8.5, 2.0 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 2.68 (s, 2H), 1.45 (s, 6H).

Step 2. Preparation of 2,2-dimethylchroman-7-ol



[0590] A mixture of 7-hydroxy-2,2-dimethylchroman-4-one (500 mg, 2.60 mmol) and HCl (conc. 10 mL) in MeOH (30 mL) was stirred at 0 °C for 10 min, then zinc power (300 mg) was added slowly. After stirring at room temperature for 16 hrs, the solvents were removed under reduced pressure and the mixture was extracted with EtOAc (150 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by reverse phase column falsh (28%-35% MeCN in 0.5% NH_4HCO_3) to give target product of 2,2-dimethylchroman-7-ol (290 mg, 62%) as a brown yellow solid. LCMS (ESI) m/z: 177.1 $[M-H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.89 (d, J = 8.0 Hz, 1H), 6.34 (dd, J = 8.5, 2.5 Hz, 1H), 6.27 (d, J = 2.5 Hz, 1H), 4.70 (s, 1H), 2.69 (t, J = 13.5, 7.0 Hz, 2H), 1.77 (t, J = 13.5, 7.0 Hz, 2H), 1.32 (s, 6H).

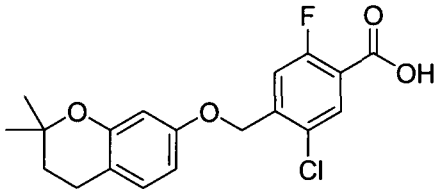
[0591] Step 3. Preparation of tert-butyl 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoate



[0592] A mixture of 2,2-dimethylchroman-7-ol (100 mg, 0.561 mmol), tert-butyl 4-(bromomethyl)-5-chloro-2-fluorobenzoate (191 mg, 0.590 mmol) and potassium carbonate (194 mg, 1.40 mmol) in acetone (30 mL) was stirred at 50 °C for 16 hrs. After cooling to room temperature, the mixture was

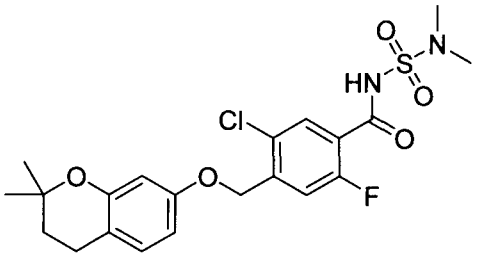
extracted with EtOAc (150 × 5 mL). The combined orgaic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product which was used in next step without further purification (290 mg, crude). LCMS (ESI) m/z: 420.8 $[M+H]^+$.

[0593] Step 4. Preparation of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoic acid



[0594] A mixture of tert-butyl 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoate (290 mg, 0.689 mmol) and trifluoroacetic acid (10 mL) in DCM (10 mL) was stirred at room temperature for 16 hrs. The solvents were removed and the residue was extracted with EtOAc (150 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by reverse phase combiflash (15%-19% MeCN in 0.5% NH_4HCO_3) to give target product of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoic acid (100 mg, 49%) as a white solid. LCMS (ESI) m/z: 364.9 $[M+H]^+$.

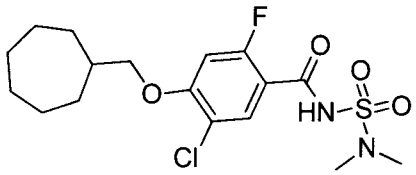
[0595] Step 5. Preparation of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-N-(N,N-dimethylsulfamoyl)-2-fluorobenzamide



[0596] A mixture of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoic acid (50 mg, 0.14 mmol), dimethyl(sulfamoyl)amine (26 mg, 0.21 mmol), N,N-Diisopropylethylamine (54 mg, 0.42 mmol) and 2-(7-aza-1H-benzotriazole-1-yl)- 1,1,3,3-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) in DMF (2.5 mL) was stirred at room temperature for 16 hrs. The mixture was diluted with HCl (2.0 N, 20 mL) and extracted with EtOAc (50 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by reverse phase combiflash (15%-25% MeCN in 0.5% NH_4HCO_3) to give target product (11.8 mg, 18%) as a white solid. LCMS (ESI) Method A: RT = 5.57 min, m/z: 471.2 $[M+H]^+$; ^{1}H-NMR (500 MHz, MeOH-d_4,): δ 7.62 (d, J = 6.0 Hz, 1H), 7.31 (d, J = 10.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.40 (dd, J = 8.0, 2.5 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 5.02 (s, 2H), 2.86 (s, 6H), 2.61 (t, J = 7.0 Hz, 2H), 1.68 (t, J = 7.0 Hz, 2H), 1.20 (s, 6H).

[0597] EXAMPLE 66

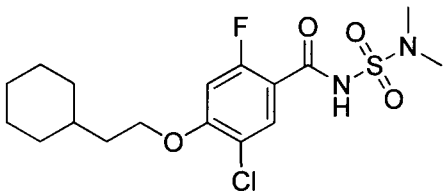
[0598] Synthesis of 5-chloro-4-(cycloheptylmethoxy)-*N*-(*N,N*-dimethylsulfamoyl)- 2-fluorobenzamide



[0599] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with cycloheptylmethanol, the title compound was obtained as a colorless solid (0.08 g, 20%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.24 (d, J = 12.3 Hz, 1H), 3.94 (d, J = 6.6 Hz, 2H), 2.87 (s, 6H), 2.00-1.25 (m, 13H); MS (ES-) m/z 405.1 , 407.1 (M - 1).

[0600] EXAMPLE 67

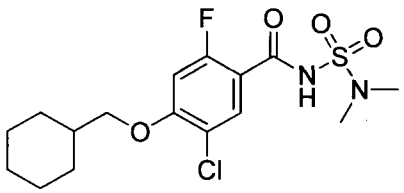
[0601] Synthesis of 5-chloro-4-(2-cyclohexylethoxy)-*N*-(*N,N*-dimethyl- sulfamoyl)-2-fluorobenzamide



[0602] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-cyclohexylethanol, the title compound was obtained as a colorless solid (0.09 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 4.17 (t, J = 6.6 Hz, 2H), 2.87 (s, 6H), 1.76-1.60 (m, 7H), 1.54-1.42 (m, 1H), 1.28-1.11 (m, 3H), 1.02-0.90 (m, 2H); MS (ES-) m/z 405.1 , 407.1 (M - 1).

[0603] EXAMPLE 68

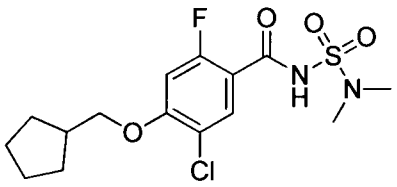
[0604] Synthesis of 5-chloro-4-(2-cyclohexylmethoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2- fluorobenzamide



[0605] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with cyclohexylmethanol, the title compound was obtained as a colorless solid (0.11 g, 28%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 3.96 (d, J = 5.8 Hz, 2H), 2.87 (s, 6H), 1.84-1.62 (m, 6H), 1.30-1.04 (m, 5H); MS (ES-) m/z 391.1 , 393.1 (M - 1).

[0606] EXAMPLE 69

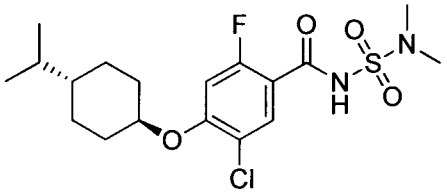
[0607] Synthesis of 5-chloro-4-(cyclopentylmethoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2- fluorobenzamide



[0608] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with cyclopentylmethanol, the title compound was obtained as a colorless solid (0.12 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 2.87 (s, 6H), 2.39-2.29 (m, 1H), 1.82-1.72 (m, 2H), 1.65-1.51 (m, 4H), 1.38-1.30 (m, 2H); MS (ES-) m/z 377.1, 379.1 (M - 1).

[0609] EXAMPLE 70

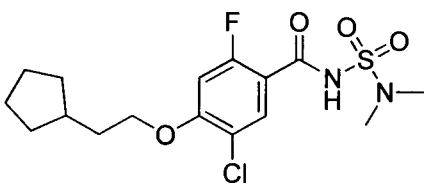
[0610] Synthesis of *trans*-5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-((4-isopropylcyclohexyl)oxy)benzamide



[0611] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N* dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with *trans*-4-isopropylcyclohexanol, the title compound was obtained as a colorless solid (0.10 g, 24%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 12.5 Hz, 1H), 4.53-4.43 (m, 1H), 2.87 (s, 6H), 2.11-2.07 (m, 2H), 1.75-1.71 (m, 2H), 1.50-1.20 (m, 3H), 1.24-1.07 (m, 3H), 0.86 (d, J = 6.8 Hz, 6H); MS (ES-) m/z 419.1, 421.1 (M - 1).

[0612] EXAMPLE 71

[0613] Synthesis of *trans*-5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4- ((4-isopropylcyclohexyl)-oxy)benzamide

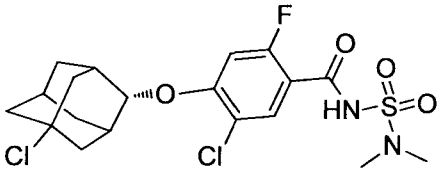
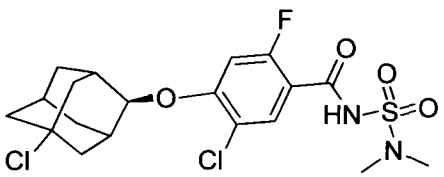


[0614] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-cyclopentylethanol, the title compound was

obtained as a colorless solid (0.11 g, 29%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 4.16 (t, J = 6.5 Hz, 2H), 2.87 (s, 6H), 1.99-1.88 (m, 1H), 1.82-1.74 (m, 4H), 1.65-1.43 (m, 4H), 1.24-1.09 (m, 2H); MS (ES-) m/z 391.1, 393.1 (M - 1).

[0615] EXAMPLE 72

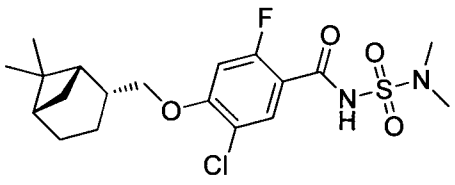
[0616] Synthesis of 5-chloro-4-(((*1R,2s,3S,5s,7s*)-5-chloroadamantan-2-yl)oxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide and 5-chloro-4-(((*1R,2r,3S,5s,7s*)-5-chloroadamantan-2-yl)oxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide

[0617] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 5-chloroadamantan-2-ol, two diasterromers were obtained by silica gel column chromatography using 10-50% gradient ethyl acetate (containing 0.2% acetic acid) in hexanes. 5-chloro-4-(((*1R,2s,3S,5s,7s*)-5-chloroadamantan-2-yl)oxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide and 5-chloro-4-(((*1R,2r,3S,5s,7s*)-5-chloroadamantan-2-yl)oxy)-*N*-(*N,N*-dimethylsulfamoyl)- 2-fluorobenzamide. Data for first eluting diastereomer: a colorless solid (0.02 g, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 12.5 Hz, 1H), 4.78-4.75 (m, 1H), 2.87 (s, 6H), 2.41-2.32 (m, 4H), 2.10 (brs, 3H), 1.96-1.92 (m, 2H) , 1.77 (br s, 4H); MS (ES-) m/z 463.1, 465.1 (M - 1). Data for second eluting diastereomer: a colorless solid (0.003 g, 2%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 12.3Hz, 1H), 4.91-4.87 (m, 1H), 2.87 (s, 6H), 2.35-2.11 (m, 9H), 1.99-1.95 (m, 2H), 1.53-1.49 (m, 2H); MS (ES-) m/z 463.1, 465.1 (M - 1).

[0618] EXAMPLE 73

[0619] Synthesis of 5-chloro-4-(((*1S,2R,5S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide

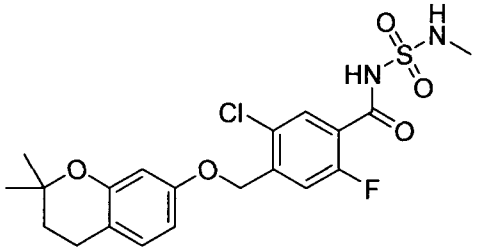


[0620] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with ((*1S,2R,5S*)-6,6-dimethylbicyclo[3.1.1]-heptan-2-yl)methanol, the title compound was obtained as a colorless solid (0.12 g, 29%): ^{1}H NMR (300

MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.72 (d, J = 6.1 Hz, 1H), 7.26 (d, J = 13.2 Hz, 1H), 4.12-4.05 (m, 2H), 2.87 (s, 6H), 2.38-2.37 (m, 1H), 2.13-1.90 (m, 6H), 1.56 (m, 1H), 1.18 (s, 3H), 1.00-0.92 (m, 4H); MS (ES-) m/z 431.1, 433.1 (M - 1).

[0621] EXAMPLE 74

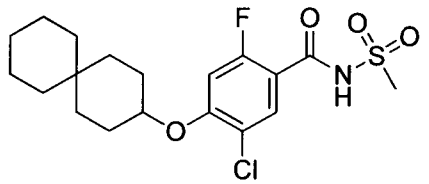
[0622] Synthesis of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluoro-N-(N-methylsulfamoyl)benzamide



[0623] A mixture of 5-chloro-4-((2,2-dimethylchroman-7-yloxy)methyl)-2-fluorobenzoic acid (50 mg, 0.14 mmol), methyl(sulfamoyl)amine (23 mg, 0.21 mmol), 1-ethyl-(3-dimethylamino- propyl)carbodiimide hydrochloride (40 mg, 0.21 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol) in DCM (20 mL) was stirred at room temperature for 16 hrs. The mixture was diluted with HCl (2.0 N, 20 mL) and extracted with EtOAc (50 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by reverse phase Combiflash (18%-25% MeCN in 0.5% NH_4HCO_3) to give target product (35.4 mg, 56%) as a pale yellow solid. LCMS (ESI) Method A: RT = 5.78 min, m/z: 456.7 $[M+H]^+$; ^{1}H-NMR (500 MHz, MeOH-d_4,): δ 7.77 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 10.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 9.0, 2.5 Hz, 1H), 6.36 (d, J = 2.5 Hz, 1H), 5.14 (s, 2H), 2.74 (t, J = 6.5 Hz, 2H), 2.71 (s, 3H), 1.80 (t, J = 6.5 Hz, 2H), 1.32 (s, 6H).

[0624] EXAMPLE 75

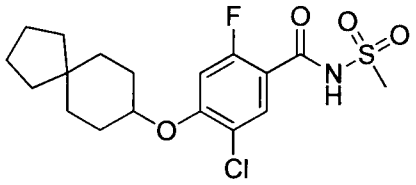
[0625] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[5.5]undecan-3- yloxy)benzamide



[0626] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with spiro[5.5]undecan-3-ol, the title compound was obtained as a colorless solid (0.08 g, 20%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 12.8 Hz, 1H), 4.68-4.61 (m, 1H), 3.33 (s, 3H), 1.83-1.74 (m, 2H), 1.65-1.52 (m, 4H), 1.38-1.23 (m, 12H); MS (ES-) m/z 416.2, 418.2 (M - 1).

[0627] EXAMPLE 76

[0628] Synthesis of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-(spiro[4.5]decan-8-yloxy)benzamide

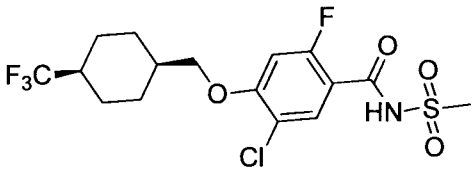


[0629] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with spiro[4.5]decan-8-ol, the title compound was obtained as a colorless solid (0.06 g, 15%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 12.8 Hz, 1H), 4.69-4.61 (m, 1H), 3.33 (s, 3H), 1.88-1.79 (m, 2H), 1.65-1.51 (m, 8H), 1.45-1.31 (m, 6H); MS (ES-) m/z 402.1, 403.1

(M - 1).

[0630] EXAMPLE 77

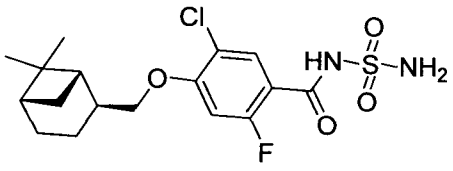
[0631] Synthesis of *cis*-5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0632] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (*cis*-4-(trifluoromethyl)cyclohexyl)- methanol, the title compound was obtained as a colorless solid (0.09 g, 14%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 12.6 Hz, 1H), 4.14 (d, J = 7.2 Hz, 2H), 3.35 (s, 3H), 2.29-2.18 (m, 1H), 2.14-2.12 (m, 1H), 1.76-1.50 (m, 8H); MS (ES-) m/z 430.1, 432.1 (M - 1).

[0633] EXAMPLE 78

[0634] Synthesis of 5-chloro-4-(((*1S,2S,5S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-methoxy)-2-fluoro-*N*-sulfamoylbenzamide

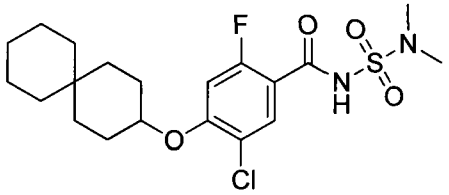


[0635] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2,4-difluoro-*N*- sulfamoylbenzamide and adamantan-1-ylmethanol with ((*1S,2S,5S*)-6,6- dimethylbicyclo[3.1.1]heptan-2-yl)methanol, the title compound was obtained as a colorless solid (0.09 g, 15%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.58 (s, 2H), 7.22 (d, J = 12.4 Hz, 1H), 3.95 (d, J = 6.8 Hz, 2H), 2.49-2.38 (m, 1H),

2.10-2.03 (m, 1H), 2.19-1.65 (m, 5H), 1.48-1.34 (m, 2H), 1.22 (s, 3H), 0.86 (s, 3H); MS (ES-) m/z 403.2, 405.2 (M - 1).

[0636] EXAMPLE 79

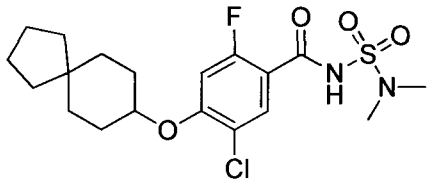
[0637] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-(spiro[5.5]undecan-3-yloxy)benzamide



[0638] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with spiro[5.5]undecan-3-ol, the title compound was obtained as a colorless solid (0.03 g, 7%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 12.6 Hz, 1H), 4.68-4.60 (m, 1H), 2.86 (s, 6H), 1.84-1.74 (m, 2H), 1.66-1.51 (m, 4H), 1.39-1.21 (m, 12H); MS (ES-) m/z 445.2, 447.2 (M - 1).

[0639] EXAMPLE 80

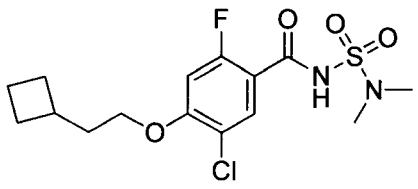
[0640] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-(spiro[4.5]decan-8-yloxy)benzamide



[0641] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with spiro[4.5]decan-8-ol, the title compound was obtained as a colorless solid (0.06 g, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 12.6 Hz, 1H), 4.68-4.61 (m, 1H), 2.87 (s, 6H), 1.88-1.77 (m, 2H), 1.65-1.51 (m, 8H), 1.44-1.32 (m, 6H); MS (ES-) m/z 431.2, 433.2 (M - 1).

[0642] EXAMPLE 81

[0643] Synthesis of 5-chloro-4-(2-cyclobutylethoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2- fluorobenzamide

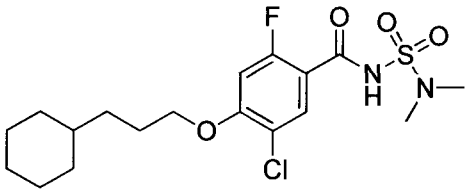


[0644] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-

2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-cyclobutylethanol, the title compound was obtained as a colorless solid (0.12 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.08 (t, J = 6.3 Hz, 2H), 2.87 (s, 6H), 2.47-2.40 (m, 1H), 2.10-1.99 (m, 2H), 1.89-1.63 (m, 6H); MS (ES-) m/z 377.2, 379.2 (M - 1).

[0645] EXAMPLE 82

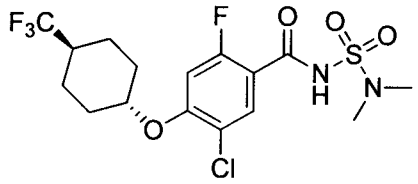
[0646] Synthesis of 5-chloro-4-(3-cyclohexylpropoxy)-*N*-(*N*,*N*-dimethylsulfamoyl)-2- fluorobenzamide



[0647] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 3-cyclohexylpropan-1-ol, the title compound was obtained as a colorless solid (0.03 g, 7%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.72 (d, J = 7.3 Hz, 1H), 7.23 (d, J = 12.3 Hz, 1H), 4.12 (t, J = 6.2 Hz, 2H), 2.87 (s, 6H), 1.80-1.58 (m, 7H), 1.35-1.11 (m, 6H), 0.94-0.88 (m, 2H); MS (ES-) m/z 419.2 , 421.2 (M - 1).

[0648] EXAMPLE 83

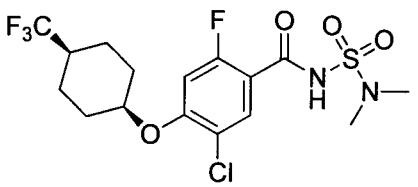
[0649] Synthesis of *trans*-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluoro-4-((4-(trifluoromethyl)cyclohexyl)oxy)benzamide



[0650] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 4-(trifluoromethyl)cyclohexanol, the title compound was obtained as a colorless solid (0.02 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 12.6 Hz, 1H), 4.61-4.53 (m, 1H), 2.87 (s, 6H), 2.45-2.32 (m, 1H), 2.18-2.10 (m, 2H), 1.97-1.89 (m, 2H), 1.55-1.44 (m, 4H); MS (ES-) m/z 445.1, 447.1 (M - 1).

[0651] EXAMPLE 84

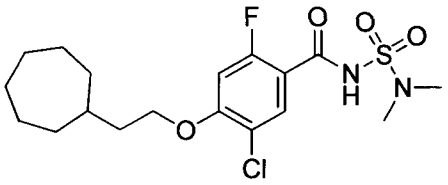
[0652] Synthesis of *cis*-5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluoro-4-((4-(trifluoromethyl)-cyclohexyl)oxy)benzamide



[0653] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 4-(trifluoromethyl)cyclohexanol, the title compound was obtained as a colorless solid (0.02 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 12.5 Hz, 1H), 4.94 (s, 1H), 2.87 (s, 6H), 2.46-2.35 (m, 1H), 2.03-1.93 (m, 2H), 1.72-1.53 (m, 6H) ; MS (ES-) m/z 445.2, 447.2 (M - 1).

[0654] EXAMPLE 85

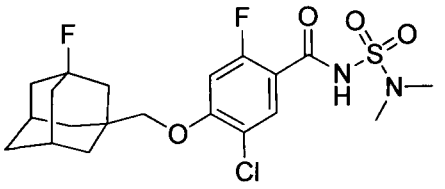
[0655] Synthesis of 5-chloro-4-(2-cycloheptylethoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2- fluorobenzamide



[0656] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-cycloheptylethanol, the title compound was obtained as a colorless solid (0.11 g, 26%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 4.16 (t, J = 6.2 Hz, 2H), 2.87 (s, 6H), 1.76-1.35 (m, 13H), 1.29-1.17 (m, 2H); MS (ES-) m/z 419.1 , 421.1 (M - 1).

[0657] EXAMPLE 86

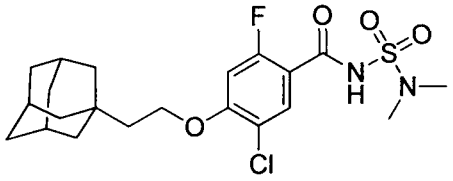
[0658] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-((3-fluoroadamantan-1-yl)methoxy)benzamide



[0659] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*- (*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 3-fluoroadamantan-1-yl methanol, the title compound was obtained as a colorless solid (0.16 g, 35%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 12.3 Hz, 1H), 3.84 (s, 2H), 2.87 (s, 6H), 2.30 (br s, 2H), 1.87-1.76 (m, 6H), 1.61-1.52 (m, 6H); MS (ES-) m/z 461.1, 463.1 (M - 1).

[0660] EXAMPLE 87

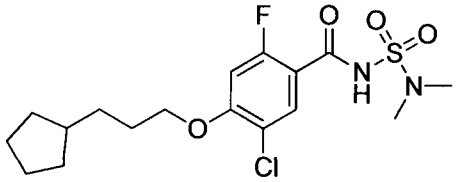
[0661] Synthesis of 4-(2-(adamantan-1-yl)ethoxy)-5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide



[0662] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with adamantan-1-ylethanol, the title compound was obtained as a colorless solid (0.15 g, 33%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 12.5 Hz, 1H), 4.18 (t, J = 7.0 Hz, 2H), 2.87 (s, 6H), 1.93-1.88 (br s, 3H), 1.70-1.54 (m, 14H); MS (ES-) m/z 457.2, 459.2 (M - 1).

[0663] EXAMPLE 90

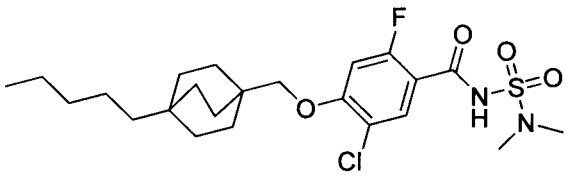
[0664] Synthesis of 5-chloro-4-(3-cyclopentylpropoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2- fluorobenzamide



[0665] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro- *N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 3-cyclopentylpropan-1-ol, the title compound was obtained as a colorless solid (0.22 g, 54%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.14 (t, J = 6.4 Hz, 2H), 2.87 (s, 6H), 1.86-1.70 (m, 5H), 1.64-1.40 (m, 6H), 1.14-1.02 (m, 2H); MS (ES-) m/z 405.2, 407.2 (M - 1).

[0666] EXAMPLE 91

[0667] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-((4-pentylbicyclo[2.2.2]octan-1-yl)- methoxy)benzamide

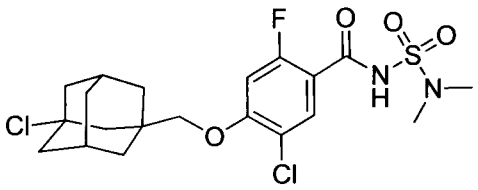


[0668] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with (4-pentylbicyclo[2.2.2]octan-1-yl)methanol, the title compound was obtained as a colorless solid (0.25 g, 51%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 12.4 Hz, 1H),

3.76 (s, 2H), 2.87 (s, 6H), 1.53-1.48 (m, 6H), 1.38-1.06 (m, 14H), 0.85 (t, J = 7.0 Hz, 3H) ; MS (ES-) m/z 487.2, 489.2 (M - 1).

[0669] EXAMPLE 92

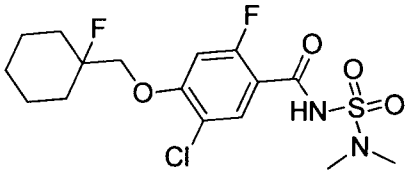
[0670] Synthesis of 5-chloro-4-((3-chloroadamantan-1-yl)methoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide



[0671] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 3-chloroadamantan-1-yl methanol, the title compound was obtained as a colorless solid (0.15 g, 31%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 12.3 Hz, 1H), 3.82 (s, 2H), 2.87 (s, 6H), 2.22 (br s, 2H), 2.14-2.02 (m, 6H), 1.70-1.55 (s, 6H) ; MS (ES-) m/z 477.1, 479.1 (M - 1).

[0672] EXAMPLE 93

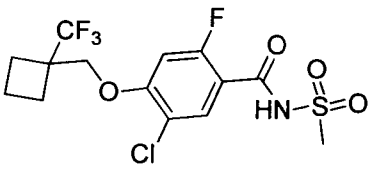
[0673] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-((1-fluorocyclohexyl)-methoxy)benzamide



[0674] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with (1-fluorocyclohexyl)methanol, the title compound was obtained as a colorless solid (0.08 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.30 (d, J = 12.3 Hz, 1H), 4.24 (d, J = 21.2 Hz, 2H), 2.88 (s, 6H), 1.96-1.87 (m, 2H), 1.72-1.50 (m, 7H), 1.37-1.24 (m, 1H); MS (ES-) m/z 409.1, 411.1 (M - 1).

[0675] EXAMPLE 94

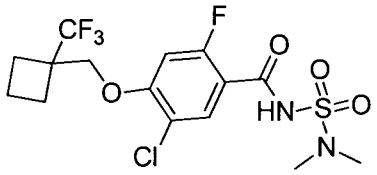
[0676] Synthesis of -chloro-2-fluoro-*N*-(methylsulfonyl)-4-((1-(trifluoromethyl)cyclobutyl)-methoxy)benzamide



[0677] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (1-(trifluoromethyl)cyclobutyl)methanol, the title compound was obtained as a colorless solid (0.05 g, 12%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 12.4 Hz, 1H), 4.41 (s, 2H), 3.35 (s, 3H), 2.39-2.26 (m, 2H), 2.19-2.09 (m, 3H), 2.01-1.90 (m, 1H); MS (ES-) m/z 402.1, 404.1 (M - 1).

[0678] EXAMPLE 95

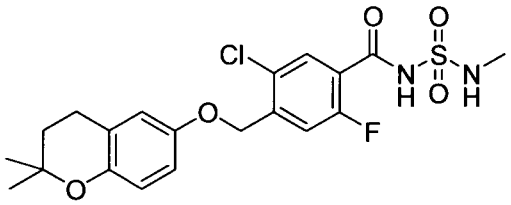
[0679] Synthesis of 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide



[0680] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*- dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with (1-(trifluoromethyl)cyclobutyl)methanol, the title compound was obtained as a colorless solid (0.05 g, 12%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 12.2 Hz, 1H), 4.41 (s, 2H), 2.88 (s, 6H), 2.38-2.26 (m, 2H), 2.19-2.08 (m, 3H), 2.02-1.91 (m, 1H); MS (ES-) m/z 431.1, 433.1 (M - 1).

[0681] EXAMPLE 96

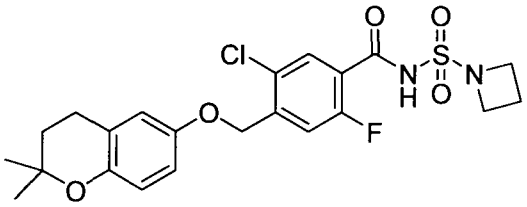
[0682] Synthesis of 5-chloro-4-((2,2-dimethylchroman-6-yloxy)methyl)-2-fluoro-N-(N-methylsulfamoyl)benzamide



[0683] The synthetic procedure was the same as Example 74. LCMS (ESI) Method A: RT = 5.20 min, m/z: 468.7 $[M+H]^+$; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.76 (d, J = 6.0 Hz, 1H), 7.51 (s, 1H), 6.80-6.75 (m, 2H), 6.63 (d, J = 9.0 Hz, 1H), 5.08 (s, 2H), 2.71 (t, J = 6.5 Hz, 2H), 2.54 (s, 3H), 1.96-1.98 (m, 1H), 1.72 (t, J = 6.5 Hz, 2H), 1.24 (s, 6H).

[0684] EXAMPLE 97

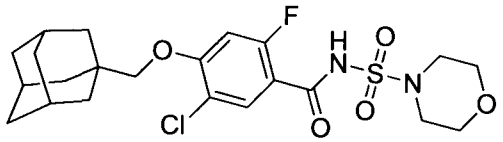
[0685] Synthesis of N-(azetidin-1-ylsulfonyl)-5-chloro-4-((2,2-dimethylchroman-6-yloxy)methyl)-2-fluorobenzamide



[0686] The synthetic procedure was the same as Example 74. LCMS (ESI) Method A: RT = 5.48 min, m/z: 483.2 $[M+H]^+$; ^{1}H-NMR (500 MHz, MeOD-d_4) δ 7.66 (d, J = 6.0 Hz, 1H), 7.38 (d, J = 10.5 Hz, 1H), 6.66-6.64 (m, 2H), 6.54 (d, J = 9.0 Hz, 1H), 5.02 (s, 2H), 4.08-4.05 (m, 4H), 2.67 (t, J = 6.5 Hz, 2H), 2.19-2.16 (m, 2H), 1.68 (t, J = 6.5 Hz, 2H), 1.19 (s, 6H).

[0687] EXAMPLE 98

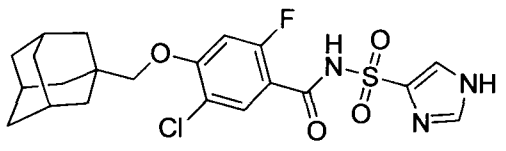
[0688] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(morpholinosulfonyl)- benzamide



[0689] To a mixture of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid (0.17 g, 0.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.22 g, 1.15 mmol) and 4-dimethylaminopyridine (0.14 g, 1.15 mmol) in anhydrous dichloromethane (10 mL) was added morpholine-4-sulfonamide (0.17 g, 1.0 mmol) at ambient temperature. The resulting mixture was stirred at ambient temperature for 16 h. The mixture was quenched with hydrochloride acid (1N, 30 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the residue was purified by silica gel column chromatography using 10-60% gradient ethyl acetate (containing 0.2% acetic acid) in hexanes to afford the title compound as an off-white solid (0.05 g, 20%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (s, 1H), 6.88 (s, 1H), 4.06 (d, J = 6.8 Hz, 2H), 3.39 (s, 3H), 2.50-2.42 (m, 1H), 2.12-2.05 (m, 1H), 1.98-1.94 (m, 1H), 1.90-1.68 (m, 4H), 1.50-1.41 (m, 2H), 1.22 (s, 3H), 0.87 (s, 3H); MS (ES-) m/z 397.2, 399.2 (M - 1); MS (ES+) m/z 399.1, 401.1 (M + 1);

[0690] EXAMPLE 99

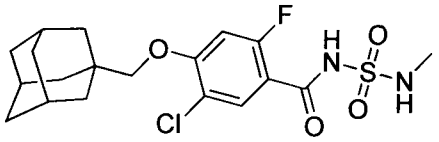
[0691] Synthesis of *N*-((1*H*-imidazol-4-yl)sulfonyl)-4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzamide



[0692] Following the procedure as described in Example 98 and making variations as required to replace morpholine-4-sulfonamide with 1H-imidazole-4-sulfonamide, the title compound was obtained as a colorless solid (0.07 g, 15%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.72 (s, 2H), 7.94-7.88 (m, 2H), 7.64 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 12.4 Hz, 1H), 3.70 (s, 2H), 1.99 (br s, 3H), 1.74-1.63 (m, 12H); MS (ES-) m/z 466.2, 468.2 (M - 1).

[0693] EXAMPLE 100

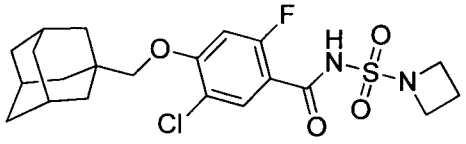
[0694] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[0695] Following the procedure as described in Example 98 and making variations as required to replace morpholine-4-sulfonamide with *N*-methylsulfamide, the title compound was obtained as a colorless solid (0.07 g, 34%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.72-7.66 (m, 2H), 7.22 (d, J = 12.4 Hz, 1H), 3.72 (s, 2H), 2.55 (d, J = 4.8 Hz, 3H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H); MS (ES-) m/z 429.3, 431.3 (M - 1); MS (ES+) m/z 431.2, 433.2 (M + 1);

[0696] EXAMPLE 101

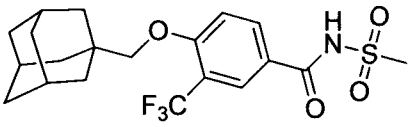
[0697] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-chloro- 2-fluorobenzamide



[0698] Following the procedure as described in Example 98 and making variations as required to replace morpholine-4-sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.08 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.73 (s, 2H), 2.22-2.12 (m, 2H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H); MS (ES-) m/z 455.3, 457.3 (M - 1); MS (ES+) m/z 457.2, 459.2 (M + 1).

[0699] EXAMPLE 102

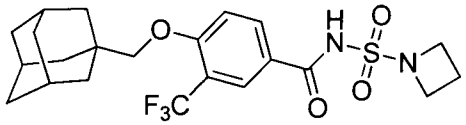
[0700] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(methylsulfonyl)-3-(trifluoromethyl)benzamide



[0701] Following the procedure as described in Example 98 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-3-(trifluoromethyl)benzoic acid and morpholine-4-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (0.11 g, 51%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.25-8.19 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 3.77 (s, 2H), 3.37 (s, 3H), 1.99 (br s, 3H), 1.75-1.63 (m, 12H); MS (ES-) m/z 430.3 (M - 1); MS (ES+) m/z 432.2 (M + 1).

[0702] EXAMPLE 103

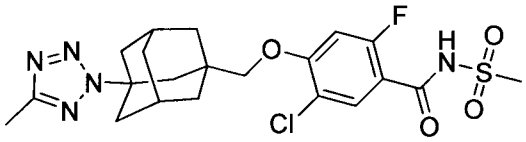
[0703] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-3-(trifluoromethyl)benzamide



[0704] Following the procedure as described in Example 98 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-3-(trifluoromethyl)benzoic acid and morpholine-4-sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.05 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.26-8.22 (m, 2H), 7.38-7.35 (m, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.76 (s, 2H), 2.20-2.09 (m, 2H), 1.99 (br s, 3H), 1.75-1.63 (m, 12H); MS (ES-) m/z 471.3 (M - 1); MS (ES+) m/z 473.2 (M + 1).

[0705] EXAMPLE 104

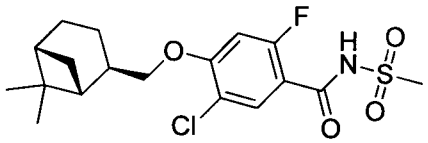
[0706] Synthesis of 5-chloro-2-fluoro-4-((3-(5-methyl-2*H*-tetrazol-2-yl)adamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide



[0707] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (3-(5-methyl-2H-tetrazol-2-yl)- adamantan-1-yl)methanol, the title compound was obtained as a colorless solid (0.07 g, 33%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 3.90 (s, 2H), 3.34 (s, 3H), 2.45 (s, 3H), 2.35-2.07 (m, 8H), 1.80-1.66 (m, 6H); MS(ES-) m/z 496.3, 498.3 (M - 1); MS (ES+) m/z 498.2, 500.2 (M + 1).

[0708] EXAMPLE 105

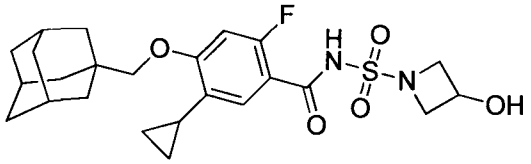
[0709] Synthesis of 5-chloro-4-(((*1R,2R,5R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-methoxy)-2-fluoro- *N*-(methylsulfonyl)benzamide



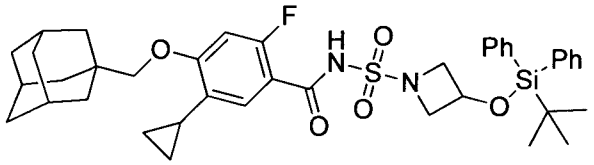
[0710] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with ((*1R,2R,5R*)-6,6-dimethylbicyclo- [3.1.1]heptan-2-yl)methanol, the title compound was obtained as a colorless solid (0.16 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.5 Hz, 1H), 3.96 (d, J = 6.8 Hz, 1H), 3.35 (s, 3H), 2.45-2.38 (m, 1H), 2.10-2.03 (m, 1H), 1.94-1.65 (m, 5H), 1.48-1.37 (m, 2H), 1.21 (s, 3H), 0.85 (s, 3H); MS (ES-) m/z 402.3, 404.3 (M - 1); MS (ES+) m/z 404.2, 406.2 (M + 1).

[0711] EXAMPLE 106

[0712] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-hydroxyazetidin-1-yl)sulfonyl)benzamide

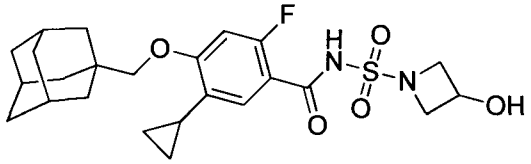


[0713] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-((3-((*tert*-butyldiphenylsilyl)- oxy)azetidin-1-yl)sulfonyl)-5-cyclopropyl-2-fluorobenzamide



[0714] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 3-((*tert*-butyl- diphenylsilyl)oxy)azetidine- 1-sulfonamide, the title compound was obtained as colorless solid (0.29 g, 40%): MS (ES+) m/z 717.3 (M + 1); MS (ES-) m/z 715.4 (M - 1).

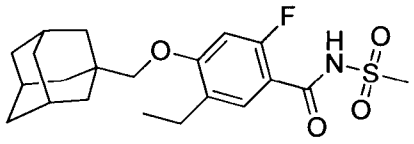
[0715] Step 2. Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-hydroxyazetidin-1- yl)sulfonyl)benzamide



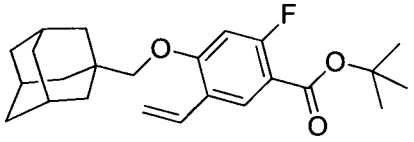
[0716] To a solution of 4-(adamantan-1-ylmethoxy)-*N*-((3-((*tert*-butyldiphenylsilyl)-oxy)azetidin-1-yl)sulfonyl)- 5-cyclopropyl-2-fluorobenzamide (0.28 g, 0.39 mmol) in anhydrous dichloromethane (10 mL) was added tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 1.6 mL, 1.56 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was quenched with aqueous hydrochloride acid solution (1N, 30 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the residue was purified by silica gel column chromatography using 10%-100% gradient ethyl acetate (containing 0.2% acetic acid) in hexanes to afford the title compound as an off-white solid (0.07 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 5.83 (d, J = 6.0 Hz, 1H), 4.45-4.35 (m, 1H), 4.14-4.09 (m, 2H), 3.89-3.84 (m, 2H), 3.65 (s, 2H), 2.09-1.99 (m, 4H), 1.75-1.67 (m, 12H), 0.94-0.88 (m, 2H), 0.69-0.66 (m, 2H); MS (ES+) m/z 479.3 (M + 1); MS (ES-) m/z 477.4 (M - 1).

[0717] EXAMPLE 107

[0718] Synthesis of 4-(adamantan-1-ylmethoxy)-5-ethyl-2-fluoro-*N*-(methylsulfonyl)benzamide

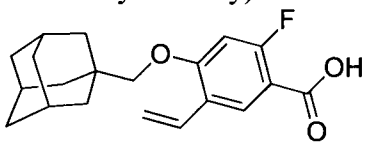


[0719] Step 1. Preparation of of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoate



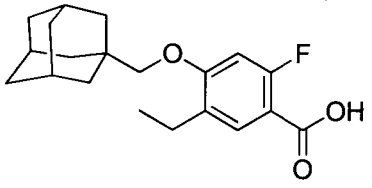
[0720] A mixture of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoate (2.00 g, 5.06 mmol), vinylboronic acid pinacol ester (1.56 g, 10.1 mmol) and sodium carbonate (1.61 g, 15.2 mmol) in dioxane (20 mL) and water (5 mL) was bubbled with a nitrogen atmosphere for 10 min, tributylphosphine tetrafluoroborate (0.15 g, 0.51 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.023 g, 0.025 mmol) was added to this reaction mixture. The reaction mixture was heated to 100 °C for 24 h and then cooled to ambient temperature. Water (50 mL) was added and the mixture extracted with ethyl acetate (100 mL x 3), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified over column chromatography, eluting with 30% dichloromethane in hexanes to give the crude product, which was used for next step without further purification: MS (ES+) m/z 398.3 (M + 1).

[0721] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoic acid



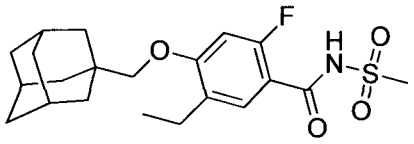
[0722] To a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoate (2.4 g, 6.2 mmol) in dichloromethane (10 mL), was added trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 16 h and then concentrated *in vacuo*. The residue was triturated in hexanes (50 mL), the solid was filtered and dried to give the title compound as a light yellow solid (1.5 g, 73% in 2 steps): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (br s, 1H), 7.92 (d, J = 8.6 Hz, 1H), 6.96-6.81 (m, 2H), 5.84-5.78 (m, 1H), 5.32-5.28 (m, 1H), 3.62 (s, 2H), 3.34 (s, 3H), 1.95 (s, 3H), 1.70-1.60 (m, 12H); MS (ES+) m/z 331.2 (M + 1); MS (ES-) m/z 329.4 (M - 1).

[0723] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-5-ethyl-2-fluorobenzoic acid



[0724] A mixture of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoic acid (1.00 g, 3.03 mmol) and 10% palladium on activated carbon (0.10 g) in ethyl acetate (150 mL) was fitted with a hydrogen balloon. The reaction mixture was stirred at ambient temperature for 42 h. The mixture was filtered through a pad of diatomaceous earth, and washed with ethyl acetate (50 mL). The filtrate was concentrated *in vacuo,* the residue was recrystallized from ethyl acetate and hexanes to afford the title compound as an off-white solid (0.75 g, 74%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (br s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 13.2 Hz, 1H), 3.61 (s, 2H), 5.57 (d, J = 7.5 Hz, 2H), 1.99 (s, 3H), 1.75-1.63 (m, 12H), 1.14 (t, J = 7.5 Hz, 3H); MS (ES+) m/z 333.2 (M + 1).

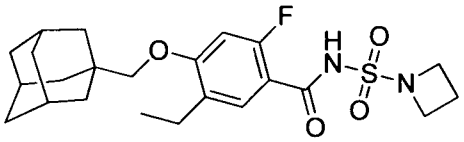
[0725] Step 4. Preparation of 4-(adamantan-1-ylmethoxy)-5-ethyl-2-fluoro-*N*-(methylsulfonyl)-benzamide



[0726] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5- cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-ethyl-2-fluorobenzoic acid, the title compound was obtained as colorless solid (0.17 g, 69%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 13.1 Hz, 1H), 3.62 (s, 2H), 3.34 (s, 3H), 2.58 (q, J = 7.5 Hz, 2H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H), 1.15 (t, J = 7.5 Hz, 3H); MS (ES+) m/z 410.2 (M + 1); MS (ES-) m/z 408.3 (M - 1).

[0727] EXAMPLE 108

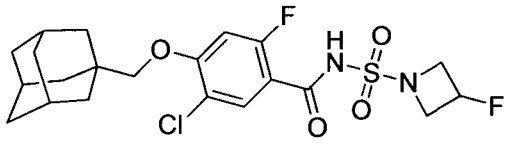
[0728] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-ethyl-2- fluorobenzamide



[0729] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-ethyl-2-fluorobenzoic acid and methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.16 g, 59%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 13.0 Hz, 1H), 4.08-4.01 (m, 4H), 3.62 (s, 2H), 2.59 (q, J = 7.5 Hz, 2H), 2.22-2.12 (m, 2H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H), 1.15 (t, J = 7.5 Hz, 3H); MS (ES+) m/z 451.2 (M + 1); MS (ES-) m/z 449.3 (M - 1).

[0730] EXAMPLE 109

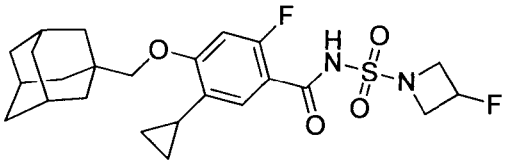
[0731] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-((3-fluoroazetidin-1-yl)-sulfonyl)benzamide



[0732] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid and methanesulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.15 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 5.49-5.43 (m, 0.5H), 5.30-5.24 (m, 0.5H), 4.45-4.32 (m, 2H), 4.26-4.13 (m, 2H), 3.73 (s, 2H), 1.99 (br s, 3H), 1.75-1.64 (m, 12H); MS (ES+) m/z 475.1, 477.1 (M + 1); MS (ES-) m/z 473.2, 475.2 (M - 1).

[0733] EXAMPLE 110

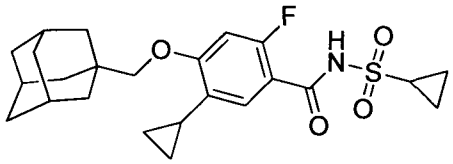
[0734] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[0735] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 3-fluoroazetidine- 1-sulfonamide, the title compound was obtained as colorless solid (0.23 g, 80%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 13.0 Hz, 1H), 5.48-5.42 (m, 0.5H), 5.29-5.23 (m, 0.5H), 4.43-4.30 (m, 2H), 4.25-4.12 (m, 2H), 3.65 (s, 2H), 2.08-1.99 (m, 4H), 1.75-1.67 (m, 12H), 0.94-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS (ES+) m/z 481.2 (M + 1); MS (ES-) m/z 479.3 (M - 1).

[0736] EXAMPLE 111

[0737] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide

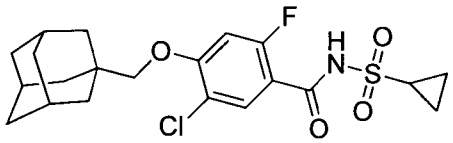


[0738] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.19 g, 71%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.93 (d, J =

13. 1 Hz, 1H), 3.65 (s, 2H), 3.12-3.03 (m, 1H), 2.07-1.99 (m, 4 H), 1.75-1.66 (m, 12 H), 1.13-1.10 (m, 4H), 0.94-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 448.2 (M + 1); MS (ES-) m/z 446.3 (M - 1).

[0739] EXAMPLE 112

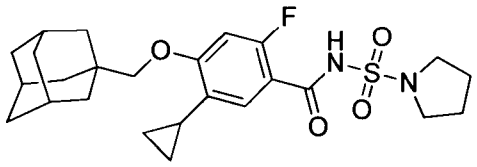
[0740] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-*N*-(cyclopropylsulfonyl)-2- fluorobenzamide



[0741] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid and methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.13 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.5 Hz, 1H), 3.73 (s, 2H), 3.12-3.03 (m, 1H), 1.99 (s, 3 H), 1.75-1.64 (m, 12 H), 1.15-1.11 (m, 4H); MS (ES+) m/z 442.1, 444.1 (M + 1); MS (ES-) m/z 440.2, 442.2 (M - 1).

[0742] EXAMPLE 113

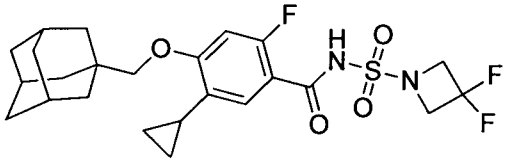
[0743] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(pyrrolidin-1- ylsulfonyl) benzamide



[0744] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with pyrrolidine-1- sulfonamide, the title compound was obtained as colorless solid (0.17 g, 85%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 13.0 Hz, 1H), 3.63 (s, 2H), 3.42-3.37 (m, 4H), 2.05-1.99 (m, 4H), 1.84-1.67 (m, 16H), 0.93-0.87 (m, 2H), 0.69-0.64 (m, 2H); MS (ES+) m/z 477.3 (M + 1); MS (ES-) m/z 475.3 (M - 1).

[0745] EXAMPLE 114

[0746] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((3,3-difluoroazetidin-1-yl)sulfonyl)-2-fluorobenzamide

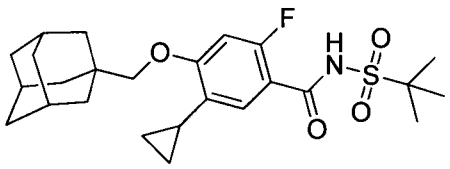


[0747] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 3,3-difluoroazetidine-1- sulfonamide, the title compound was obtained as colorless solid (0.20 g, 80%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H),

6.96 (d, J = 13.0 Hz, 1H), 4.58 (t, J = 12.8 Hz, 4H), 3.65 (s, 2H), 2.08-1.99 (m, 4H), 1.75-1.67 (m, 12H), 0.95-0.88 (m, 2H), 0.69-0.64 (m, 2H); MS (ES+) m/z 499.2 (M + 1); MS (ES-) m/z 497.3 (M - 1).

[0748] EXAMPLE 115

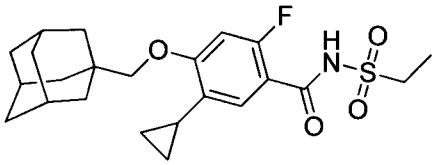
[0749] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(*tert*-butylsulfonyl)-5-cyclopropyl-2-fluorobenzamide



[0750] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with *tert*-butylsulfonamide, the title compound was obtained as colorless solid (0.17 g, 73%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.41 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 12.8 Hz, 1H), 3.63 (s, 2H), 2.06-1.99 (m, 4H), 1.75-1.66 (m, 12H), 1.38 (s, 9H), 0.93-0.87 (m, 2H), 0.68-0.63 (m, 2H); MS (ES+) m/z 464.2 (M + 1); MS (ES-) m/z 462.2 (M - 1).

[0751] EXAMPLE 116

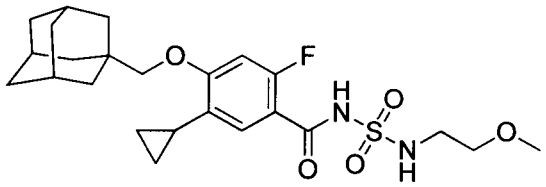
[0752] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-(ethylsulfonyl)- 2-fluorobenzamide



[0753] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with ethanesulfonamide, the title compound was obtained as colorless solid (0.17 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.1 Hz, 1H), 3.64 (s, 2H), 3.47 (q, J = 7.3 Hz, 2H), 2.06-1.99 (m, 4H), 1.75-1.66 (m, 12H), 1.24 (t, J = 7.3 Hz, 3H), 1.38 (s, 9H), 0.94-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS (ES+) m/z 436.2 (M + 1); MS (ES-) m/z 434.3 (M - 1).

[0754] EXAMPLE 117

[0755] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(*N*-(2-methoxyethyl)sulfamoyl)benzamide

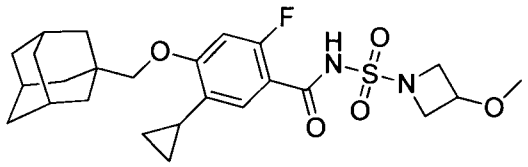


[0756] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 2-methoxyethyl- sulfamoylamine, the title compound was obtained as colorless solid (0.24 g, 53%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.76 (t, J = 5.8 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 13.0 Hz, 1H), 4.45 (t, J = 5.0 Hz, 1H), 3.63 (s, 2H), 3.39 (t, J = 6.0 Hz, 2H),

3.19 (s, 3H), 3.12-3.06 (m, 2H), 2.08-1.99 (m, 4H), 1.75-1.66 (m, 12H), 0.94-0.87 (m, 2H), 0.69-0.64 (m, 2H); MS (ES+) m/z 481.2 (M + 1); MS (ES-) m/z 479.3 (M - 1).

[0757] EXAMPLE 118

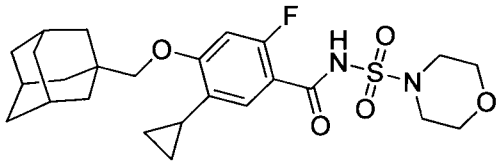
[0758] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-methoxyazetidin-1-yl)sulfonyl)benzamide



[0759] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 3-methoxyazetidine-1- sulfonamide, the title compound was obtained as colorless solid (0.22 g, 76%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 4.21-4.13 (m, 3H), 3.95-3.93 (m, 2H), 3.65 (s, 2H), 3.17 (s, 3H), 2.08-1.99 (m, 4H), 1.75-1.67 (m, 12H), 0.94-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS (ES+) m/z 493.3 (M + 1); MS (ES-) m/z 491.4 (M - 1).

[0760] EXAMPLE 119

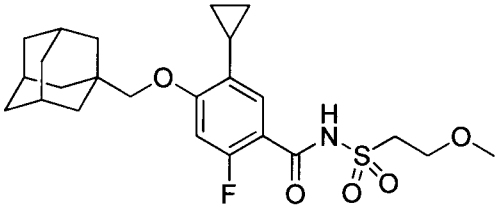
[0761] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(morpholinosulfonyl)benzamide



[0762] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with morpholine-4- sulfonamide, the title compound was obtained as colorless solid (0.15 g, 59%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.71 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 13.0 Hz, 1H), 3.65-3.62 (m, 4H), 3.27-3.24 (m, 4H), 2.06-1.99 (m, 4H), 1.75-1.66 (m, 12H), 0.93-0.87 (m, 2H), 0.70-0.64 (m, 2H); MS (ES+) m/z 493.2 (M + 1); MS (ES-) m/z 491.3 (M - 1).

[0763] EXAMPLE 120

[0764] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2-methoxyethyl)-sulfonyl)benzamide

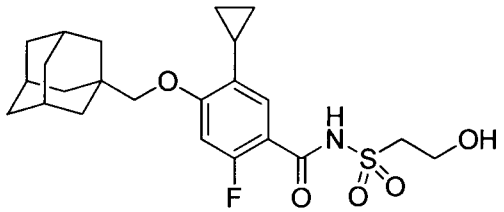


[0765] Following the procedure as described in preparation of Example 50 step 5 and making variation as required to replace methanesulfonamide with 2-methoxyethane-1- sulfonamide, the title compound was

obtained as a colorless solid (0.46 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.60 (m, 1H), 7.63-7.53 (m, 1H), 6.61-6.50 (m, 1H), 3.91-3.74 (m, 4H), 3.56 (s, 2H), 3.31 (s, 3H), 2.08-2.01 (m, 4H), 1.83-1.64 (m, 12H), 0.99-0.89 (m, 2H), 0.70-0.61 (m, 2H); MS (ES +) *m/z* 466.3 (M +1).

[0766] EXAMPLE 121

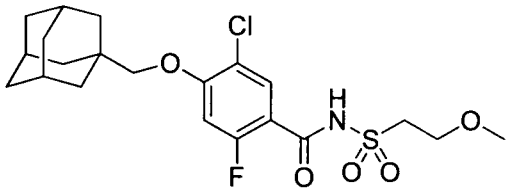
[0767] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2-hydroxyethyl)-sulfonyl)benzamide



[0768] To a cooled (0 °C) stirred solution of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide (0.30 g, 0.64 mmol) in methylene chloride (6 mL) was added a solution of boron tribromide (0.12 mL, 1.29 mmol) and 2,6-lutidine (0.15 mL, 1.29 mmol) in methylene chloride (1 mL) dropwise. The reaction mixture was stirred at 0 °C for 2 h and at ambient temperature for 1 h, then cooled to 0 °C and quenched with saturated sodium bicarbonate solution (15 mL). The mixture was diluted with methylene chloride (15 mL), layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a 10% to 75% gradient of ethyl acetate in hexanes to afford the title compound as colorless solid (0.07 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (br. s, 1H), 7.64-7.52 (m, 1H), 6.64-6.50 (m, 1H), 4.22-4.07 (m, 2H), 3.86-3.74 (m, 2H), 3.56 (s, 2H), 2.57 (s, 1H), 2.09-1.99 (m, 4H), 1.84-1.63 (m, 12H), 1.00-0.89 (m, 2H), 0.69-0.59 (m, 2H); MS (ES +) *m/z* 452.3 (M +1).

[0769] EXAMPLE 122

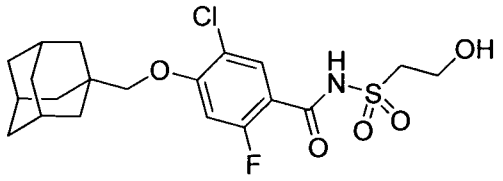
Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-((2-methoxyethyl)- sulfonyl)benzamide



[0770] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5- cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-chloro-2- fluorobenzoic acid and methanesulfonamide with 2-methoxyethane-1-sulfonamide, the title compound was obtained as a colorless solid (0.05 g, 9%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68-8.54 (m, 1H), 8.13-8.03 (m, 1H), 6.74-6.62 (m, 1H), 3.91-3.74 (m, 4H), 3.59 (s, 2H), 3.31 (s, 3H), 2.05 (s, 3H), 1.85-1.64 (m, 12H); MS (ES -) *m/z* 458.3 (M -1), 460.3 (M -1).

[0771] EXAMPLE 123

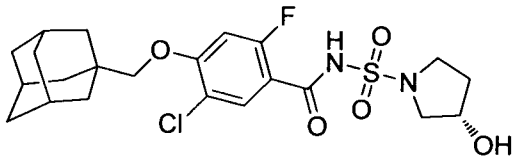
[0772] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-((2-hydroxyethyl)-sulfonyl)benzamide



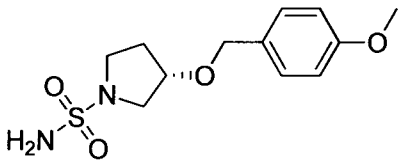
[0773] Following the procedure as described in Example 121 and making variation as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2- methoxyethyl)sulfonyl)benzamide with 4-(adamantan-1-ylmethoxy)-5 -chloro-2-fluoro- *N*-((2-methoxyethyl)sulfonyl)benzamide, the title compound was obtained as a colorless solid (0.04 g, 15%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.61 (m, 1H), 8.11-8.03 (m, 1H), 6.75-6.64 (m, 1H), 4.23-4.08 (m, 2H), 3.86-3.76 (m, 2H), 3.59 (s, 2H), 2.50-2.40 (m, 1H), 2.12-1.96 (m, 3H), 1.86-1.62 (m, 12H); MS (ES -) *m/z* 444.3 (M -1), 446.3 (M -1);

[0774] EXAMPLE 124

[0775] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(((*S*)-3-hydroxypyrrolidin-1-yl)sulfonyl)benzamide

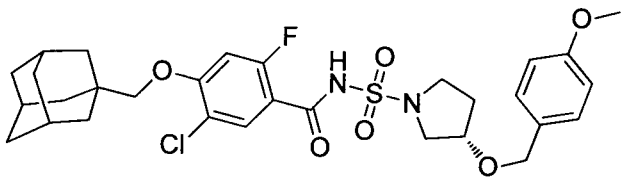


[0776] Step 1. Preparation of (*S*)-3-((4-methoxybenzyl)oxy)pyrrolidine-1-sulfonamide



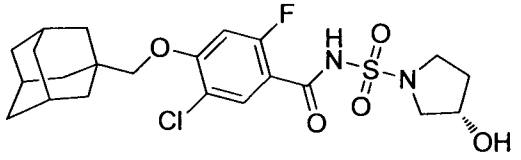
[0777] A mixture of (*S*)-3-((4-methoxybenzyl)oxy)pyrrolidine (4.50 g, 21.7 mmol) and sulfamide (2.50 g, 26.0 mmol) in dimethoxyethane (100 mL) was refluxed for 72 h. The reaction was concentrated *in vacuo*. Purification of the residue by column chromatography (30% to 100% gradient ethyl acetate in hexanes) afforded the title compound as a colorless solid (3.80 g, 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.27-7.24 (m, 2H), 6.91-6.88 (m, 2H), 6.74 (s, 2H), 4.39 (s, 2H), 4.16-4.11 (m, 1H), 3.74 (s, 3H), 3.30-3.25 (m, 1H), 3.18-3.10 (m, 3H), 2.00-1.88 (m, 2H); MS (ES+) m/z 287.2 (M + 1); MS (ES-) m/z 285.3 (M - 1).

[0778] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(((*S*)-3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide



[0779] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid and methanesulfonamide with (*S*)-3-((4-methoxybenzyl)oxy)pyrrolidine-1-sulfonamide, the title compound was obtained as colorless solid (0.17 g, 47%): MS (ES+) m/z 607.1, 609.1 (M + 1); MS (ES-) m/z 605.3, 607.3 (M - 1).

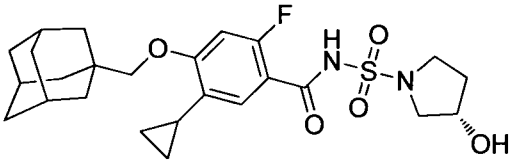
[0780] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(((*S*)-3-hydroxypyrrolidin-1-yl)sulfonyl)benzamide.



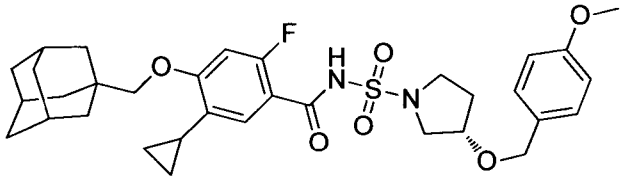
[0781] A mixture of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-(((*S*)-3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide (0.17 g, 0.28 mmol) in dichloromethane (18 mL) and water (2 mL) was added 2,3-dichloro-5,6-dicyano- 1,4-benzoquinone (0.08 g, 0.36 mmol) at ambient temperature and stirred for 16 h. Water (20 mL) was added and the mixture extracted with ethyl acetate (80 mL x 2), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was filtered through a short silicon gel column, eluted with 5%-60% gradient ethyl acetate in hexanes to give the title compound as colorless solid (0.08 g, 55%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 5.07 (brs, 1H), 4.32-4.27 (m, 1H), 3.71 (s, 2H), 3.56-3.48 (m, 3H), 3.23-3.19 (m, 1H), 1.99 (s, 3H), 1.93-1.63 (m, 14H); MS (ES+) m/z 487.2, 489.1 (M + 1); MS (ES-) m/z 485.3, 487.3 (M - 1).

[0782] EXAMPLE 125

[0783] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(((*S*)-3-hydroxypyrrolidin-1-yl)sulfonyl)benzamide



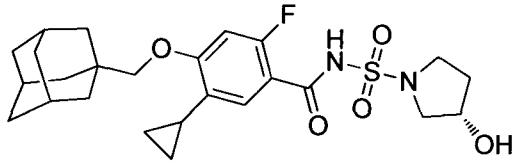
[0784] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(((*S*)-3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide



[0785] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with (*S*)-3-((4- methoxybenzyl)- oxy)pyrrolidine-1-sulfonamide, the title

compound was obtained as colorless solid (0.31 g, 84%): MS (ES+) m/z 613.2 (M + 1); MS (ES-) m/z 611.3 (M - 1).

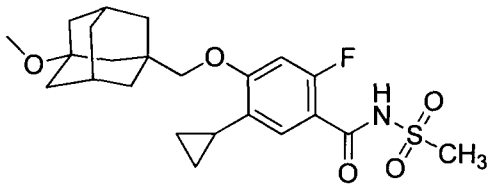
[0786] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(((*S*)-3-hydroxypyrrolidin-1-yl)sulfonyl)benzamide



[0787] Following the procedure as described in Example 124 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5- chloro-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoic acid, the title compound was obtained as off-white solid (0.04 g, 17%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 12.9 Hz, 1H), 5.07 (br s, 1H), 4.32-4.27 (m, 1H), 3.63 (s, 2H), 3.55-3.48 (m, 3H), 3.20-3.16 (m, 1H), 2.07-1.99 (m, 4H), 1.93-1.63 (m, 14H), 0.93-0.87 (m, 2H), 0.69-0.63 (m, 2H); MS (ES+) m/z 493.2 (M + 1); MS (ES-) m/z 491.3 (M - 1).

[0788] EXAMPLE 126

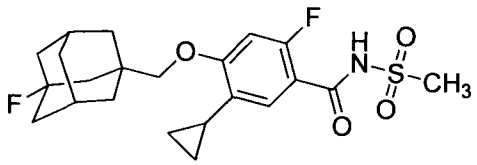
[0789] Synthesis of 5-cyclopropyl-2-fluoro-4-((3-methoxyadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide

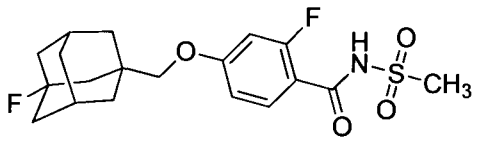


[0790] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro- *N*-(methylsulfonyl)- benzamide with 5-chloro-2-fluoro-4-((3-methoxyadamantan- 1-yl)methoxy)-*N*- (methylsulfonyl)benzamide, the title compound was obtained as colorless solid (0.06 g, 42%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.1 Hz, 1H), 3.73 (s, 2H), 3.34 (s, 3H), 3.12 (s, 3H), 2.21 (s, 2H), 2.07-1.98 (m, 1H), 1.70-1.56 (m, 12H), 0.94-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS (ES+) m/z 452.2 (M + 1); MS (ES-) m/z 450.3 (M - 1).

[0791] EXAMPLE 127

[0792] Synthesis of 5-cyclopropyl-2-fluoro-4-((3-fluoroadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide and 2-fluoro-4-((3-fluoroadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide

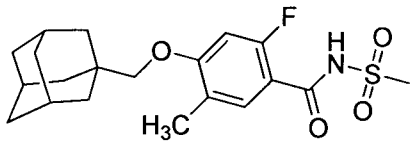




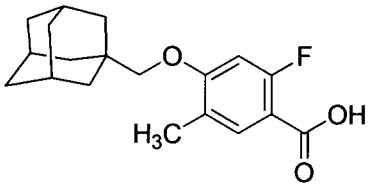
[0793] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2- fluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2-fluoro-4-((3-fluoroadamantan-1- yl)methoxy)-*N*-(methylsulfonyl)benzamide, 5-cyclopropyl-2-fluoro-4- ((3-fluoroadamantan-1-yl)methoxy)-*N*-(methylsulfonyl)benzamide was obtained as colorless solid (0.09 g, 35%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 13.0 Hz, 1H), 3.77 (s, 2H), 3.34 (s, 3H), 2.30 (s, 2H), 2.07-1.98 (m, 1H), 1.83-1.78 (m, 6H), 1.62-1.58 (m, 6H), 0.94-0.88 (m, 2H), 0.70-0.64 (m, 2H); MS (ES+) m/z 440.2 (M + 1); MS (ES-) m/z 438.3 (M - 1). 2-fluoro-4-((3-fluoroadamantan-1- yl)methoxy)-*N*- (methylsulfonyl)benzamide was also obtained as a colorless solid (0.02 g, 8%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.63 (t, J = 8.7 Hz, 1H), 6.98-6.86 (m, 2H), 3.75 (s, 2H), 3.33 (s, 3H), 2.28 (s, 2H), 1.82-1.73 (m, 6H), 1.61-1.54 (m, 6H); MS (ES+) m/z 400.2 (M + 1); MS (ES-) m/z 398.2 (M - 1).

[0794] EXAMPLE 128

[0795] Synthesis of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-methyl-N-(methylsulfonyl)benzamide

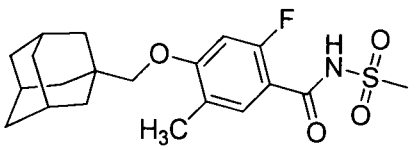


[0796] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-methylbenzoic acid



[0797] To a solution of 1-adamantane methanol (2.40 g, 14.40 mmol) in anhydrous dimethylsulfoxide (20 ml) was added potassium *tert*-butoxide (4.86 g, 43.30 mmol) and the suspension was stirred at ambient temperature for 30 min. 5-chloro-2,4-difluorobenzoic acid (2.50 g, 14.40 mmol) was added to the reaction mixture and stirred at 50 °C for 72 h. The reaction mixture was acidified to pH = 1 with cold aqueous hydrochloric acid solution (1N), followed by addition of 25% aqueous ammonium chloride solution (200 mL). The solid was collected by filtration and washed with water and a mixture of hexanes/diethyl ether (3/1, v/v). Recrystallization of the crude product from ethyl acetate and hexanes to afford the title compound as a beige color solid (0.77 g, 17%): MS (ES+) m/z 437.2 (M +1).

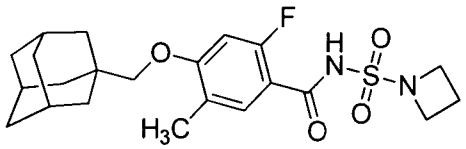
[0798] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-methyl-*N*-(methylsulfonyl)benzamide



[0799] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-methylbenzoic acid, the title compound was obtained as colorless solid (0.06 g, 27%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 3.62 (s, 2H), 3.33 (s, 3H), 2.15 (s, 3H), 1.99 (s, 3H), 1.75-1.66 (m, 12H); MS (ES+) m/z 396.2 (M + 1); MS (ES-) m/z 394.2 (M - 1).

[0800] EXAMPLE 129

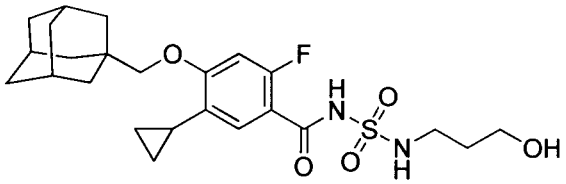
[0801] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro- 5-methylbenzamide



[0802] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-methylbenzoic acid and methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.06 g, 27%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 12.9 Hz, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.62 (s, 2H), 2.19-2.14 (m, 5H), 1.99 (s, 3H), 1.75-1.66 (m, 12H); MS (ES+) m/z 437.2 (M + 1); MS (ES-) m/z 435.2 (M - 1).

[0803] EXAMPLE 130

[0804] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(*N*-(3-hydroxypropyl)sulfamoyl)benzamide

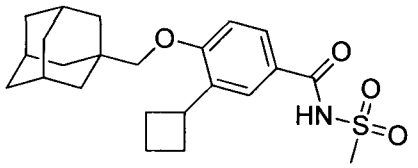


[0805] To a stirred solution of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid (0.30 g, 0.87 mmol) in dichloromethane (15 mL) were added *N*-(3-dimethyl- aminopropyl)-*N*'-ethylcarbodiimide hydrochloride (0.38 g, 2.00 mmol) and 4-(dimethylamino)pyridine (0.25 g, 2.00 mmol). The reaction stirred at ambient temperature for 10 min, 3-(sulfamoylamino)propyl 2,2,2-trifluoroacetate (0.50 g, 2.00 mmol) was added and stirring continued at ambient temperature for 72 h. sodium carbonate solution (3M, 10 mL) was added and stirred at ambient temperature for 4 h, aqueous hydrochloric acid (3N) were added to pH = 1 and diluted with ethyl acetate (200 mL), washed with water and brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by reversed-phase column chromatography afforded the title compound as colorless solid (0.11 g, 27%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.50 (s, 1H), 7.66 (br s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 12.9 Hz, 1H), 4.45 (t, J =

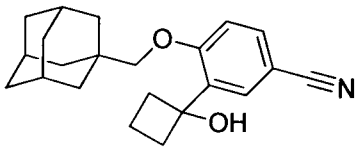
5.0 Hz, 1H), 3.63 (s, 2H), 3.43-3.37 (m, 2H), 3.00-2.93 (m, 2H), 2.07-1.99 (m, 4H), 1.75-1.56 (m, 14H), 0.93-0.87 (m, 2H), 0.69-0.64 (m, 2H); MS (ES+) m/z 481.2 (M + 1); MS (ES-) m/z 479.3 (M - 1).

[0806] EXAMPLE 131

[0807] Synthesis of 4-(adamantan-1-ylmethoxy)-3-cyclobutyl-*N*-(methylsulfonyl)benzamide

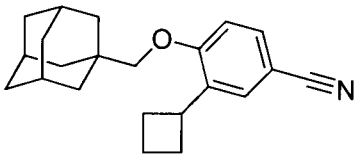


[0808] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-3-(1-hydroxycyclobutyl)benzonitrile



[0809] To a cooled (0 °C) stirred solution of 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile (3.20 g, 9.24 mmol) in tetrahydrofuran (40 mL) was added a solution of isopropylmagnesium chloride lithium chloride complex in tetrahydrofuran (1.3 M, 15.0 mL, 19.5 mmol) dropwise. The reaction mixture was stirred at 0 °C for 2 h and cyclobutanone (1.52 mL, 20.33 mmol) was added. Stirring was continued at 0 °C for 2 h and quenched with saturated ammonium chloride solution (30 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column chromatography eluting with a 10% to 25% gradient of ethyl acetate in hexanes to afford 4-(adamantan-1-ylmethoxy)-3-(1-hydroxycyclobutyl)benzonitrile as colorless solid (2.34 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.53 (m, 2H), 7.00-6.93 (m, 1H), 3.64 (s, 2H), 3.43 (s, 1H), 2.59-2.36 (m, 4H), 2.17-2.00 (m, 4H), 1.84-1.61 (m, 13H).

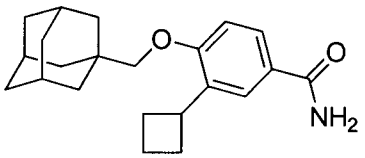
[0810] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-3-cyclobutylbenzonitrile



[0811] To a cooled (0 °C) stirred solution of 4-(adamantan-1-ylmethoxy)-3-(1-hydroxycyclobutyl)-benzonitrile (1.00 g, 2.96 mmol) in methylene chloride (30 mL) was added triethylsilane(2.4 mL, 14.80 mmol) followed by trifluoroacetic acid (2.3 mL, 29.60 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and diluted with 1M aqueous sodium hydroxide solution (30 mL). The mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a 5% to 10% gradient of ethyl acetate in

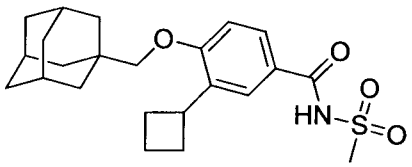
hexanes to afford 4-(adamantan-1-ylmethoxy)-3-cyclobutylbenzonitrile as colorless solid in quantitative yield (0.95 g): MS (ES +) *m/z* 322.2 (M +1);

[0812] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-3-cyclobutylbenzamide



[0813] Following the procedure as described in Example 38 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile with 4-(adamantan-1-ylmethoxy)-3-cyclobutylbenzonitrile, the title compound was obtained as a colorless solid (0.88 g, 88%): MS (ES +) *m/z* 340.3 (M +1);

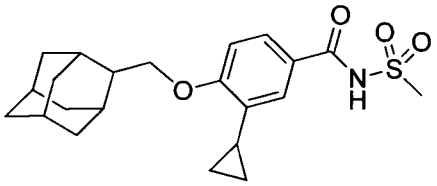
[0814] Step 4. Preparation of 4-(adamantan-1-ylmethoxy)-3-cyclobutyl-*N*-(methylsulfonyl)- benzamide



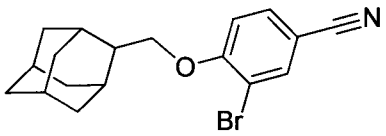
[0815] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2- methoxypyridin-3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-3-cyclobutylbenzamide, the title compound was obtained as a colorless solid (0.05 g, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.70-7.61 (m, 2H), 6.87-6.80 (m, 1H), 3.80-3.65 (m, 1H), 3.54 (s, 2H), 3.44 (s, 3H), 2.45-2.32 (m, 2H), 2.24-2.00 (m, 6H), 1.94-1.61 (m, 13H); MS (ES +) *m/z* 418.2 (M +1);

[0816] EXAMPLE 132

[0817] Synthesis of 4-(adamantan-2-ylmethoxy)-3-cyclopropyl-*N*-(methylsulfonyl)benzamide

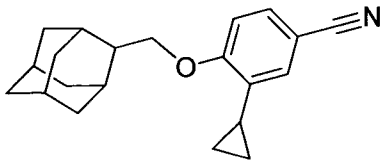


[0818] Step 1. Preparation of 4-(adamantan-2-ylmethoxy)-3-bromobenzonitrile



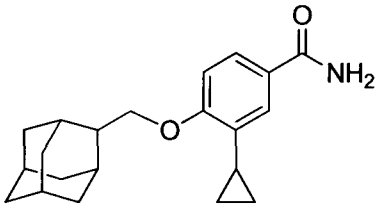
[0819] Following the procedure as described in Example 38 step 1 and making variation as required to replace adamantan-1-ylmethanol with adamantan-2-ylmethanol (*J. Am. Chem. Soc.* **2012**, 134(2), 675), the title compound was obtained as a colorless solid (1.32 g, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 1H), 7.62-7.54 (m, 1H), 6.99-6.92 (m, 1H), 4.19-4.12 (m, 2H), 2.36-2.27 (m, 1H), 2.06-1.74 (m, 12H), 1.68-1.58 (m, 2H);

[0820] Step 2. Preparation of 4-(adamantan-2-ylmethoxy)-3-cyclopropylbenzonitrile



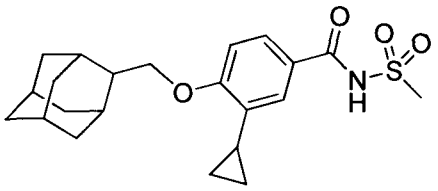
[0821] Following the procedure as described in Example 39 step 1 and making variation as required to replace 4-(adamantan-1-ylmethoxy)-3-bromobenzonitrile with 4-(adamantan-2-ylmethoxy)-3-bromobenzonitrile the title compound was obtained as a colorless solid (0.68 g, 84%): MS (ES +) *m/z* 308.3 (M +1).

[0822] Step 3. Preparation of 4-(adamantan-2-ylmethoxy)-3-cyclopropylbenzamide



[0823] Following the procedure as described in Example 38 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzonitrile with 4-(adamantan-2-ylmethoxy)-3-cyclopropylbenzonitrile, the title compound was obtained as a colorless solid (0.62 g, 95%): MS (ES +) *m/z* 326.3 (M +1);

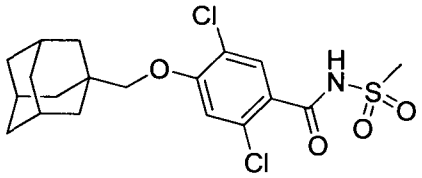
[0824] Step 4. Preparation of 4-(adamantan-2-ylmethoxy)-3-cyclopropyl-*N*-(methylsulfonyl)- benzamide



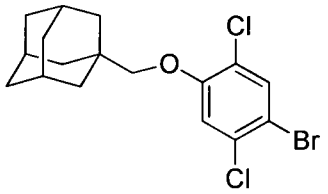
[0825] Following the procedure as described in Example 38 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2- methoxypyridin-3-yl)benzamide with 4-(adamantan-2-ylmethoxy)-3-cyclopropylbenzamide, the title compound was obtained as a colorless solid (0.09 g, 26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.65-7.59 (m, 1H), 7.36-7.31 (m, 1H), 6.95-6.87 (m, 1H), 4.19-4.10 (m, 2H), 3.43 (s, 3H), 2.35-2.25 (m, 1H), 2.21-2.08 (m, 1H), 2.05-1.74 (m, 12H), 1.68-1.56 (m, 2H), 1.02-0.91 (m, 2H), 0.74-0.63 (m, 2H); MS (ES +) *m/z* 404.3 (M +1);

[0826] EXAMPLE 133

[0827] Synthesis of 4-(adamantan-1-ylmethoxy)-2,5-dichloro-*N*-(methylsulfonyl)benzamide

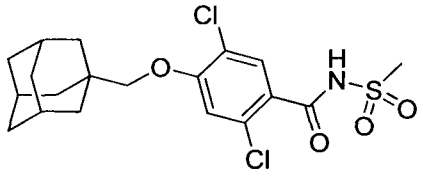


[0828] Step 1. Preparation of 1-((4-bromo-2,5-dichlorophenoxy)methyl)adamantane



[0829] A mixture of 4-bromo-2,5-dichlorophenol (1.35 g, 5.58 mmol), adamantan-1-ylmethyl methanesulfonate (Fr. Demande, 2909090, May 30, 2008) (1.5 g, 6.14 mmol), and potassium carbonate (0.85 g, 6.14 mmol) in *N,N*-dilmethylformamide (10 mL) was stirred at 65 °C for 16 h and at 125 °C for 48 h. The reaction mixture was cooled down to ambient temperature, diluted with water (40 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column chromatography eluting with a 5% to 10% gradient of ethyl acetate in hexanes to afford 1-((4-bromo-2,5-dichlorophenoxy)methyl)adamantine as a colorless solid (1.7 g, 71%): MS (ES +) *m/z* 391.3 (M +1);

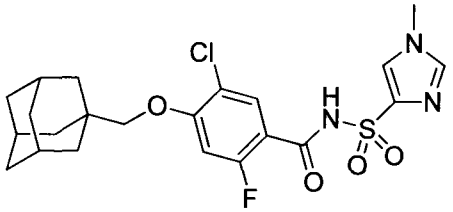
[0830] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-2,5-dichloro-*N*-(methylsulfonyl)- benzamide



[0831] Following the procedure as described in Example 47 step 5 and making variations as required to replace 1-((4-bromo-2-chloro-5-fluorobenzyl)oxy)- adamantane with 1-((4-bromo-2,5-dichlorophenoxy)methyl)adamantane, the title compound was obtained as a colorless solid (0.09 g, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.99 (s, 1H), 6.91 (s, 1H), 3.60 (s, 2H), 3.42 (s, 3H), 2.09-2.01 (m, 3H), 1.83-1.64 (m, 12H); MS (ES -) *m/z* 430.2 (M -1), 432.2 (M -1).

[0832] EXAMPLE 134

[0833] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluoro-*N*-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)benzamide

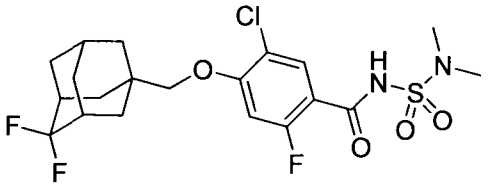


[0834] Following the procedure as described in Example 50 step 5 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoic acid and methanesulfonamide with 1-methyl-1*H*-imidazole-4-sulfonamide, the title compound was obtained as a colorless solid (0.16 g, 33%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03-8.01 (m, 1H), 7.85-7.80 (m, 1H), 7.66-7.60 (m, 1H), 7.21-7.14 (m,

1H), 3.73 (s, 3H), 3.70 (s, 2H), 1.98 (s, 3H), 1.78-1.57 (m, 12H); MS (ES +) *m/z* 482.2 (M +1), 484.2 (M +1).

[0835] EXAMPLE 135

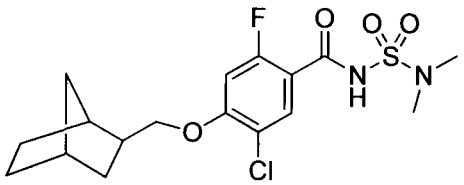
[0836] Synthesis of 5-chloro-4-((4,4-difluoroadamantan-1-yl)methoxy)-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide



[0837] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 4,4-difluoro-1-(hydroxymethyl)adamantane, the title compound was obtained as a colorless solid (0.21 g, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 8.16-8.03 (m, 1H), 6.73-6.60 (m, 1H), 3.63 (s, 2H), 3.03 (s, 6H), 2.37-2.25 (m, 2H), 2.11-1.84 (m, 5H), 1.81-1.66 (m, 6H); MS (ES -) *m/z* 479.2 (M -1), 481.1 (M -1).

[0838] EXAMPLE 136

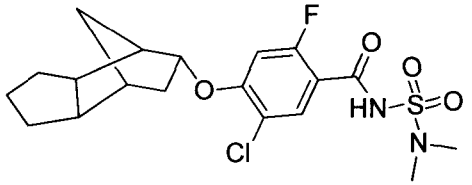
[0839] Synthesis of 4-(bicyclo[2.2.1]heptan-2-ylmethoxy)-5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide



[0840] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-Norbornanemethanol, the title compound was obtained as a colorless solid (0.17 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.54 (m, 1H), 8.12-8.01 (m, 1H), 6.77-6.61 (m, 1H), 4.15-3.67 (m, 2H), 3.01 (s, 6H), 2.49-2.21 (m, 3H), 2.10-1.74 (m, 1H), 1.64-1.05 (m, 6H), 0.83-0.71 (m, 1H); MS (ES -) *m/z* 403.2 (M -1), 405.2 (M -1).

[0841] EXAMPLE 137

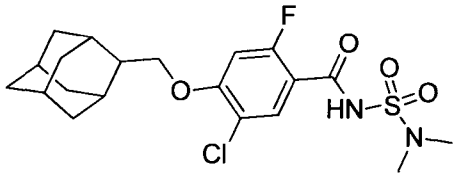
[0842] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-((octahydro-1*H*-4,7-methanoinden-5-yl)oxy)benzamide



[0843] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with 2-tricyclo[5.2.1.0{2,6}]decan-8-ol, the title compound was obtained as a colorless solid (0.03 g, 7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70-8.58 (m, 1H), 8.10-8.03 (m, 1H), 6.70-6.58 (m, 1H), 4.27-4.09 (m, 1H), 3.03 (s, 6H), 2.28 (s, 1H), 2.17-2.10 (m, 1H), 2.02-1.65 (m, 6H), 1.65-1.56 (m, 1H), 1.54-1.39 (m, 2H), 1.36-1.17 (m, 1H), 1.13-0.90 (m, 2H); MS (ES +) *m/z* 431.1 (M +1), 433.1 (M +1);

[0844] EXAMPLE 138

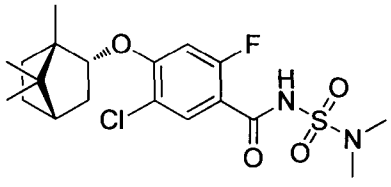
[0845] Synthesis of 4-(adamantan-2-ylmethoxy)-5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluorobenzamide



[0846] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with adamantan-2-ylmethanol (*J. Am. Chem. Soc.* **2012**, 134(2), 675), the title compound was obtained as a colorless solid (0.14 g, 27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.57 (m, 1H), 8.13-8.03 (m, 1H), 6.82-6.67 (m, 1H), 4.23-4.03 (m, 2H), 3.03 (s, 6H), 2.37-2.27 (m, 1H), 2.04-1.73 (m, 11H), 1.69-1.54 (m, 3H); MS (ES -) *m/z* 443.2 (M -1), 445.2 (M -1);

[0847] EXAMPLE 139

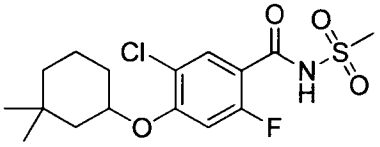
[0848] Synthesis of 5-chloro-*N*-(*N,N*-dimethylsulfamoyl)-2-fluoro-4-(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)benzamide



[0849] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(*N*,*N*-dimethylsulfamoyl)-2,4-difluorobenzamide and adamantan-1-ylmethanol with [(1*S*)-*endo*]-(-)-borneol, the title compound was obtained as a colorless solid (0.17 g, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.20-8.00 (m, 1H), 6.67-6.43 (m, 1H), 4.47-4.25 (m, 1H), 3.03 (s, 6H), 2.55-2.20 (m, 2H), 1.92-1.69 (m, 2H), 1.51-1.19 (m, 2H), 1.19-0.74 (m, 10H); MS (ES -) *m/z* 431.2 (M -1), 433.2 (M -1).

[0850] EXAMPLE 140

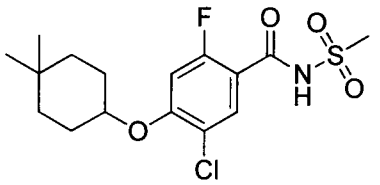
[0851] Synthesis of 5-chloro-4-((3,3-dimethylcyclohexyl)oxy)-2-fluoro-*N*-(methylsulfonyl)- benzamide



[0852] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 3,3-dimethylcyclohexanol (*Can. J. Chem.* **1980,** 58(18), 1993), the title compound was obtained as a colorless solid (0.14 g, 26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.17-8.00 (m, 1H), 6.78-6.55 (m, 1H), 4.55-4.33 (m, 1H), 3.42 (s, 3H), 2.12-2.02 (m, 1H), 1.86-1.73 (m, 2H), 1.65-1.35 (m, 4H), 1.32-1.19 (m, 1H), 1.06-0.94 (m, 6H); MS (ES -) *m/z* 376.1 (M -1), 378.1 (M -1).

[0853] EXAMPLE 141

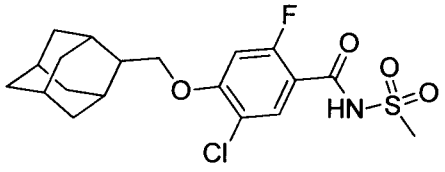
[0854] Synthesis of 5-chloro-4-((4,4-dimethylcyclohexyl)oxy)-2-fluoro-*N*- (methylsulfonyl)benzamide



[0855] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 4,4-dimethylcyclohexanol (*J. Am. Chem. Soc.* **2009**, 131(1), 251), the title compound was obtained as a colorless solid (0.24 g, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.17-8.03 (m, 1H), 6.78-6.61 (m, 1H), 4.45-4.30 (m, 1H), 3.42 (s, 3H), 1.97-1.70 (m, 4H), 1.63-1.48 (m, 2H), 1.38-1.17 (m, 2H), 1.01-0.95 (m, 6H); MS (ES -) *m/z* 376.1 (M -1), 378.1 (M -1).

[0856] EXAMPLE 142

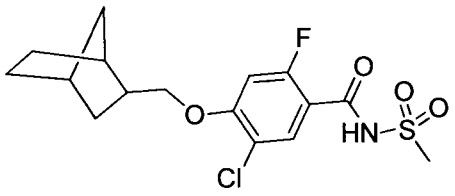
[0857] Synthesis of 4-(adamantan-2-ylmethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide



[0858] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with adamantan-2-ylmethanol (*J. Am. Chem. Soc.* **2012**, 134(2), 675), the title compound was obtained as a colorless solid (0.22 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.22-7.99 (m, 1H), 6.88-6.62 (m, 1H), 4.23-4.09 (m, 2H), 3.43 (s, 3H), 2.38-2.26 (m, 1H), 2.07-1.71 (m, 11H), 1.69-1.51 (m, 3H); MS (ES +) *m/z* 416.1 (M +1), 418.1 (M +1);

[0859] EXAMPLE 143

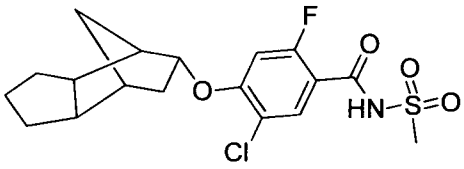
[0860] Synthesis of 4-(bicyclo[2.2.1]heptan-2-ylmethoxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide



[0861] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 2-Norbornanemethanol, the title compound was obtained as a colorless solid (0.32 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.15-8.05 (m, 1H), 6.82-6.61 (m, 1H), 4.16-3.70 (m, 2H), 3.43 (s, 3H), 2.58-2.15 (m, 3H), 2.12-1.74 (m, 1H), 1.69-1.05 (m, 6H), 0.95-0.62 (m, 1H) MS (ES -) *m/z* 374.1 (M -1), 376.1 (M -1);

[0862] EXAMPLE 144

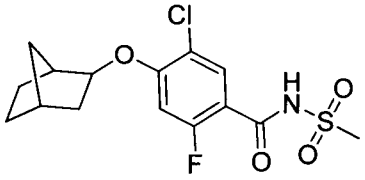
[0863] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((octahydro-1*H*-4,7-methanoinden-5-yl)oxy)benzamide



[0864] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with tricyclo[5.2.1.0 {2,6}]decan-8-ol, the title compound was obtained as a colorless solid (0.21 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76-8.57 (m, 1H), 8.18-7.95 (m, 1H), 6.78-6.51 (m, 1H), 4.29-4.10 (m, 1H), 3.42 (s, 3H), 2.28 (br s, 1H), 2.19-2.09 (m, 1H), 2.02-1.65 (m, 6H), 1.65-1.38 (m, 3H), 1.36-1.16 (m, 1H), 1.13-0.87 (m, 2H); MS (ES -) *m/z* 400.1 (M -1), 402.1 (M -1).

[0865] EXAMPLE 145

[0866] Synthesis of 4-(bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)- benzamide

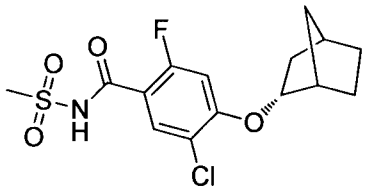


[0867] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with *exo*-Norborneol, the title compound was obtained as a colorless solid (0.33 g,

49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.14-8.04 (m, 1H), 6.73-6.59 (m, 1H), 4.32-4.17 (m, 1H), 3.42 (s, 3H), 2.56-2.49 (m, 1H), 2.44-2.34 (m, 1H), 1.89-1.79 (m, 1H), 1.76-1.49 (m, 4H), 1.32-1.11 (m, 3H): MS (ES-) *m/z* 360.1 (M-1), 362.1 (M -1);

[0868] EXAMPLE 146

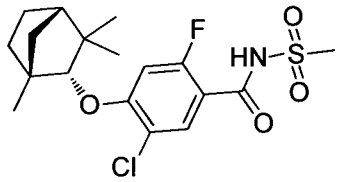
[0869] Synthersis of 4-((*1S,2R,4R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)- benzamide



[0870] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (+)-*endo*-2-Norborneol, the title compound was obtained as a colorless solid (0.35 g, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.15-8.06 (m, 1H), 6.69-6.57 (m, 1H), 4.76-4.61 (m, 1H), 3.42 (s, 3H), 2.72-2.63 (m, 1H), 2.40-2.29 (m, 1H), 2.20-1.93 (m, 2H), 1.75-1.30 (m, 5H), 1.23-1.11 (m, 1H); MS (ES-) *m/z* 360.1 (M-1), 362.1 (M-1);

[0871] EXAMPLE 147

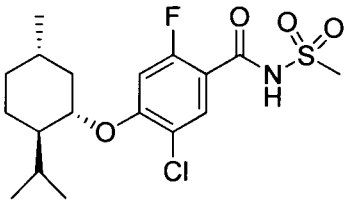
[0872] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((*1R,2R,4S*)-1,3,3-trimethylbicyclo-[2.2.1]heptan-2-yl)oxy)benzamide



[0873] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (*1R*)-*endo*-(+)-Fenchyl alcohol, the title compound was obtained as a colorless solid (0.28 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.15-8.04 (m, 1H), 6.75-6.63 (m, 1H), 4.02-3.92 (m, 1H), 3.42 (s, 3H), 2.18-2.03 (m, 1H), 1.85-1.71 (m, 1H), 1.68-1.45 (m, 3H), 1.34-1.03 (m, 8H), 0.83 (s, 3H); MS (ES +) *m/z* 404.1 (M +1), 406.1 (M +1);

[0874] EXAMPLE 148

[0875] Synthesis of 5-chloro-2-fluoro-4-(((*1S,2R,5S*)-2-isopropyl-5-methylcyclohexyl)oxy)-*N*-(methylsulfonyl)benzamide

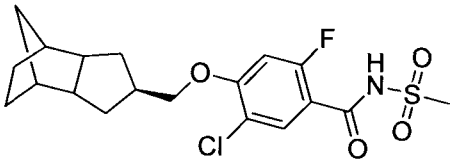


[0876] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with *D*-Menthol, the title compound was obtained as a colorless solid (0.24 g,

32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.25-7.97 (m, 1H), 6.81-6.60 (m, 1H), 4.23-3.98 (m, 1H), 3.42 (s, 3H), 2.20-2.03 (m, 2H), 1.83-1.44 (m, 5H), 1.27-1.02 (m, 2H), 1.01-0.84 (m, 6H), 0.79-0.69 (m, 3H); MS (ES +) *m/z* 406.1 (M +1), 408.1 (M +1);

[0877] EXAMPLE 149

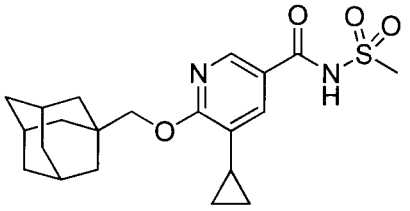
[0878] Synthesis of 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((*2s,3aR,4S,7R,7aS*)-octahydro-1*H*-4,7-methanoinden-2-yl)methoxy)benzamide



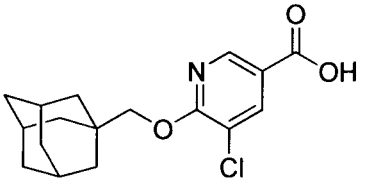
[0879] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with ((*2s,3aR,4S,7R,7aS*)-octahydro-1*H*- 4,7-methanoinden-2-yl)methanol, the title compound was obtained as a colorless solid (0.15 g, 35%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 12.5 Hz, 1H), 3.92 (d, J = 6.8 Hz, 2H), 3.34 (s, 3H), 2.49-2.36 (m, 2H), 2.22-2.10 (m, 3H), 1.75-1.30 (m, 9H), 1.04-1.00 (m, 1H); MS (ES-) m/z 414.1, 416.1 (M - 1).

[0880] EXAMPLE 150

[0881] Synthesis of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-(methylsulfonyl)nicotinamide

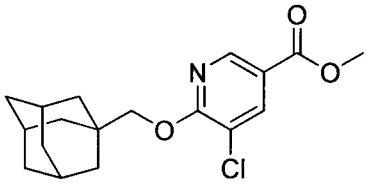


[0882] Step 1. Preparation of 6-(adamantan-1-ylmethoxy)-5-chloronicotinic acid



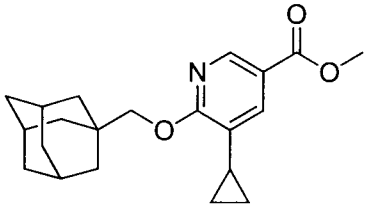
[0883] A mixture of 1-adamantylmethanol (5.32 g, 32.00 mmol), 5,6-dichloronicotinic acid (6.14 g, 32.00 mmol) and potassium *tert*-butoxide (8.3 g, 73.60 mmol) in anhydrous dimethyl sulfoxide (100 mL) was heated to 80 °C under nitrogen for 1 h. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (500 mL) and 1.0 M aqueous hydrochloric acid (300 mL). The layers were separated and the organic layer was washed with 1.0 M aqueous hydrochloric acid (100 mL), brine (2 x 100 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was triturated with diethyl ether to afford the title compound as a white solid (4.32 g, 42%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.23 (br s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 3.95 (s, 1H), 2.00-1.88 (m, 3H), 1.71-1.50 (m, 12H); MS (ES-) *m/z*: 320.3, 322.3 (M - 1).

[0884] Step 2. Preparation of methyl 6-(adamantan-1-ylmethoxy)-5-chloronicotinate



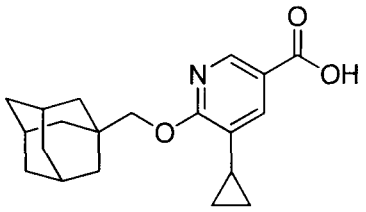
[0885] A solution of 6-(adamantan-1-ylmethoxy)-5-chloronicotinic acid (4.20 g, 13.10 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (5.00 g, 26.10 mmol), triethylamine (3.6 mL, 26.10 mmol) and methanol (1.05 mL, 26.10 mmol) in methylene chloride (100 mL) was stirred under nitrogen for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL). The mixture was washed with a 1:1(v/v) mixture of 1 M aqueous hydrochloric acid/brine (2 x 100 mL), brine (2 x 100 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 10% ethyl acetate in hexanes to afford the title compound as a white solid (1.90g, 43%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66-8.62 (m, 1H), 8.19-8.16 (m, 1H), 3.99 (s, 2H), 3.89 (s, 3H), 2.04-1.96 (m, 3H), 1.78-1.62 (m, 12H).

[0886] Step 3. Preparation of methyl 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinate



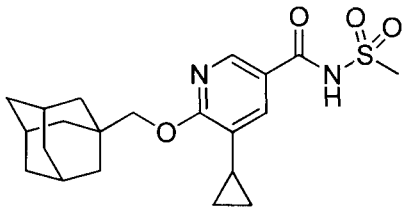
[0887] A mixture of methyl 6-(adamantan-1-ylmethoxy)-5-chloronicotinate (1.29 g, 3.84 mmol), cyclopropylboronic acid (0.43 g, 4.99 mmol), potassium phosphate (3.26 g, 15.40 mmol), tricyclohexylphosphine tetrafluoroborate (0.14 g, 0.38 mmol) and palladium acetate (0.04 g, 0.19 mmol)in degassed toluene (50 mL) and degassed water (5 mL) was refluxed under nitrogen for 7 h. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (100 mL), washed with water (50 mL), saturated ammonium chloride (50 mL) and brine (50 mL); dried over anhydrous sodium sulfate, filtered through diatomaceous earth and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 5% ethyl acetate in hexanes to afford the title compound as a white solid (1.17g, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J= 2.2 Hz, 1H), 7.67 (d, J= 2.2 Hz, 1H), 3.95 (s, 2H), 3.85 (s, 3H), 2.09-1.96 (m, 4H), 1.78-1.63 (m, 12H), 0.99-0.91 (m, 2H), 0.72-0.65 (m, 2H); MS (ES+) *m/z*: 342.22 (M + 1).

[0888] Step 4. Preparation of 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid



[0889] A mixture of methyl 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinate (1.17 g, 3.43 mmol) and lithium hydroxide monohydrate (0.58 g, 13.70 mmol) in tetrahydrofuran (60 mL) and water (10 mL) was refluxed for 2 h. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (100 mL); washed with 1 M aqueous hydrochloric acid (80 mL) and brine (80 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo* to afford the title compound which was used without further characterization. MS (ES+) *m/z*: 328.2 (M + H).

[0890] Step 5. Preparation of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-(methylsulfonyl)-nicotinamide

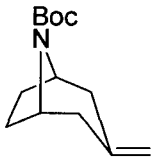


[0891] A solution of 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid (0.43 g, 1.31 mmol) and carbonyldiimidazole (0.42 g, 2.62 mmol) in anhydrous tetrahydrofuran (22 mL) was refluxed under nitrogen for 30 min. The reaction mixture was cooled to ambient temperature and treated with 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.59 mL, 3.93 mmol) and methylsulfonamide (0.54 g, 3.93 mmol). The resulting mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with ethyl acetate (60 mL), washed with 1 M aqueous hydrochloric acid (2 x 30 mL) and brine (50 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with 30% ethyl acetate (containing 0.2% acetic acid) in hexanes to afford the title compound as a white solid (0.31 g, 58%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 8.47 (d, J = 2.5 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 3.93 (s, 2H), 3.33 (s, 3H), 2.07-1.98 (m, 1H), 1.97-1.90 (m, 3H), 1.72-1.56 (m, 12 H), 0.98-0.90 (m, 2H), 0.76-0.70 (m, 2H); MS (ES+) *m/z*: 405.2 (M + H).

[0892] EXAMPLE 151

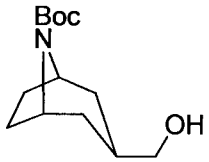
[0893] Synthesis of 5-chloro-2-fluoro-N-methanesulfonyl-4-{[(1R,3S,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl]methoxy}benzamide

[0894] Step 1. Preparation of tert-butyl 3-methylidene-8-azabicyclo[3.2.1]octane-8-carboxylate



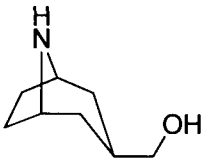
[0895] To a solution of methyltriphenylphosphonium bromide (2.38 g, 6.6 mmol) in dry THF at 0 °C was added n-BuLi (2.7 mL, 2.5 M) dropwise. After stirring at 0 °C for 30 min, (1R,5S)-tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (500 mg, 2.2 mmol) was added and the mixture was stirred at 0 °C for additional 16 hrs. The reaction was quenched by sat. NH_4Cl and extracted with EtOAc (50 mL × 3) and purified by SGC (eluting with petroleum ether/ethyl acetate = 20/1) to give target compound (130 mg, 27%). ^1H NMR (500 MHz, $CDCl_3$) δ 4.77 (t, J = 4.0 Hz, 2H), 4.21 (br s, 1H), 4.11 (br s, 1H), 2.43-2.33 (m, 2H), 2.01 (s, 1H), 1.98 (s, 1H), 1.79 (d, J = 3.0 Hz, 2H), 1.53-1.49 (m, 2H), 1.43 (s, 9H).

[0896] Step 2. Preparation of tert-butyl 3-(hydroxymethyl)-8-azabicyclo[3.2.1]- octane-8-carboxylate



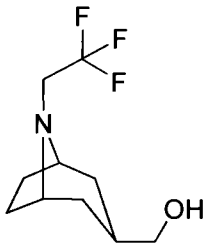
[0897] To a solution of tert-butyl 3-methylidene-8-azabicyclo[3.2.1]octane-8-carboxylate (0.8 g , 3.6 mmol) in dry THF (30 mL) at 0 °C was added a solution of borane-THF complex (4.7 mL, 1 M) and the resulting reaction was allowed to stir at room temperature for 48 hrs. The reaction was cooled to 0 °C then treated with NaOH (5.4 mL, 2 M) and hydrogen peroxide solution (1.8 mL, 35%). After stirring at room temperature for 3 hrs, the resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by SGC (eluting with petroleum ether/ethyl acetate = 20/1) to give the desired product (0.9 g, 90%). LCMS (ESI) m/z: 239.9 $[M-H]^-$.

[0898] Step 3. Preparation of 8-azabicyclo[3.2.1]octan-3-ylmethanol



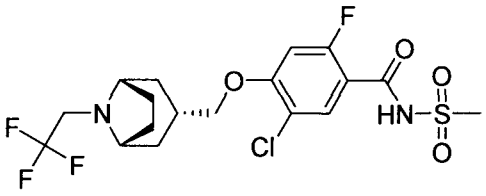
[0899] A mixture of (1R,5S)-tert-butyl 3-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8- carboxylate (0.9 g, 3.7 mmol) and HCl in dioxane (2 N, 5.0 mL) was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to afford the desired product (300 mg crude), which was used in the next step without further purification. LCMS (ESI) m/z: 139.7 $[M-H]^-$.

[0900] Step 4. Preparation of 8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl)methanol



[0901] A mixture of 8-aza-bicyclo[3.2.1]octan-3-ylmethanol (300 mg, 2.4 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (660 mg, 2.8 mmol) and $NaHCO_3$ (400 mg, 4.8 mmol) in ethanol (10 mL) was stirred at 80 °C for 4 hrs. The mixture was diluted with ethyl acetate (100 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by SGC (eluting with petroleum ether/ethyl acetate = 10/1) to give the desired product (180 mg, 38% yield). LCMS (ESI) m/z: 222.0 $[M-H]^-$.

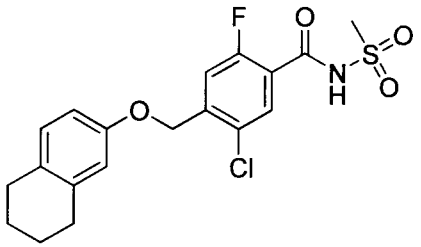
[0902] Step 5. Preparation of 5-chloro-2-fluoro-N-methanesulfonyl-4-{[(1R,3S,5S)-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octan-3-yl]methoxy}benzamide



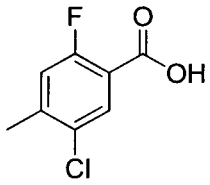
[0903] A mixture of (8-(2,2,2-trifluoroethyl)-8-aza-bicyclo[3.2.1]octan-3-yl)methanol (60 mg, 0.27 mmol), 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (78 mg, 0.27 mmol) and potassium t-butoxide (60 mg, 0.54 mmol) in DMSO (2 mL) was stirred at room temperature for 16 hrs. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were concentrated in vacuo and the residue was purified by reverse phase Combiflash (20%-50% MeCN in 0.1% NH_4HCO_3) to give the desired product (22.5 mg, 23%). LCMS (ESI) Method A: RT = 5.12 min, m/z: 472.7$[M+H]^+$; ^{1}H-NMR (500 MHz, MeOD-d_4) δ 7.81 (d, J = 7.5 Hz, 1H), 7.01(d, J = 12.0 Hz, 1H), 4.09 (d, J = 8.0 Hz, 2H), 3.33-3.29 (m, 5H), 3.06-3.00 (m, 2H), 2.31-2.18 (m, 3H), 2.04-2.01 (m, 2H), 1.70-1.62 (m, 4H).

[0904] EXAMPLE 152

[0905] Synthesis of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-((5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)benzamide

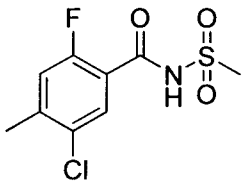


[0906] Step 1. Preparation of 5-chloro-2-fluoro-4-methylbenzoic acid



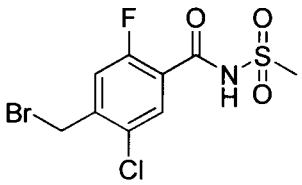
[0907] To a solution of 1-bromo-5-chloro-2-fluoro-4-methylbenzene (11.3 g, 50 mmol) in dry THF (100 mL) was added isopropylmagnesium chloride (30 mL, 2 M) dropwise. After stirring at room temperature for 30 min, dry CO_2 was added and the mixture was stirred at room temperature for additional 30 min. The reaction was quenched by sat. NH_4Cl and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with water (50 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give the desired product (4.7 g, 49%). LCMS (ESI) m/z: 187.0 $[M-H]^-$.

[0908] Step 2. Preparation of 5-chloro-2-fluoro-4-methyl-N-(methylsulfonyl)benzamide



[0909] A solution of 5-chloro-2-fluoro-4-methylbenzoic acid (1 g, 5.2 mmol), methanesulfonamide (760 mg, 8.0 mmol), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 g, 8.0 mmol) and 4-dimethylaminopyridine (1.5 g, 8.0 mmol) in DCM (20 mL) was stirred at room temperature for 16 hrs. The reaction was quenched by water (5 mL), adjusted pH to 1 with HCl (1 M) and the resulting mixture was extracted with DCM (100 mL × 3). The combined organic layers were concentrated in vacuo and the residue was recrystallized with petroleum ether and ethyl acetate to give desired product (1.6 g crude). LCMS (ESI) m/z: 263.9 $[M+H]^+$.

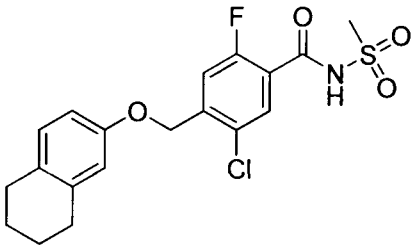
[0910] Step 3. Preparation of 4-(bromomethyl)-5-chloro-2-fluoro-N-(methylsulfonyl)benzamide



[0911] A mixture of 5-chloro-2-fluoro-4-methyl-N-(methylsulfonyl)benzamide (0.8 g, 3.0 mmol), N-bromosuccinimide (1.6 g, 9.0 mmol) and azodiisobutyronitrile (16 mg, 0.09 mmol) in 1,2-dichloroethane (20 mL) was stirred at 90 °C for 16 hrs. The reaction was quenched with $Na_2S_2O_3$ (10 mL, 10%), extracted with 1,2-dichloroethane (20 mL × 3), dried over anhydrous Na_2SO_4, concentrated and

the residue was used in next step without further purification (1.1 g , crude). LCMS (ESI) m/z: 342.0 $[M+H]^+$.

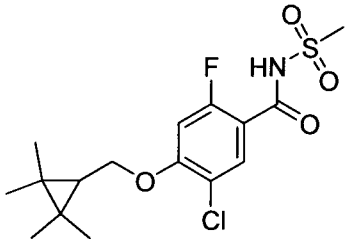
[0912] Step 4. Preparation of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-((5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)benzamide



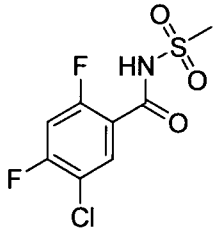
[0913] A mixture of 4-(bromomethyl)-5-chloro-2-fluoro-N-(methylsulfonyl)benzamide (40 mg, 0.12 mmol), 5,6,7,8-tetrahydronaphthalen-2-ol (40 mg, 0.24 mmol) and K_2CO_3 (60 mg, 0.24 mmol) in acetone (10 mL) was stirred at 50 °C for 4 h. The reaction was filtered and purified by reverse phase Combiflash (20%-50% MeCN in 0.1% formic acid) to give target compound (7.7 mg, 16%) as a white solid. LCMS (ESI) Method A: RT = 4.12 min, m/z: 412.1 $[M+H]^+$. ^{1}H-NMR (400 MHz, MeOD-d_4) δ 7.80 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 5.6 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.74-6.68 (m, 2H), 5.11 (s, 2H), 3.20 (s, 3H), 2.74-2.70 (m, 4H), 1.80-1.77 (m, 4H).

[0914] EXAMPLE 153

[0915] Synthesis of 5-chloro-2-fluoro-N-(methylsulfonyl)-4-((2,2,3,3-tetramethyl-cyclopropyl)methoxy)benzamide



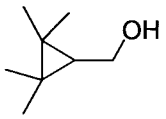
[0916] Step 1. Preparation of 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide



[0917] To a mixture of 5-chloro-2,4-dilfluorobenzoic acid (0.291 g, 1.51 mmol), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.438 g, 2.29 mmol), and 4-dimethylaminopyridine (0.420 g, 3.44 mmol) in THF (5 mL) was added methanesulfonamide (0.222 g, 2.33 mmol). After stirred at room temperature for 18 hrs, the mixture was diluted with DCM (10 mL) and

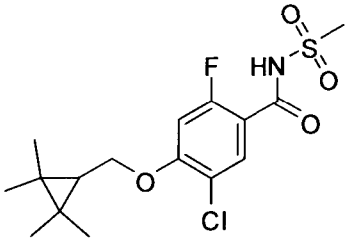
washed with 2 N HCl (15 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (0.388 g, 95%) as a white solid. LCMS (ESI) m/z: 268.1 $[M-H]^+$.

[0918] Step 2. Preparation of (2,2,3,3-Tetramethylcyclopropyl)methanol



[0919] To a stirred solution of 2,2,3,3-tetramethylcyclopetanecarboxylic acid (500 mg, 3.50 mmol) in THF (25 mL) at 0 °C was added borane dimethylsulfide complex in THF (2.0 M, 1.8 mL, 3.5 mmol). The mixture was then warmed to 50 °C and stirred for 3 h. After cooling to room temperature, methanol (10 mL) was added carefully. The resulting mixture was filtered and the filtrate was concentrated to afford (2,2,3,3-tetramethylcyclopropyl)methanol (250 mg, 56%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (d, J = 8.0 Hz, 2H), 1.10 (s, 6H), 1.02 (s, 6H), 0.54 (t, J = 8.0 Hz, 1H).

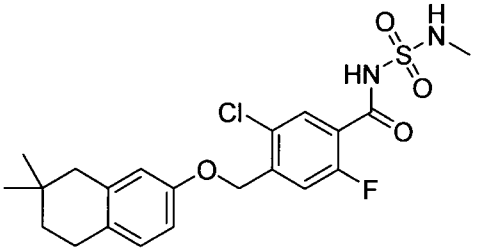
[0920] Step 3. Preparation of 5-Chloro-2-fluoro-*N*-(methylsulfonyl)-4-((2,2,3,3-tetramethyl-cyclopropyl)methoxy)benzamide



[0921] To a stirred solution of (2,2,3,3-tetramethylcyclopropyl)methanol (48 mg, 0.37 mmol) in dry DMSO (5 mL) was added potassium t-butoxide (124 mg, 1.11 mmol) at room temperature. After stirring for 30 min, 5-chloro-2,4-difluoro-N-(methylsulfonyl)benzamide (50 mg, 0.20 mmol) was added and the reaction mixture was stirred at room temperature for 16 hrs. The mixture was cooled to 0 °C, quenched by hydrochloride acid (1N, 30 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with water (40 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by prep HPLC (20%-50% MeCN in 0.1% formic acid) to afford the title compound as a white solid (7mg, 10%). LCMS (ESI) Method A: RT = 5.28 min, m/z: 268.1 $[M-109]^+$; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.13 (br s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.21-7.10 (m, 1H), 4.18 (d, J = 7.0 Hz, 2H), 3.02 (s, 3H), 1.10 (s, 6H), 1.03 (s, 6H), 0.74 (t, J = 7.5 Hz, 1H).

[0922] EXAMPLE 154

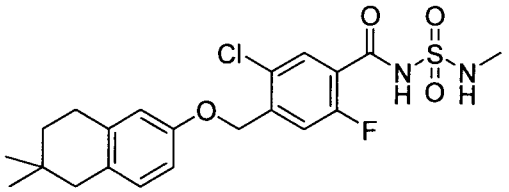
[0923] Synthesis of 5-Chloro-2-fluoro-*N*-(methylsulfonyl)-4-((2,2,3,3-tetramethyl-cyclopropyl)methoxy)benzamide



[0924] The synthetic procedure was the same as Example 152. LCMS (ESI) Method B: RT = 6.09 min, m/z: 455.1 $[M+H]^+$; ^{1}H-NMR (500 MHz, MeOD-d_4): δ 7.76 (d, J = 6.5 Hz, 1H), 7.43 (d, J = 10.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.78-6.76 (m, 1H), 6.72 (s, 1H), 5.10 (s, 2H), 2.67 (t, J = 13 Hz, 2H), 2.51-2.47 (m, 5H), 1.50 (t, J = 13.5 Hz, 2H), 0.93 (s, 6H).

[0925] EXAMPLE 155

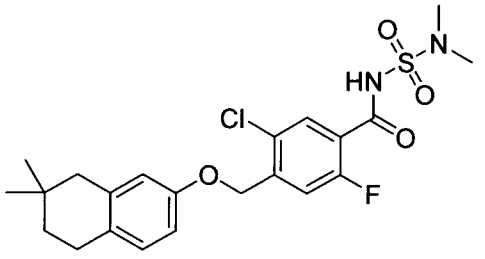
[0926] Synthesis of 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-2-fluoro-N-(N-methylsulfamoyl)benzamide



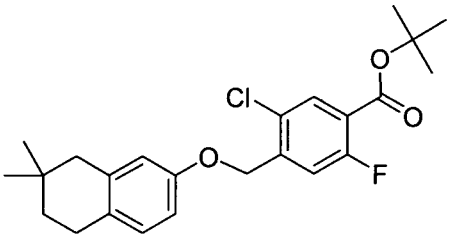
[0927] The synthetic procedure was the same as Example 152. LCMS (ESI) Method A: RT = 6.34 min, m/z: 455.1 $[M+H]^+$; ^{1}H-NMR (500 MHz, MeOD-d_4): δ 7.75 (d, J = 6.5 Hz, 1H), 7.41 (d, J = 10.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.78-6.76 (m, 2H), 5.10 (s, 2H), 2.72 (t, J = 7.0 Hz, 2H), 2.46-2.42 (m, 5H), 1.49 (t, J = 6.5 Hz, 2H), 0.93 (s, 6H).

[0928] EXAMPLE 156

[0929] Synthesis of 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-N-(N,N-dimethylsulfamoyl)-2-fluorobenzamide

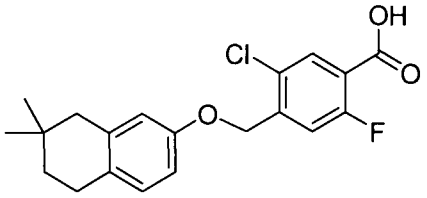


[0930] Step 1. Preparation of tert-butyl 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-2-fluorobenzoate



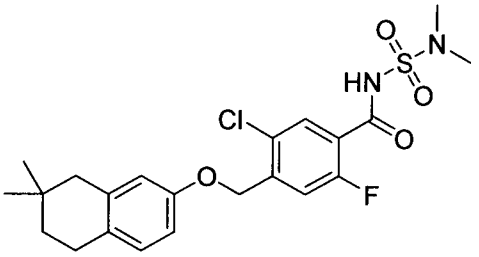
[0931] A solution of tert-butyl 4-(bromomethyl)-5-chloro-2-fluorobenzoate (200 mg, 0.62 mmol), 7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (109 mg, 0.62 mmol) and potassium carbonate (257 mg, 1.86 mmol) in acetone (20 mL) was stirred at 50 °C for 4 hrs. The reaction mixture was filtered, the filtrate was concentrated and purified by SGC (eluting with petroleum ether/ethyl acetate from 100/ 1 to 25/ 1) to get the desired compound (220 mg, 85%).

[0932] Step 2. Preparation of 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-2-fluorobenzoic acid



[0933] To a solution of tert-butyl 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-2-fluorobenzoate (220 mg, 0.53 mmol) in DCM (5 mL) was added trifluoroactic acid (5 mL). After stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure and the residue was used in next step without further purification (0.22 g, crude). LCMS (ESI) m/z: 361.0 $[M-H]^+$.

[0934] Step 3. Preparation of 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-N-(N,N-dimethylsulfamoyl)-2-fluorobenzamide

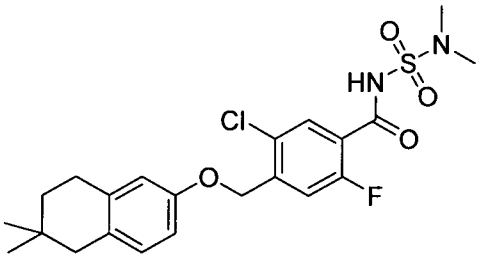


[0935] A solution of 5-chloro-4-((7,7-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-2-fluorobenzoic acid (50 mg, 0.14 mmol), dimethyl(sulfamoyl)amine (326 mg, 0.20 mmol), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (38 mg, 0.20 mmol) and 4-dimethylaminopyridine (38 mg, 0.20 mmol) in DCM (3 mL) was stirred at room temperature for 16 hrs. The reaction was quenched with water (5 mL), adjusted pH to 5 with HCl (1M) and extracted with DCM

(30 mL × 3). The combined organic layers were concentrated and purified by reverse phase combiflash (20%-50% MeCN in 0.1% formic acid) to give the desired product (14.6 mg, 19%) as a white solid. LCMS (ESI) Method A: RT = 6.47 min, m/z 466.9 $[M-H]^+$; ^{1}H-NMR (500 MHz, MeOD-d_4) δ 7.63 (d, J = 5.5 Hz, 1H), 7.32 (d, J = 11.0 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.66-6.63 (m, 1H), 6.56 (d, J = 2.0 Hz, 1H), 5.03 (s, 2H), 2.83 (s, 6H), 2.64 (t, J = 13.0 Hz, 2H), 2.40 (s, 2H), 1.46 (t, J = 13.5 Hz, 2H), 0.88 (s, 6H).

[0936] EXAMPLE 157

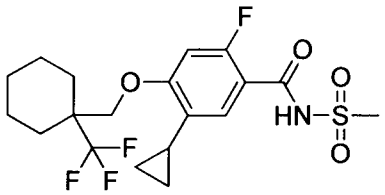
[0937] Synthesis of 5-chloro-4-((6,6-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-N-(N,N-dimethylsulfamoyl)-2-fluorobenzamide



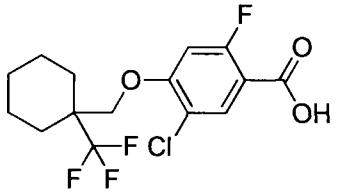
[0938] The synthetic procedure was the same as Example 156. LCMS (ESI) Method A: RT = 6.61 min, m/z: 468.7 $[M+H]^+$; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.76 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 11.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.77-6.75 (m, 2H), 5.13 (s, 2H), 2.89 (s, 6H), 2.80 (t, J = 6.5 Hz, 2H), 2.48 (s, 2H), 1.57 (t, J = 6.5 Hz, 2H), 0.99 (s, 6H).

[0939] EXAMPLE 158

[0940] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



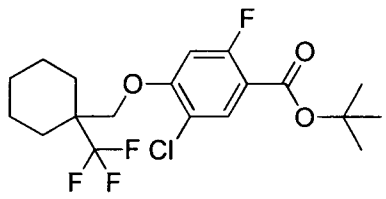
[0941] Step 1. Preparation of 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)benzoic acid



[0942] To a solution of (1-(trifluoromethyl)cyclohexyl)methanol (3.20 g, 17.57 mmol) in anhydrous dimethylsulfoxide (50 ml) was added potassium *tert*-butoxide (4.90 g, 43.66 mmol) and the reaction mixture was stirred at ambient temperature for 30 minutes. 5-chloro-2,4-difluorobenzoic acid (3.38 g, 17.55 mmol) was added to the reaction mixture, and stirring was continued for 2 hours. The reaction mixture was acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with ethyl acetate, the combined organic extracts was washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (30% ethyl acetate in

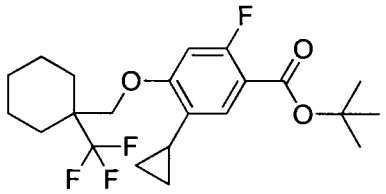
hexanes) afforded the title compound (5.20 g, 83%) containing *o*-substituted regioisomer, which was used for next step without further purification: MS(ES-) *m/z* 355.2, 353.2 (M - 1).

[0943] Step 2. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)-methoxy)benzoate



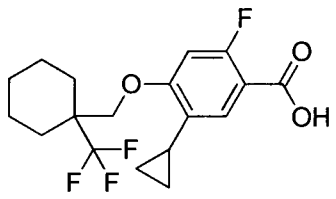
[0944] To a solution of 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)- methoxy)benzoic acid (5.20 g, 14.65 mmol) and *N,N*-dimethylpyridin-4-amine (0.5g, 4.16 mmol) in *tert*-butanol (50 mL) was added di-*tert*-butyldicarbonate (9.60 g, 43.98 mmol). The reaction mixture was heated at 50 °C for 6 hours. Additional di-*tert*-butyldicarbonate (4.80 g, 21.99 mmol) was added; stirring was continued for 17 hours at 50 °C and concentrated in *vacuo*. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to afford the title compound (4.37 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 11.7 Hz, 1H), 4.10 (s, 2H), 1.97-1.88 (m, 3H), 1.76-1.62 (m, 5H), 1.56 (s, 9H), 1.48-1.23 (m, 2H).

[0945] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzoate



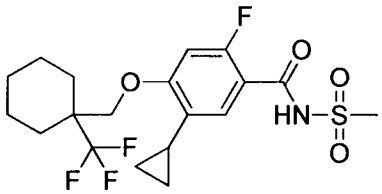
[0946] To a mixture of *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)-methoxy)benzoate (4.37 g, 10.63 mmol), cyclopropylboronic acid (1.37 g, 15.93 mmol), potassium phosphate (10.15 g, 47.81 mmol) and tricyclohexylphosphine tetrafluoroborate (0.39 g, 1.06 mmol) in toluene (60 mL) and water (3 mL) under a nitrogen atmosphere was added palladium acetate (0.12 g, 0.53 mmol). The reaction mixture was heated at 100 °C for 18 hours and then cooled to ambient temperature. Water (20 mL) was added and the mixture, and extracted with ethyl acetate, the combined organic extracts was washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded the title compound (3.70 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 12.3 Hz, 1H), 4.07 (s, 2H), 1.99-1.88 (m, 4H), 1.76-1.62 (m, 5H), 1.55 (s, 9H), 1.48-1.24 (m, 2H), 0.91-0.82 (m, 2H), 0.62-0.55 (m, 2H).

[0947] Step 4. Preparation of 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzoic acid



[0948] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)-methoxy)benzoate (3.70 g, 8.88 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated in *vacuo*. The residue was triturated in hexanes (10 mL), the solid was filtered and dried to give the title compound (2.20 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 12.3 Hz, 1H), 4.11 (s, 2H), 2.03-1.88 (m, 3H), 1.76-1.60 (m, 5H), 1.50-1.21 (m, 3H), 0.94-0.83 (m, 2H), 0.64-0.55 (m, 2H); MS(ES+) *m/z* 361.1 (M + 1).

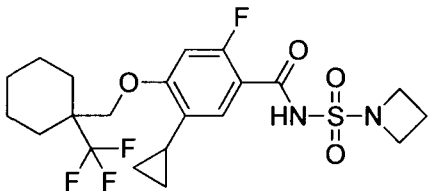
[0949] Step 5. Preparation of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)- 4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0950] To a stirred solution of 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzoic acid (0.36 g, 1.00 mmol) in dichloromethane (20 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.29 g, 1.50 mmol) and 4-dimethylaminopyridine (0.28 g, 2.30 mmol). The reaction was stirred at ambient temperature for 10 minutes, methanesulfonamide (0.15 g, 1.56 mmol) was added and the stirring was continued at ambient temperature for 17 hours. 5% aqueous hydrochloric acid solution (10 mL) were added and diluted with ethyl acetate (100 mL), washed with water and brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (30% ethyl acetate in hexanes) afforded the title compound (0.27 g, 62%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.59 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 14.1 Hz, 1H), 4.12 (s, 2H), 3.39 (s, 3H), 2.03-1.88 (m, 3H), 1.76-1.63 (m, 5H), 1.48-1.23 (m, 3H), 0.94-0.87 (m, 2H), 0.64-0.58 (m, 2H); MS(ES-) *m/z* 436.2 (M - 1).

[0951] EXAMPLE 159

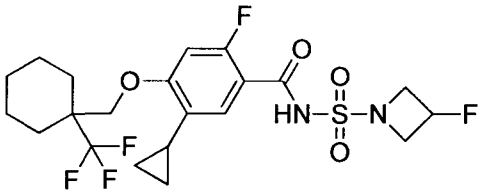
[0952] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0953] Following the procedure as described in Example 158 step 5, and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.30 g, 63%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.62 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 14.1 Hz, 1H), 4.23 (t, J = 7.5 Hz, 4H), 4.12 (s, 2H), 2.31-2.20 (m, 2H), 2.05-1.89 (m, 3H), 1.78-1.62 (m, 5H), 1.48-1.23 (m, 3H), 0.93-0.87 (m, 2H), 0.66-0.59 (m, 2H); MS(ES-) *m/z* 477.2 (M - 1).

[0954] EXAMPLE 160

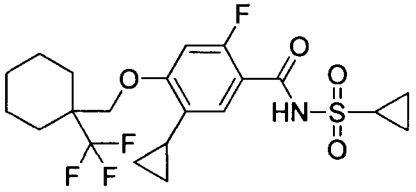
[0955] Synthesis of 5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)-sulfonyl)-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0956] Following the procedure as described in Example 158 step 5 and making variations as required to replace methanesulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.27 g, 54%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (br s, 1H), 7.60 (d, J = 9.0 Hz, 1H), 6.60 (d, J = 14.1 Hz, 1H), 5.39-5.13 (m, 1H), 4.52-4.32 (m, 4H), 4.12 (s, 2H), 2.31-2.20 (m, 2H), 2.05-1.87 (m, 2H), 1.78-1.62 (m, 4H), 1.48-1.23 (m, 3H), 0.94-0.87 (m, 2H), 0.65-0.59 (m, 2H); MS(ES-) *m/z* 495.1 (M - 1).

[0957] EXAMPLE 161

[0958] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide

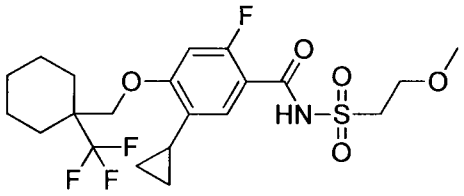


[0959] Following the procedure as described in Example 158 step 5, and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.24 g, 51%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 15.9 Hz, 1H), 7.61 (d, J = 9.3 Hz, 1H),

6.59 (d, J = 14.1 Hz, 1H), 4.12 (s, 2H), 3.13-3.03 (m, 1H), 2.04-1.88 (m, 3H), 1.76-1.63 (m, 5H), 1.48-1.23 (m, 5H), 1.69-1.08 (m, 2H), 0.94-0.86 (m, 2H), 0.65-0.58 (m, 2H); MS (ES-) *m/z* 462.2 (M - 1); MS (ES+) *m/z* 464.1 (M +1).

[0960] EXAMPLE 162

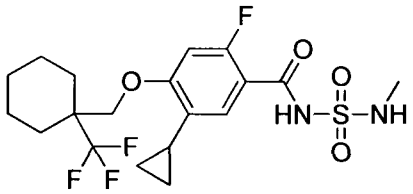
[0961] Synthesis of 5-cyclopropyl-2-fluoro-*N*-((2-methoxyethyl)- sulfonyl)-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[0962] Following the procedure as described in Example 158 step 5, and making variations as required to replace methanesulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained (0.03 g, 6%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 15.6 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 14.1 Hz, 1H), 4.12 (s, 2H), 3.87-3.75 (m, 4H), 3.29 (s, 3H), 2.03-1.88 (m, 3H), 1.78-1.63 (m, 5H), 1.48-1.28 (m, 3H), 0.94-0.86 (m, 2H), 0.65-0.58 (m, 2H); MS(ES-) *m/z* 480.1 (M - 1); MS(ES+) *m/z* 482.0 (M +1).

[0963] EXAMPLE 163

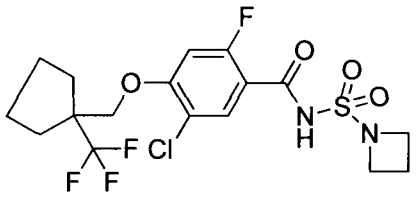
[0964] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(*N*-methylsulfamoyl)-4-((1-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



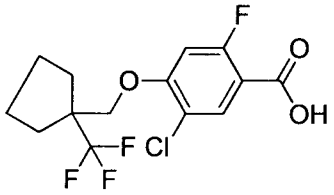
[0965] Following the procedure as described in Example 158 step 5 and making variations as required to replace methanesulfonamide with (methylsulfamoyl)amine, the title compound was obtained (0.22 g, 65%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 15.3 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 14.1 Hz, 1H), 5.26-5.22 (m, 1H), 4.12 (s, 2H), 2.75 (d, J = 4.5 Hz, 3H), 2.04-1.88 (m, 3H), 1.74-1.63 (m, 5H), 1.50-1.27 (m, 3H), 0.94-0.86 (m, 2H), 0.64-0.58 (m, 2H); MS(ES-) *m/z* 451.1 (M - 1). MS(ES+) *m/z* 453.0 (M +1).

[0966] EXAMPLE 164

[0967] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)-cyclopentyl)methoxy)benzamide

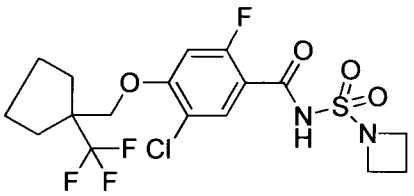


[0968] Step 1. Preparation of 5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclopentyl)methoxy)benzoic acid



[0969] To a solution of (1-(trifluoromethyl)cyclopentyl)methanol (2.80 g, 16.65 mmol) in anhydrous dimethylsulfoxide (50 ml) was added potassium *tert*-butoxide (4.50 g, 40.106 mmol) and the reaction mixture was stirred at ambient temperature for 30 minutes. 5-chloro-2,4-difluorobenzoic acid (3.20 g, 16.62 mmol) was added to the reaction mixture, and stirring was continued for 2 hours. The reaction mixture was acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with ethyl acetate, the combined organic extracts was washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (30% ethyl acetate in hexanes) afforded the title compound (5.00 g, 88%) containing o-substituted regioisomer, which was used for next step without further purification: MS(ES-) *m/z* 339.2, 341.2 (M - 1).

[0970] Step 2. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)-cyclopentyl)methoxy)benzamide

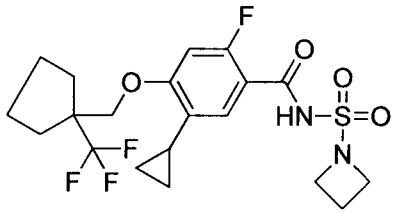


[0971] To a stirred solution of 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclopentyl)- methoxy)benzoic acid (0.34 g, 1.00 mmol) in dichloromethane (20 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.29 g, 1.50 mmol) and 4-dimethylaminopyridine (0.28 g, 2.30 mmol). The reaction mixture was stirred at ambient temperature for 10 minutes, azetidine-1-sulfonamide (0.20 g, 1.50 mmol) was added and the stirring was continued at ambient temperature for 17 hours. 5% aqueous hydrochloric acid solution (10 mL) were added and diluted

with ethyl acetate (100 mL), washed with water and brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (30% ethyl acetate in hexanes) afforded the title compound (0.22 g, 46%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 8.11 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 12.9 Hz, 1H), 4.22 (br s, 4H), 4.03 (s, 2H), 2.31-2.17 (m, 2H), 2.08-1.92 (m, 2H), 1.89-1.70 (m, 6H); MS(ES+) *m/z* 459.0, 461.0 (M + 1); MS(ES-) *m/z* 457.1, 459.1 (M - 1).

[0972] EXAMPLE 165

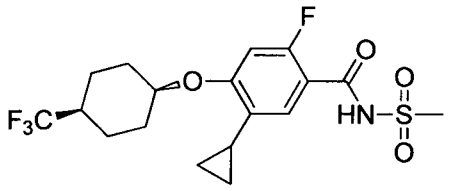
[0973] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclopentyl)methoxy)benzamide



[0974] To a mixture of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)-cyclopentyl)methoxy)benzamide (0.18 g, 0.39 mmol), cyclopropylboronic acid (0.40 g, 4.65 mmol) and potassium phosphate (2.55 g, 12.00 mmol) in toluene (20 mL) and water (1.0 mL) was sparged with a nitrogen atmosphere for 10 minutes, tricyclohexylphosphine tetrafluoroborate (0.17 g, 0.48 mmol) and palladium acetate (0.05 g, 0.22 mmol) was added to this reaction mixture. The reaction mixture was heated to 100 °C for 96 hours under a nitrogen atmosphere and then cooled to ambient temperature. 5% aqueous hydrochloric acid (20 mL) was added and the mixture was extracted with ethyl acetate (100 mL x 3), the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% gradient ethyl acetate in hexanes) afforded the title compound (0.11 g, 61%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 16.2 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 6.57 (d, J = 14.1 Hz, 1H), 4.23 (t, J = 7.5Hz, 4H), 3.99 (s, 2H), 2.31-2.20 (m, 2H), 2.08-1.94 (m, 3H), 1.89-1.70 (m, 6H), 0.95-0.88 (m, 2H), 0.67-0.60 (m, 2H); MS(ES+) *m/z* 465.1 (M + 1), MS(ES-) *m/z* 463.1(M - 1).

[0975] EXAMPLE 166

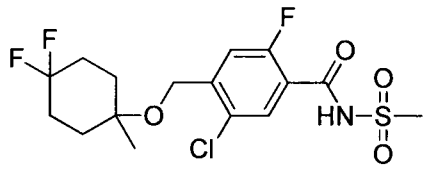
[0976] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-((*trans*-4-(trifluoromethyl)-cyclohexyl)oxy)benzamide



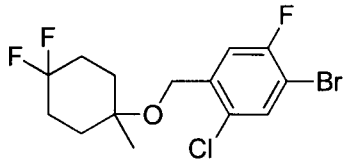
[0977] Following the procedure as described in Example 165 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclopentyl)methoxy)benzamide with 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((*trans*-4- (trifluoromethyl)cyclohexyl)oxy)benzamide, the title compound was obtained (0.24 g, 57%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 16.2 Hz,1H), 7.61 (d, J = 9.0 Hz, 1H), 6.55 (d, J = 14.7 Hz, 1H), 4.69-4.65 (m, 1H), 3.39 (s, 3H), 2.24-1.95 (m, 4H), 1.83-1.55 (m, 6H), 0.97-0.89 (m, 2H), 0.66-0.60 (m, 2H); MS(ES-) *m/z* 422.2 (M - 1); MS(ES+) *m/z* 424.1 (M + 1).

[0978] EXAMPLE 167

[0979] Synthesis of 5-chloro-4-(((4,4-difluoro-1-methylcyclohexyl)oxy)methyl)-2-fluoro-N-(methylsulfonyl)benzamide

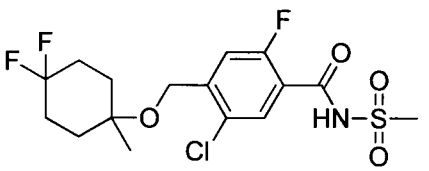


[0980] Step 1. Preparation of 1-bromo-5-chloro-4-(((4,4-difluoro-1-methylcyclohexyl)oxy)-methyl)-2-fluorobenzene



[0981] To a solution of 4-bromo-2-chloro-5-fluorobenzyl 2,2,2-trichloroacetimidate (4.00 g, 10.40 mmol) and 4,4-difluoro-1-methylcyclohexanol (1.21 g, 8.05 mmol) in methylene chloride (50 mL) and cyclohexane (25 mL) was added trifluoromethanesulfonic acid (0.1 mL, 0.14 mmol) at 0 ?C. The reaction mixture was stirred for 56 hours at ambient temperature and quenched by addition of saturated sodium bicarbonate solution (10 mL), and then diluted with methylene chloride (100 mL). The organic layer was separated and washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) and recrystalization from methanol afforded the title compound (0.54 g, 17%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 6.0 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 4.37 (s, 2H), 2.11-1.86 (m, 6H), 1.72-1.59 (m, 2H), 1.26 (s, 3H).

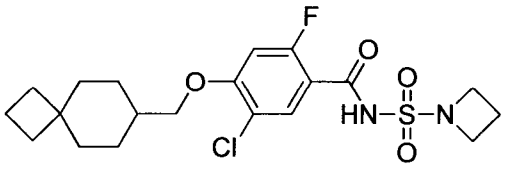
[0982] Step 2. Preparation of 5-chloro-4-(((4,4-difluoro-1-methylcyclohexyl)- oxy)methyl)-2-fluoro-*N*-(methylsulfonyl)benzamide



[0983] A mixture of 1-bromo-5-chloro-4-(((4,4-difluoro-1-methylcyclohexyl)-oxy)methyl)-2-fluorobenzene (0.20 g, 0.50 mmol), methanesulfonamide (0.14 g, 1.50 mmol), molybdenumhexacarbonyl (0.13 g, 0.50 mmol) and triethylamine (0.3 mL, 2.15 mmol) in dioxane was sparged with nitrogen for 5 minutes, xantphos (0.05 g, 0.09 mmol) and palladium acetate (0.01 g, 0.045 mmol) were added to the reaction mixture. The reaction mixture was heated at 100 □C for 1 hour under microwave irradiation (300 psi) and then cooled to ambient temperature, diluted with methylene chloride (100 mL) and saturated ammonium chloride (20 mL). The organic layer was washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% gradient ethyl acetate in hexanes) afforded the title compound (0.06 g, 28%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, J = 15.0 Hz, 1H), 8.05 (d, J = 6.9 Hz, 1H), 7.42 (d, J = 12.9 Hz, 1H), 4.47 (s, 2H), 3.42 (s, 3H), 2.11-1.89 (m, 6H), 1.74-1.62 (m, 2H), 1.27 (s, 3H); MS(ES-) *m/z* 412.1, 414.1 (M - 1).

[0984] EXAMPLE 168

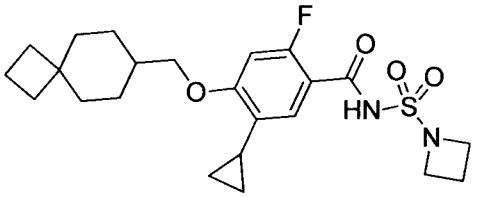
[0985] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide



[0986] To a solution of spiro[3.5]nonan-7-ylmethanol (0.58 g, 3.76 mmol) in anhydrous dimethyl sulfoxide (20 mL) was added potassium *t*-butoxide (1.05 g, 9.35 mmol) at ambient temperature. After stirring at ambient temperature for 30 minutes, *N*-(azetidin-1-ylsulfonyl)-5- chloro-2,4-difluorobenzamide (1.17 g, 3.76 mmol) was added to the reaction mixture; stirring was continued at ambient temperature for 2 hours. The mixture was cooled to 0 °C and quenched with 5% aqueous hydrochloride acid (10 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (2 x 40 mL) and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the crude product was purified by silica gel column chromatography using 10-40% ethyl acetate (containing 0.2% acetic acid) in hexanes to afford the title compound as a colorless solid (0.60 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 15.6 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 13.8 Hz, 1H), 4.23 (t, J = 7.8 Hz, 4H), 3.82 (d, J = 6.3 Hz, 2H), 2.32-2.20 (m, 2H), 1.88-1.66 (m, 11H), 1.35-1.24 (m, 2H), 1.18-1.05 (m, 2H); MS(ES+) *m/z* 445.1, 447.1 (M + 1), MS(ES-) *m/z* 443.2, 445.2 (M - 1).

[0987] EXAMPLE 169

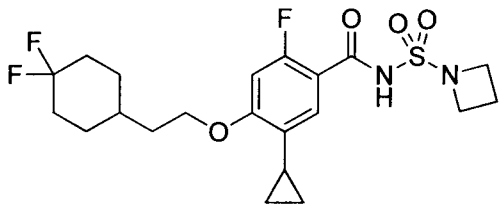
[0988] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[3.5]nonan-7-ylmethoxy)benzamide



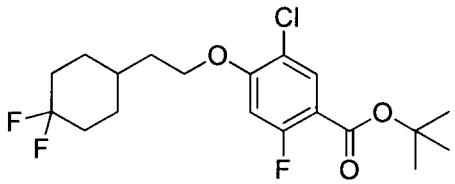
[0989] Following the procedure as described in Example 165 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclopentyl)methoxy)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4- (spiro[3.5]nonan-7-ylmethoxy)benzamide, the title compound was obtained (0.06 g 19%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 16.2 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 6.56 (d, J = 14.5 Hz, 1H), 4.24 (t, J = 7.7 Hz, 4H), 3.81 (d, J = 6.1 Hz, 2H), 2.26 (q, J = 7.7 Hz, 2H), 2.09-2.00 (m, 1H), 1.90-1.63 (m, 10H), 1.36-1.10 (m, 5H), 0.96-0.89 (m, 2H), 0.69-0.63 (m, 2H); MS (ES-) *m/z* 449.3 (M - 1).

[0990] EXAMPLE 170

[0991] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(2-(4,4-difluorocyclohexyl)-ethoxy)-2-fluorobenzamide



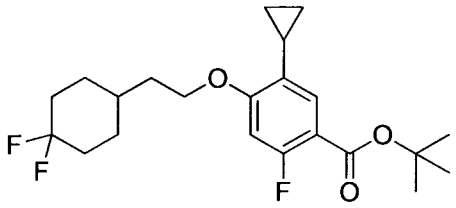
[0992] Step 1. Preparation of *tert*-butyl 5-chloro-4-(2-(4,4-difluorocyclohexyl)-ethoxy)-2-fluorobenzoate



[0993] To a of solution ethyl 2-(4,4-difluorocyclohexyl)acetate (1.44 g, 7.00 mmol) in anhydrous tetrahydrofuran (23 mL) and anhydrous methanol (0.6 mL) was added lithium borohydride (4 M in tetrahydrofuran, 3.5 mL, 16.00 mmol) at 0 °C and the mixture was heated to reflux for 2 hours. The mixture was then cooled to 0 °C and quenched with methanol until gas evolution ceased. The solution was warmed to ambient temperature then poured into water (50 mL). The aqueous layer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine; dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the crude alcohol (0.98 g), which was dissolved

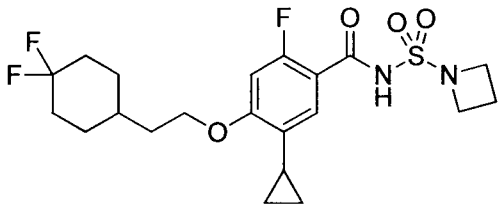
in anhydrous dimethylsulfoxide (6 mL), *tert*-butyl 5-chloro-2,4-difluorobenzoate (1.64 g, 6.60 mmol) and cesium carbonate (4.11 g, 12.6 mmol) was added. The reaction mixture was heated at 70 °C for 2 hours and then cooled to ambient temperature and diluted with water (60 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic layers were washed with brine; dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 10% ethyl acetate in hexanes) to afford the title compound (0.681g, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 12.1 Hz, 1H), 4.08 (t, J = 6.6 Hz, 2H), 2.17-2.07 (m, 2H), 1.77-1.62 (m, 5H), 1.57 (s, 9H), 1.42-1.29 (m, 4H).

[0994] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-(2-(4,4-difluorocyclohexyl)ethoxy)-2-fluorobenzoate



[0995] To a solution of *tert*-butyl 5-chloro-4-(2-(4,4-difluorocyclohexyl)ethoxy)-2- fluorobenzoate (0.681g, 1.70 mmol) in toluene-water (v/v 20:1, 10.5 mL) was added cyclopropylboronic acid (0.227 g, 2.60 mmol), tricyclohexylphosphine tetrafluoroborate (0.064 g, 0.17 mmol) and potassium phosphate tribasic (1.658 g, 7.80 mmol). The mixture was sparged with nitrogen gas for 10 minutes and sonicated for an additional 5 minutes. Palladium (II) acetate (0.019 g, 0.082 mmol) was added and the reaction mixture heated at 100 °C under nitrogen for 16 hours. The mixture was then cooled to ambient temperature then charged with additional cyclopropylboronic acid (0.227 g, 2.60 mmol), tricyclohexylphosphine tetrafluoroborate (0.070 g, 0.19 mmol) and palladium(II) acetate (0.021 g, 0.094 mmol). The mixture was heated to 100 °C and stirred for an additional 24 hours. The solution was then cooled to ambient temperature and filtered through diatomaceous earth with ethyl acetate. The solution was concentrated *in vacuo* and purified by column chromatography (0% to 20% ethyl acetate in hexanes) to afford the title compound (0.173 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 12.7 Hz, 1H), 4.04 (t, J = 6.2 Hz, 2H), 2.15-2.07 (m, 2H), 2.02-1.95 (m, 1H), 1.88-1.61 (m, 7H), 1.57 (s, 9H), 1.43-1.31 (m, 2H), 0.92-0.86 (m, 2H), 0.66-0.61 (m, 2H).

[0996] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- (2-(4,4-difluorocyclohexyl)-ethoxy)-2-fluorobenzamide

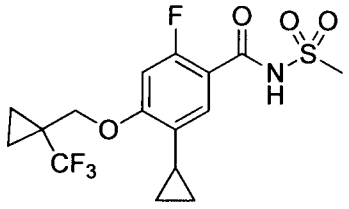


[0997] To a solution of *tert*-butyl 5-chloro-4-(2-(4,4-difluorocyclohexyl)ethoxy)- 2-fluorobenzoate (0.167 g, 0.42 mmol) in anhydrous dichloromethane (1 mL) was added trifluoroacetic acid (0.50 mL) and the mixture was stirred at ambient temperature for 1 hour. The solution was then concentrated *in vacuo*. The crude solid was carried directly to the next step without further purification: MS (ES-) *m/z* 341.3 (M - 1).

[0998] The crude acid was dissolved in anhydrous dichloromethane (11 mL). To this solution was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.124 g, 0.64 mmol) and 4-dimethylaminopyridine (0.119 g, 0.98 mmol), and the solution was stirred at ambient temperature for 5 minutes. Azetidine-1-sulfonamide (0.09 g, 0.69 mmol) was added to the reaction mixture and stirred for 16 hours. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with 5% aqueous hydrochloric acid (2 x 50 mL) and water (50 mL); and the combined aqueous layers were extracted with ethyl acetate (2 x 50 mL). The combined organic layers were then washed with brine (50 mL), dried with anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 30% ethyl acetate in hexanes) to afford the title compound (0.05 g, 25% in two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 16.0 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 6.59 (d, J = 14.3 Hz, 1H), 4.25 (t, J = 7.5 Hz, 4H), 4.09 (t, J = 6.2 Hz, 2H), 2.35-2.22 (m, 2H), 2.17-1.99 (m, 2H), 1.92-1.28 (m, 8H), 1.45-1.28 (m, 2H), 0.97-0.85 (m, 2H), 0.70-0.65 (m, 2H); MS (ES-) *m/z* 459.2(M - 1).

[0999] EXAMPLE 171

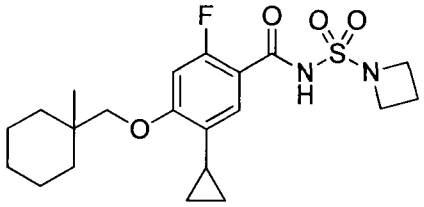
[01000] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-((1-(trifluoromethyl)-cyclopropyl)methoxy)benzamide



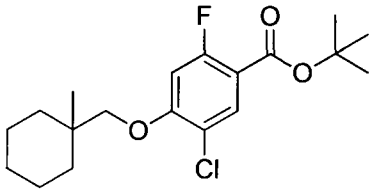
[01001] Following the procedure as described in Example 165 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclopentyl)- methoxy)benzamide with 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((1-(trifluoromethyl)- cyclopropyl)-methoxy)benzamide. Purification by reverse-phase preparative HPLC to yield the title compound (0.047 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (br s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 12.9 Hz, 1H), 4.23 (s, 2H), 3.31 (s, 3H), 2.09-2.00 (m, 1H), 1.16-1.11 (m, 2H), 1.07-1.02 (m, 2H), 0.93-0.86 (m, 2H), 0.72-0.66 (m, 2H); MS (ES-) *m/z* 394.1(M - 1).

[01002] EXAMPLE 172

[01003] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-methylcyclohexyl)methoxy)benzamide

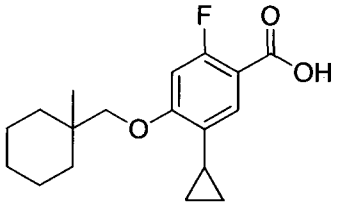


[01004] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((1-methylcyclohexyl)- methoxy)benzoate



[01005] To a solution of (1-methylcyclohexyl)methanol (4.98 g, 38.80 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (20.67 g, 83.10 mmol) in anhydrous dimethylsulfoxide (80 mL) was added cesium carbonate (25.14 g, 77.20 mmol). The mixture was heated to 70 °C and stirred for 16 hours. The mixture was then cooled to ambient temperature, filtered through a pad of diatomaceous earth and the solid was washed with ethyl acetate. The combined organic layers were washed with water and brine; dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 10% ethyl acetate in hexanes) to afford the title compound (6.26 g, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 6.62 (d, J = 12.2 Hz, 1H), 3.70 (s, 2H), 1.57 (s, 9 H), 1.52-1.31 (m, 10H), 1.08 (s, 3H).

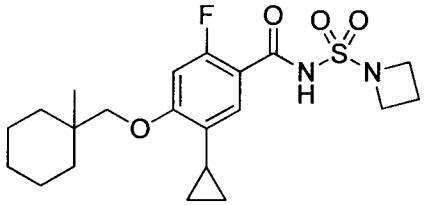
[01006] Step 2. Preparation of 5-cyclopropyl-2-fluoro-4-((1-methylcyclohexyl)methoxy)benzoic acid



[01007] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((1-methylcyclohexyl)methoxy)benzoate (1.63 g, 4.6 mmol) in toluene-water (v/v 20:1, 21 mL) was added tribasic potassium phosphate (4.37 g, 20.60 mmol), cyclopropylboronic acid (0.581 g, 6.80 mmol) and tricyclohexylphosphine tetrafluoroborate (0.168 g, 0.46 mmol). The mixture was sonicated for 5 minutes, and then sparged with nitrogen for 10 minutes; palladium acetate (0.053 g, 0.23 mmol) was added and the reaction mixture was heated to 100 °C and stirred for 16 hours under a nitrogen atmosphere. The reaction mixture was cooled to ambient temperature

and poured into water. The aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in anhydrous dichloromethane (8 mL) and trifluoroacetic acid (4 mL) was added. The mixture was stirred at ambient temperature for 3 hours and then concentrated *in vacuo*. The crude solid obtained was triturated with hexanes to provide the title compound (0.62 g, 44%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.80 (br s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 13.2 Hz, 1H), 3.79 (s, 2H), 2.06-1.96 (m, 1H), 1.48-1.17 (m, 10H), 1.04 (s, 3H), 0.92-0.86 (m, 2H), 0.61-0.56 (m, 2H).

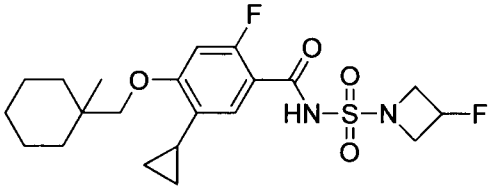
[01008] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-methylcyclohexyl)methoxy)benzamide



[01009] To a solution of 5-cyclopropyl-2-fluoro-4-((1-methylcyclohexyl)methoxy)benzoic acid (0.152 g, 0.50 mmol) in anhydrous dichloromethane (12 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.150 g, 0.78 mmol) and 4-dimethylaminopyridine (0.140 g, 1.10 mmol). The reaction mixture was stirred at ambient temperature for 10 minutes, and then azetidine-1-sulfonamide (0.106 g, 0.78 mmol) was added to the reaction mixture and stirred for 16 hours. The reaction mixture was poured into 5% aqueous hydrochloric acid, the layers separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL); dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% to 25% ethyl acetate in hexanes) to afford the title compound (0.15 g, 71%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br s, 1 H), 7.15 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 13.0 Hz, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.80 (s, 2H), 2.14-1.98 (m, 3H), 1.49-1.23 (m, 10H), 1.04 (s, 3H), 0.93-0.86 (m, 2H), 0.70-0.65 (m, 2H); MS(ES-) *m/z* 423.2 (M - 1).

[01010] EXAMPLE 173

[01011] Synthesis of 5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)-4-((1-methylcyclohexyl)methoxy)benzamide

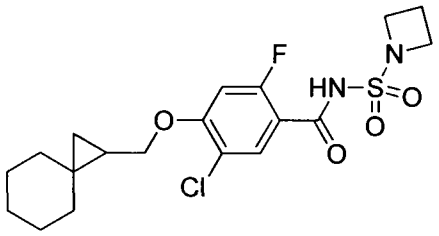


[01012] Following the procedure as described in EXAMPLE 172 step 3 and making variations as required to replace azetidine-1-sulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained

(0.14 g, 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 17.0 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 6.59 (d, J = 14.5 Hz, 1H), 5.37-5.18 (m, 1H), 4.53-4.34 (m, 4H), 3.72 (s, 2H), 2.09-1.99 (m, 1H) 1.55-1.25 (m, 10H), 1.09 (s, 3H), 0.97-0.90 (m, 2H), 0.69-0.63 (m, 2H); MS (ES-) *m/z* 441.2 (M - 1).

[01013] EXAMPLE 173

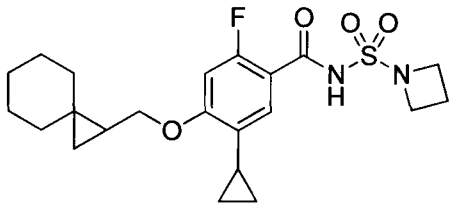
[01014] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(spiro[2.5]octan-1-ylmethoxy)benzamide



[01015] To a solution of spiro[2.5]octan-1-ylmethanol (prepared according to Huang and Forsyth, *Tetrahedron* **1997**, *53*, 16341) (0.40 g, 2.87 mmol) in anhydrous dimethylsulfoxide (5 mL) was added potassium *tert*-butoxide (0.81 g, 7.24 mmol) and the reaction mixture was stirred for 30 minutes at ambient temperature. To this reaction mixture was added *N*-(azetidin-1-ylsulfonyl)-5-chloro-2,4-difluorobenzamide (0.90 g, 2.89 mmol) and stirred for 2 hours. The mixture was poured into 1 M aqueous hydrochloric acid, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and brine; dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 30% ethyl acetate in hexanes) to afford the title compound (0.49 g, 39%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (br s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.5 Hz, 1H), 4.35-4.31 (dd, J = 10.9, 6.3 Hz, 1H), 4.04 (t, J = 7.7 Hz, 5H), 2.17 (q, J = 7.7 Hz, 2H), 1.77-0.94 (m, 11H), 0.57-0.55 (dd, J = 8.5, 4.3 Hz, 1H), 0.30 (t, J = 4.7 Hz, 1H); MS (ES-) *m/z* 429.20 (M – 1).

[01016] EXAMPLE 174

[01017] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-1-ylmethoxy)benzamide

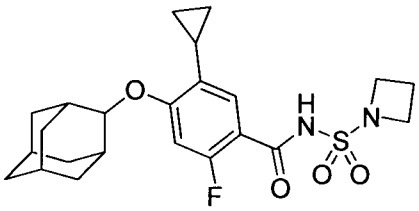


[01018] Following the procedure as described in Example 165 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclopentyl)methoxy)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4- (spiro[2.5]octan1-ylmethoxy)benzamide, the title

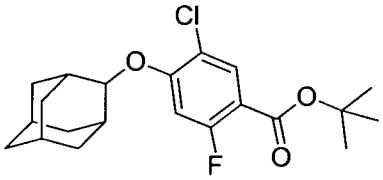
compound was obtained (0.03 g, 7%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 7.58 (d, J = 9.1 Hz, 1H), 6.58 (d, J = 14.4 Hz, 1H), 4.24 (t, J = 7.7 Hz, 5H), 3.86 (t, J = 9.6 Hz, 1H), 2.26 (q, J = 7.7 Hz, 2H), 2.15-2.05 (m, 1H), 1.79-1.18 (m, 10H), 1.14-1.04 (m, 1H), 0.96-0.92 (m, 2H), 0.77-0.58 (m, 3H), 0.28 (t, J = 5.0 Hz, 1H); MS (ES-) *m/z* 435.2 (M - 1).

[01019]EXAMPLE 175

[01020]Synthesis of 4-(adamantan-2-yloxy)-*N*-(azetidin-1-ylsulfonyl)- 5-cyclopropyl-2-fluorobenzamide

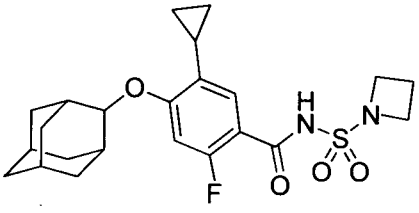


[01021]Step 1. Preparation of *tert*-butyl 4-(adamantan-2-yloxy)-5-chloro-2-fluorobenzoate



[01022]To a solution of 2-adamantanol (3.09 g, 20.26 mmol) in anhydrous dimethylsulfoxide (40 mL) was added *tert*-butyl 5-chloro-2,4-difluorobenzoate (6.56 g, 26.38 mmol) and cesium carbonate (13.20 g, 40.51 mmol), and the reaction mixture was heated at 70 °C for 16 hours. The solution was then cooled to ambient temperature and charged with an additional portion of 2-adamantanol (0.51 g, 3.34 mmol) and the reaction mixture was heated at 70 °C for an additional 24 hours. This process was repeated twice by addition of 2-adamantanol (0.49 g, 3.21 mmol) and (0.51 g, 3.31 mmol) respectively over an additional 48 hours. The mixture was cooled to ambient temperature and diluted with water (300 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL); dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes and then triturated with methanol to give the title compound (1.63 g, 16%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 12.5 Hz, 1H), 4.49 (br s, 1H), 2.20-2.10 (m, 4H), 1.99-1.68 (m, 10H), 1.57 (s, 9H).

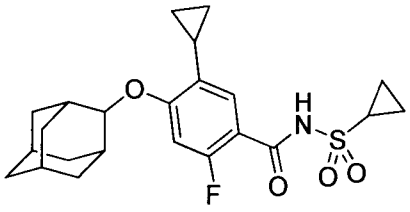
[01023]Step 2. Preparation of 4-(adamantan-2-yloxy)-*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide



[01024] To a solution of *tert*-butyl 4-(adamantan-2-yloxy)-5-chloro-2-fluorobenzoate in toluene-water (v/v 20:1, 20 mL) was added cyclopropylboronic acid (0.57 g, 6.65 mmol) and tribasic potassium phosphate (4.10 g, 19.31 mmol). The mixture was then sparged with argon for 5 minutes and was then charged with tricyclohexylphosphine tetrafluoroborate (0.33 g, 0.90 mmol) and palladium acetate (0.11 g, 0.47 mmol) and the reaction mixture was heated at 110 °C for 16 hours. The reaction mixture was cooled to ambient temperature, filtered through a pad of diatomaceous earth and washed with ethyl acetate, concentrated *in vacuo*. to give the crude product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 12.9 Hz, 1H), 4.45 (br s, 1H), 2.18-2.04 (m, 6H), 1.94-1.81 (m, 9H), 1.56 (s, 9H), 0.92-0.86 (m, 2H), 0.67-0.62 (m, 2H). The crude product was dissolved in anhydrous dichloromethane (6 mL), and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred for 2 hours at ambient temperature; concentrated *in vacuo* to give the crude carboxylic acid (1.02 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.6 Hz, 1H), 6.56 (d, J = 13.2 Hz, 1H), 4.49 (br s, 1H), 2.20-1.70 (m, 12H), 1.62-1.53 (m, 1H), 1.34-1.17 (m, 2H), 0.96-0.90 (m, 2H), 0.69-0.64 (m, 2H). The crude carboxylic acid (0.34 g, 1.03 mmol) was dissolved in anhydrous dichloromethane (27 mL) and added 1-ethyl-3-(3-dimethylaminopropyl)- carbodiimide hydrochloride (0.30 g, 1.56 mmol) and 4-dimethylaminopyridine (0.30 g, 2.42 mmol), after stirring for 5 minutes, azetidine-1-sulfonamide (0.23 g, 1.69 mmol) was added and stirring was continued for 16 hours at ambient temperature. The mixture was then poured into a 5% aqueous solution of hydrochloric acid, the layers separated and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layers were then washed with distilled water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 30% ethyl acetate in hexanes) to afford the title compound (0.11g, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 16.5 Hz, 1H), 7.63 (d, J = 9.3 Hz, 1H), 6.56 (d, J = 14.8 Hz, 1H), 4.53-4.48 (m, 1H), 4.25 (t, J = 7.74 Hz, 4H), 2.32-2.07 (m, 7H), 2.01-1.79 (m, 8H), 1.62-1.58 (m, 2H), 0.97-0.90 (m, 2H), 0.71-0.65 (m, 2H); MS (ES-) *m/z* 447.2 (M - 1).

[01025] EXAMPLE 176

[01026] Synthesis of 4-(adamantan-2-yloxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)- 2-fluorobenzamide

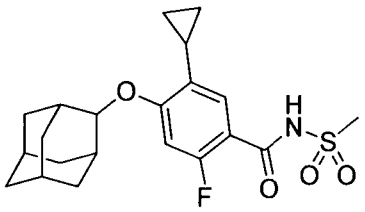


[01027] Following the procedure as described in Example 175 step 2 and making variations as required to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.15 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 16.1 Hz, 1H), 7.60 (d, J = 9.2 Hz, 1H), 6.55 (d, J = 14.8 Hz, 1H), 4.53-4.48 (m, 1H), 3.14-3.05 (m, 1H), 2.20-2.05 (m, 5H), 2.00 (s, 1H), 1.97-1.78 (m, 7H),

1.61-1.57 (m, 2H), 1.47-1.41 (m, 2H), 1.17-1.10 (m, 2H), 0.96-0.90 (m, 2H), 0.69-0.63 (m, 2H); MS (ES-) *m/z* 432.2 (M - 1).

[01028] EXAMPLE 177

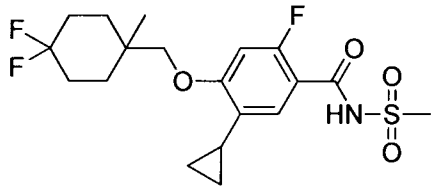
[01029] Synthesis of 4-(adamantan-2-yloxy)-5-cyclopropyl-2-fluoro- *N*-(methylsulfonyl)benzamide



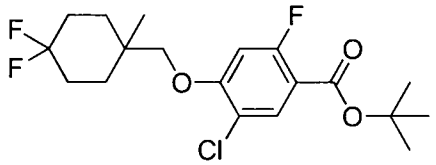
[01030] Following the procedure as described in Example 175 step 2 and making variations as required to replace cyclopropanesulfonamide with methanesulfonamide, the title compound was obtained (0.20 g, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 16.3 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H), 6.55 (d, J = 14.8 Hz, 1H), 4.53-4.47 (m, 1H), 3.41 (s, 3H), 2.20-1.79 (m, 12H), 1.09 (s, 3H), 0.98-0.91 (m, 2H), 0.69-0.64 (m, 2H); MS (ES-) *m/z* 406.2 (M - 1).

[01031] EXAMPLE 178

[01032] Synthesis of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluoro- *N*-(methylsulfonyl)benzamide

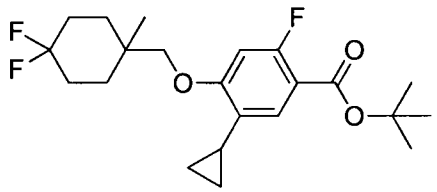


[01033] Step 1. Preparation of *tert*-butyl 5-chloro-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoate



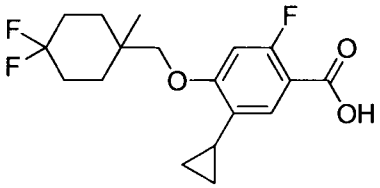
[01034] A mixture of (4,4-difluoro-1-methylcyclohexyl)methanol (3.05 g, 18.56 mmol)(PCT Int. Appl., WO2012025857, 2012), cesium carbonate (12.09 g, 37.12 mmol), and *tert*-butyl 5-chloro-2,4-difluorobenzoate (6.0 g, 24.13 mmol) in dimethylsulfoxide (70 mL) was stirred at 70 °C for 16 hours, cooled to ambient temperature and diluted with ethyl acetate (150 mL); washed with water (2 x 300 mL), brine (150 mL); dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography eluting with a gradient of ethyl acetate in hexanes (0 - 5%) afforded the title compound (3.69 g, 51%) as colorless oil: MS (ES +) *m/z* 393.1 (M +1).

[01035] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)- methoxy)-2-fluorobenzoate



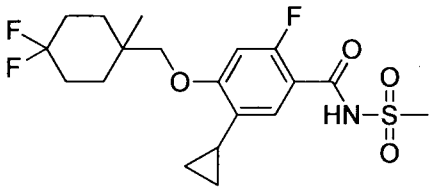
[01036] Following the procedure as described in Example 158 step 3, and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)- methoxy)benzoate with *tert*-butyl 5-chloro-4-((4,4-difluoro-1-methylcyclohexyl)- methoxy)-2-fluorobenzoate, the title compound was obtained as colorless oil (3.69 g, 99 %): MS (ES +) *m/z* 399.2 (M + 23).

[01037] Step 3. Preparation of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid



[01038] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl-4-((4,4-difluoro-1- methylcyclohexyl)methoxy)-2-fluorobenzoate, the title compound was obtained as a colorless solid (2.74 g, 86 %): MS (ES+) *m/z* 343.2 (M + 1).

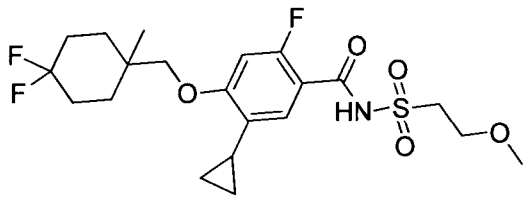
[01039] Step 4. Preparation of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[01040] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.144 g, 53 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79-8.65 (m, 1H), 7.68-7.56 (m, 1H), 6.64-6.53 (m, 1H), 3.76 (s, 2H), 3.42 (s, 3H), 2.08-1.73 (m, 7H), 1.69-1.58 (m, 2H), 1.17 (s, 3H), 1.00-0.89 (m, 2H), 0.69-0.60 (m, 2H); MS (ES +) *m/z* 420.1 (M +1).

[01041] EXAMPLE 179

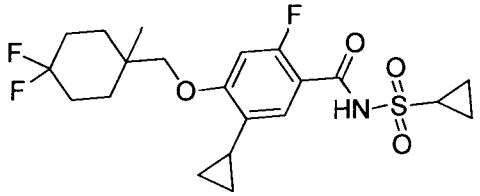
[01042] Synthesis of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide



[01043] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained (0.162 g, 55%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.57 (m, 1H), 7.68-7.55 (m, 1H), 6.63-6.51 (m, 1H), 3.94-3.70 (m, 6H), 3.31 (s, 3H), 2.08-1.75 (m, 7H), 1.68-1.58 (m, 2H), 1.17 (s, 3H), 0.99-0.89 (m, 2H), 0.70-0.60 (m, 2H); MS (ES +) *m/z* 464.1 (M +1).

[01044] EXAMPLE 180

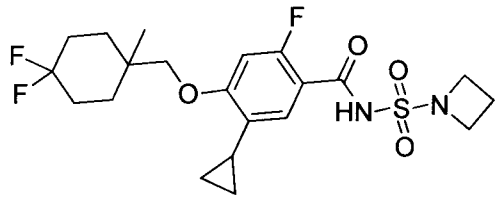
[01045] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)- 4-((4,4-difluoro-1-methylcyclohexyl)-methoxy)-2-fluorobenzamide



[01046] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.17 g, 61%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.62 (m, 1H), 7.68-7.58 (m, 1H), 6.63-6.50 (m, 1H), 3.76 (s, 2H), 3.15-3.05 (m, 1H), 2.09-1.74 (m, 7H), 1.69-1.57 (m, 2H), 1.50-1.41 (m, 2H), 1.22-1.09 (m, 5H), 1.00-0.89 (m, 2H), 0.70-0.60 (m, 2H); MS (ES +) *m/z* 446.1 (M +1).

[01047] EXAMPLE 181

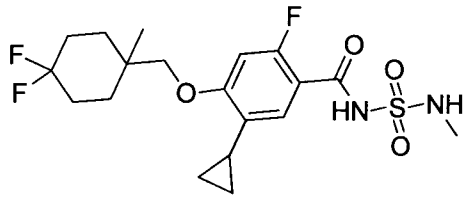
[01048] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((4,4-difluoro-1-methylcyclohexyl)-methoxy)-2-fluorobenzamide



[01049] Following the procedure as described in Example158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.17 g, 56%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.59 (m, 1H), 7.69-7.61 (m, 1H), 6.64-6.52 (m, 1H), 4.31-4.19 (m, 4H), 3.76 (s, 2H), 2.35-2.20 (m, 2H), 2.08-1.73 (m, 7H), 1.69-1.58 (m, 2H), 1.17 (s, 3H), 0.99-0.89 (m, 2H), 0.71-0.61 (m, 2H); MS (ES +) *m/z* 461.1 (M +1).

[01050] EXAMPLE 182

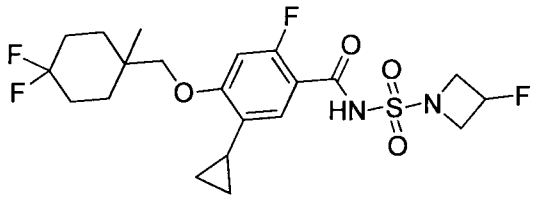
[01051] Synthesis of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[01052] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with (methylsulfamoyl)amine, the title compound was obtained (0.13 g, 47%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.62 (m, 1H), 7.66-7.56 (m, 1H), 6.65-6.51 (m, 1H), 5.30-5.18 (m, 1H), 3.76 (s, 2H), 2.82-2.71 (m, 3H), 2.09-1.73 (m, 7H), 1.69-1.59 (m, 2H), 1.17 (s, 3H), 1.01-0.90 (m, 2H), 0.70-0.61 (m, 2H); MS (ES +) *m/z* 435.1 (M +1).

[01053] EXAMPLE 183

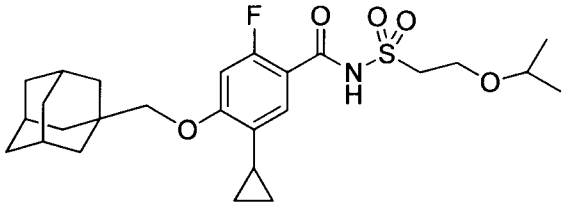
[01054] Synthesis of 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01055] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluoro-1-methylcyclohexyl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.06 g, 20%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81-8.63 (m, 1H), 7.70-7.58 (m, 1H), 6.66-6.50 (m, 1H), 5.45-5.13 (m, 1H), 4.59-4.29 (m, 4H), 3.77 (s, 2H), 2.09-1.74 (m, 7H), 1.69-1.60 (m, 2H), 1.17 (s, 3H), 1.01-0.89 (m, 2H), 0.71-0.60 (m, 2H); MS (ES +) *m/z* 479.1 (M +1).

[01056] EXAMPLE 184

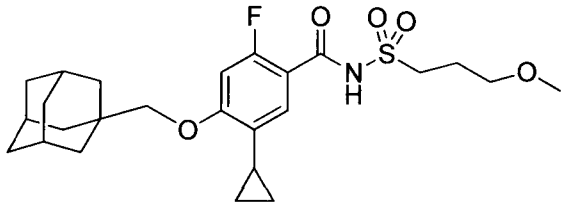
[01057] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2- fluoro-N-((2-isopropoxyethyl)-sulfonyl)benzamide



[01058] Following the procedure as described in Example 50 step 5 and making variations as required to replace methanesulfonamide with 2-methoxyethane-1-sulfonamide, the title compound was obtained as a colorless solid (0.155 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.55 (m, 1H), 7.64-7.55 (m, 1H), 6.62-6.50 (m, 1H), 3.94-3.72 (m, 4H), 3.62-3.48 (m, 3H), 2.11-1.97 (m, 4H), 1.86-1.64 (m, 12H), 1.09-0.99 (m, 6H), 0.99-0.88 (m, 2H), 0.70-0.59 (m, 2H); MS (ES +) *m/z* 494.2 (M +1).

[01059] EXAMPLE 185

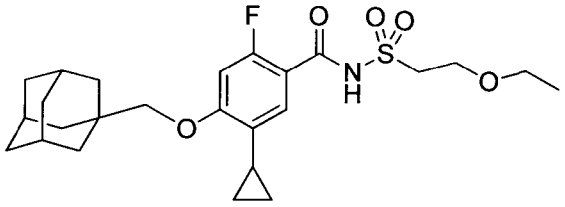
[01060] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-methoxypropyl)-sulfonyl)benzamide



[01061] Following the procedure as described in Example 50 step 5, and making variations as required to replace methanesulfonamide with 3-methoxypropane-1-sulfonamide, the title compound was obtained as a colorless solid (0.15 g, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.54 (m, 1H), 7.62-7.54 (m, 1H), 6.61-6.51 (m, 1H), 3.72-3.63 (m, 2H), 3.56 (s, 2H), 3.53-3.46 (m, 2H), 3.31 (s, 3H), 2.19-2.00 (m, 6H), 1.84-1.65 (m, 12H), 0.99-0.89 (m, 2H), 0.70-0.61 (m, 2H); MS (ES -) *m/z* 478.3 (M -1).

[01062] EXAMPLE 186

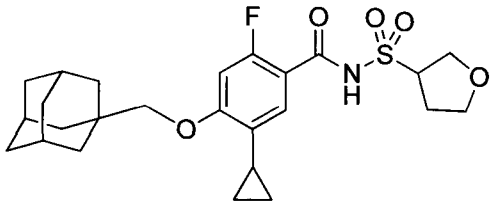
[01063] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((2-ethoxyethyl)sulfonyl)-2-fluorobenzamide



[01064] Following the procedure as described in Example 50 step 5, and making variations as required to replace methanesulfonamide with 2-ethoxyethanesulfonamide, the title compound was obtained as a colorless solid (0.114 g, 24%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67-8.54 (m, 1H), 7.62-7.54 (m, 1H), 6.61-6.51 (m, 1H), 3.72-3.63 (m, 2H), 3.56 (s, 2H), 3.53-3.46 (m, 2H), 3.31 (s, 3H), 2.19-2.00 (m, 6H), 1.84-1.65 (m, 12H), 0.99-0.89 (m, 2H), 0.70-0.61 (m, 2H); MS (ES -) *m/z* 478.3 (M -1).

[01065] EXAMPLE 187

[01066] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((tetrahydrofuran-3-yl)sulfonyl)benzamide

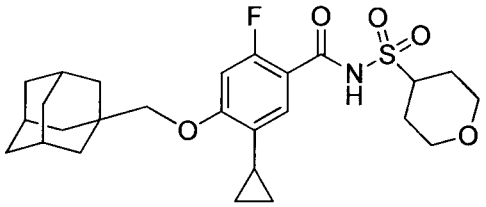


[01067] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide with

4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide and to replace methanesulfonyl chloride with tetrahydrofuran-3-sulfonyl chloride, the title compound was obtained as a colorless solid (0.14 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.60 (m, 1H), 7.60-7.53 (m, 1H), 6.63-6.53 (m, 1H), 4.62-4.48 (m, 1H), 4.33-4.23 (m, 1H), 4.16-3.82 (m, 3H), 3.56 (s, 2H), 2.58-2.44 (m, 1H), 2.42-2.26 (m, 1H), 2.10-1.99 (m, 4H), 1.84-1.66 (m, 12H), 1.00-0.89 (m, 2H), 0.70-0.61 (m, 2H); MS (ES +) *m/z* 478.1 (M +1).

[01068] EXAMPLE 188

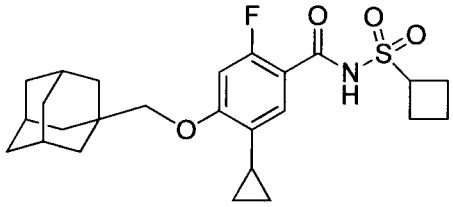
[01069] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((tetrahydro-2H-pyran-4-yl)sulfonyl)benzamide



[01070] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide and to replace methanesulfonyl chloride with tetrahydro-2*H*-pyran-4-sulfonyl chloride, the title compound was obtained as a colorless solid (0.15 g, 30%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55-8.44 (m, 1H), 7.60-7.52 (m, 1H), 6.62-6.52 (m, 1H), 4.17-3.90 (m, 3H), 3.56 (s, 2H), 3.47-3.36 (m, 2H), 2.12-1.95 (m, 8H), 1.84-1.65 (m, 12H), 1.00-0.90 (m, 2H), 0.71-0.58 (m, 2H); MS (ES +) *m/z* 492.21 (M +1).

[01071] EXAMPLE 189

[01072] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(cyclobutylsulfonyl)-5-cyclopropyl-2-fluorobenzamide

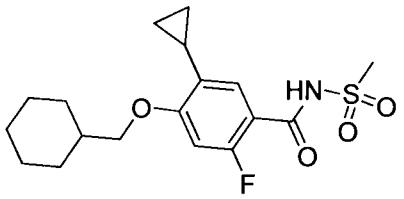


[01073] Following the procedure as described in Example 38 step 4 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-3-(2-methoxypyridin-3-yl)benzamide with 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide and to replace methanesulfonyl chloride with cyclobutanesulfonyl chloride, the title compound was obtained as a colorless solid (0.05 g, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57-8.44 (m, 1H), 7.60-7.52 (m, 1H), 6.61-6.48 (m, 1H), 4.61-4.46 (m, 1H), 3.55 (s,

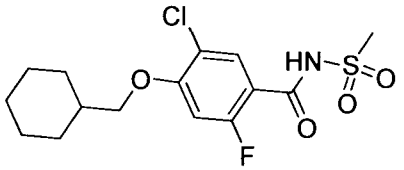
2H), 2.74-2.56 (m, 2H), 2.45-2.29 (m, 2H), 2.12-1.97 (m, 6H), 1.84-1.64 (m, 12H), 0.99-0.88 (m, 2H), 0.71-0.58 (m, 2H); MS (ES +) *m/z* 462.2 (M +1).

[01074] EXAMPLE 190

[01075] Synthesis of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro- *N*-(methylsulfonyl)benzamide

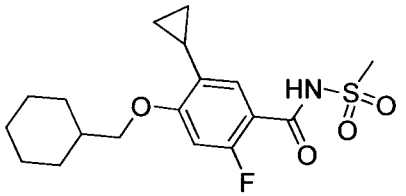


[01076] Step 1. 5-chloro-4-(cyclohexylmethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[01077] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with cyclohexylmethanol, the title compound was obtained as a colorless solid (0.53 g, 39%): MS (ES -) *m/z* 362.2, 364.2 (M -1).

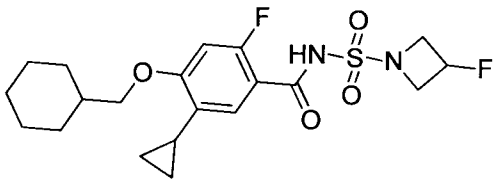
[01078] Step 2. Preparation of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



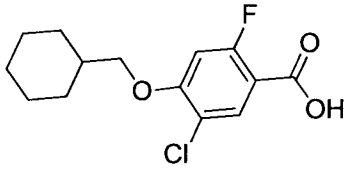
[01079] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-4-(cyclohexylmethoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.19 g, 14%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.66 (m, 1H), 7.61-7.52 (m, 1H), 6.62-6.52 (m, 1H), 3.86-3.78 (m, 2H), 3.41 (s, 3H), 2.12-1.99 (m, 1H), 1.95-1.66 (m, 6H), 1.40-1.03 (m, 5H), 0.99-0.89 (m, 2H), 0.69-0.61 (m, 2H); MS (ES -) *m/z* 368.3 (M -1).

[01080] EXAMPLE 191

[01081] Synthesis of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide

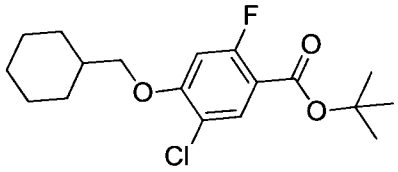


[01082] Step 1. Preparation of 5-chloro-4-(cyclohexylmethoxy)-2-fluorobenzoic acid



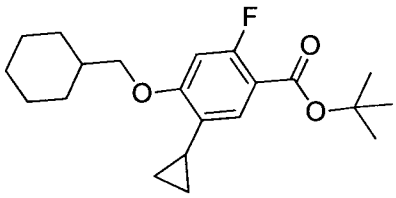
[01083] Following the procedure as described in Example 158 step 1, and making variations as required to replace (1-(trifluoromethyl)cyclohexyl)-methanol with cyclohexylmethanol, the title compound was obtained as colorless solid (41.16 g, 92 %) containing o-substituted regioisomer, which was used for next step without further purification: MS (ES-) *m/z* 285.2, 287.2 (M - 1).

[01084] Step 2. Preparation of *tert*-butyl 5-chloro-4-(cyclohexylmethoxy)-2-fluorobenzoate



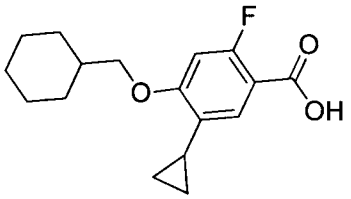
[01085] Following the procedure as described in Example 158 step 2 and making variations as required to replace 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)benzoic acid with 5-chloro-4-(cyclohexylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a colorless oil (15.37 g, 43 %): MS (ES+) *m/z* 381.2 (M + 39).

[01086] Step 3. Preparation of *tert*-butyl 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoate



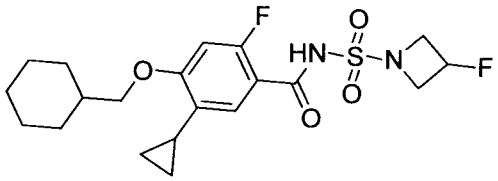
[01087] Following the procedure as described in Example 158 step 3 and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)- methoxy)benzoate with *tert*-butyl 5-chloro-4-(cyclohexylmethoxy)-2-fluorobenzoate, the title compound was obtained as colorless oil (13.73 g, 88 %): MS (ES+) *m/z* 387.2 (M + 39).

[01088] Step 4. Preparation of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid



[01089] Following the procedure as described in Example 158 step 4 and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)- methoxy)benzoate with *tert*-butyl 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoate, the title compound was obtained as a colorless solid (6.64 g, 58 %): MS (ES-) *m/z* 291.3 (M - 1).

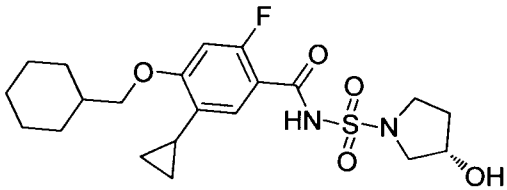
[01090] Step 5. Preparation of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3- fluoroazetidin-1-yl)sulfonyl)benzamide



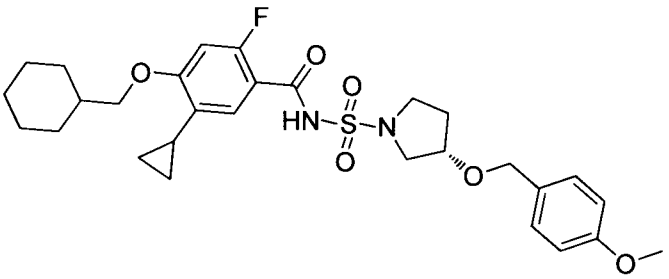
[01091] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.09 g, 35%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80-8.64 (m, 1H), 7.62-7.52 (m, 1H), 6.64-6.52 (m, 1H), 5.45-5.12 (m, 1H), 4.59-4.31 (m, 4H), 3.89-3.76 (m, 2H), 2.13-1.99 (m, 1H), 1.96-1.68 (m, 6H), 1.42-1.03 (m, 5H), 1.00-0.89 (m, 2H), 0.72-0.62 (m, 2H); MS (ES +) *m/z* 429.2 (M +1).

[01092] EXAMPLE 192

[01093] Synthesis of (*S*)-4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro- *N*-((3-hydroxypyrrolidin-1-yl)sulfonyl)benzamide

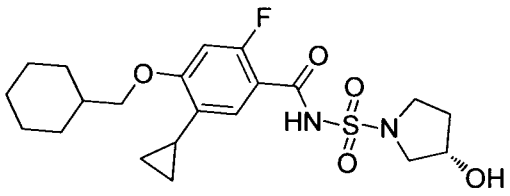


[01094] Step 1. Preparation of (*S*)-4-(cyclohexylmethoxy)-5-cyclopropyl-2- fluoro-N-((3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide



[01095] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with (3*S*)-3-((4-methoxybenzyl)oxy)- cyclopentane-1-sulfonamide, the title compound was obtained (0.22 g, 56%) as a colorless solid: MS (ES +) *m/z* 561.2 (M +1);

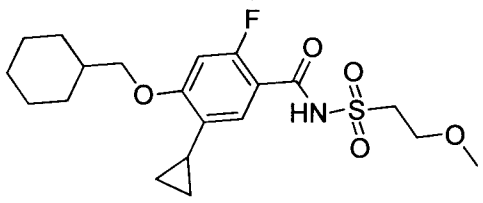
[01096] Step 2. Preparation of (*S*)-4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-hydroxypyrrolidin-1- yl)sulfonyl)benzamide



[01097] Following the procedure as described in Example 124 step 3 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-chloro-2- fluoro-*N*-(((*S*)-3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide with (*S*)-4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*- ((3-((4-methoxybenzyl)oxy)pyrrolidin-1-yl)sulfonyl)benzamide, the title compound was obtained as colorless solid (0.14 g, 78 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86-8.76 (m, 1H), 7.58-7.46 (m, 1H), 6.63-6.48 (m, 1H), 4.55-4.35 (m, 1H), 3.92-3.77 (m, 3H), 3.71-3.59 (m, 3H), 2.48 (br s, 1H), 2.13-1.96 (m, 3H), 1.95-1.67 (m, 6H), 1.42-1.02 (m, 5H), 0.98-0.85 (m, 2H), 0.69-0.57 (m, 2H); MS (ES +) *m/z* 441.1 (M +1).

[01098] EXAMPLE 193

[01099] Synthesis of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro- *N*-((2-methoxyethyl)-sulfonyl)benzamide

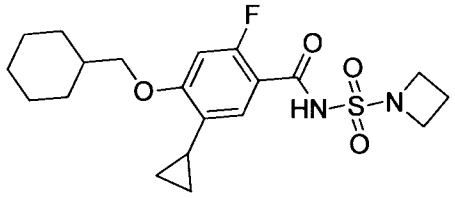


[01100] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with

4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained (0.16 g, 40%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70-8.59 (m, 1H), 7.58-7.51 (m, 1H), 6.61-6.51 (m, 1H), 3.90-3.74 (m, 6H), 3.31 (s, 3H), 2.11-1.99 (m, 1H), 1.95-1.67 (m, 6H), 1.41-1.04 (m, 5H), 0.98-0.89 (m, 2H), 0.69-0.61 (m, 2H); MS (ES -) *m/z* 412.3 (M -1);

[01101] EXAMPLE 194

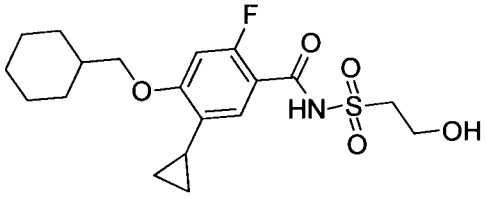
[01102] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-(cyclohexylmethoxy)- 5-cyclopropyl-2-fluorobenzamide



[01103] Following the procedure as described in preparation of Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.13 g, 47%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.61 (m, 1H), 7.62-7.55 (m, 1H), 6.62-6.51 (m, 1H), 4.30-4.18 (m, 4H), 3.86-3.76 (m, 2H), 2.34-2.20 (m, 2H), 2.13-2.00 (m, 1H), 1.96-1.67 (m, 6H), 1.41-1.02 (m, 5H), 0.99-0.87 (m, 2H), 0.72-0.61 (m, 2H); MS (ES -) *m/z* 409.3 (M -1).

[01104] EXAMPLE 195

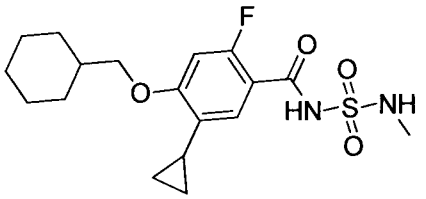
[01105] Synthesis of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*- ((2-hydroxyethyl)-sulfonyl)benzamide



[01106] Following the procedure as described in Example 121 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2-methoxyethyl)- sulfonyl)benzamide with 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2-methoxyethyl)- sulfonyl)benzamide, the title compound was obtained as colorless solid (0.03 g, 14 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.65 (m, 1H), 7.60-7.49 (m, 1H), 6.63-6.51 (m, 1H), 4.19-4.09 (m, 2H), 3.86-3.74 (m, 4H), 2.59-2.49 (m, 1H), 2.10-1.98 (m, 1H), 1.94-1.68 (m, 6H), 1.39-1.04 (m, 5H), 0.99-0.90 (m, 2H), 0.70-0.61 (m, 2H); MS (ES -) *m/z* 398.3 (M -1).

[01107]EXAMPLE 196

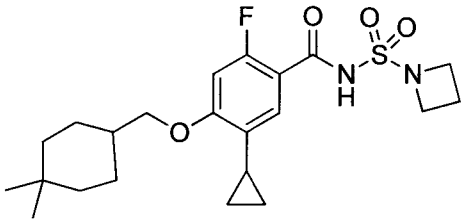
[01108]Synthesis of 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluoro- *N*-(*N*-methylsulfamoyl)benzamide



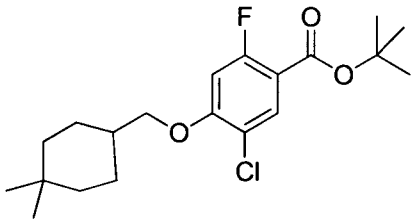
[01109]Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 4-(cyclohexylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with (methylsulfamoyl)amine, the title compound was obtained (0.13 g, 25%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76-8.65 (m, 1H), 7.57-7.50 (m, 1H), 6.62-6.52 (m, 1H), 5.31-5.22 (m, 1H), 3.86-3.78 (m, 2H), 2.79-2.74 (m, 3H), 2.11-1.99 (m, 1H), 1.95-1.65 (m, 6H), 1.41-1.03 (m, 5H), 0.98-0.89 (m, 2H), 0.69-0.61 (m, 2H); MS (ES -) *m/z* 383.3 (M -1).

[01110]EXAMPLE 197

[01111]Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((4,4-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



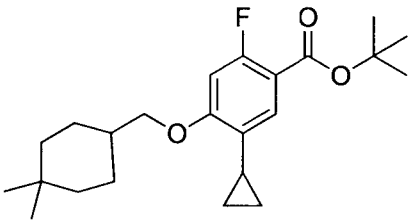
[01112]Step 1. Preparation of *tert*-butyl 5-chloro-4-((4,4-dimethyl-cyclohexyl)methoxy)-2-fluorobenzoate



[01113]To a cooled to 0 °C solution of 4,4-dimethylcyclohexanecarbaldehyde (1.42 g, 10.13 mmol) (PCT Int. Appl., WO 2012087519, 2012) in dry methanol (22 mL) was added sodium borohydride (0.766 g, 20.25 mmol). The reaction mixture was stirred at 0 °C for 1 hour, and then concentrated in *vacuo*. The residue was diluted with saturated aqueous ammonium chloride solution (25 mL) and extracted with ethyl acetate (3 x 85 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to afford the product (1.23 g) as a colorless oil. The oil was dissolved in dimethylsulfoxide (30 mL) and cesium carbonate (5.64 g, 17.3 mmol) was added followed by *tert*-butyl 5-chloro-2,4-difluorobenzoate (3.23 g, 12.97 mmol). The mixture was stirred at

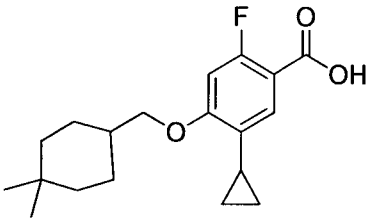
70 °C for 16 hours, then cooled to ambient temperature and diluted with ethyl acetate (150 mL). The mixture was washed with water (2 x 200 mL) and brine (150 mL); dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (0 - 10% ethyl acetate in hexanes) afforded the title compound (2.87 g, 89%) as colorless oil: MS (ES +) *m/z* 371.1 (M +1).

[01114] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((4,4-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate



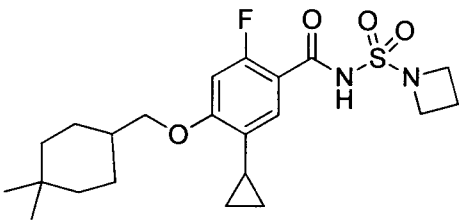
[01115] Following the procedure as described in Example 158 step 3, and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-chloro-4-((4,4-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate, the title compound was obtained as a pale yellow oil (2.13 g, 73 %): MS (ES +) *m/z* 399.2 (M +23).

[01116] Step 3. Preparation of 5-cyclopropyl-4-((4,4-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid



[01117] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl-4-((4,4-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate, the title compound was obtained as a colorless solid (0.356 g, 20 %): MS (ES+) *m/z* 321.2 (M + 1).

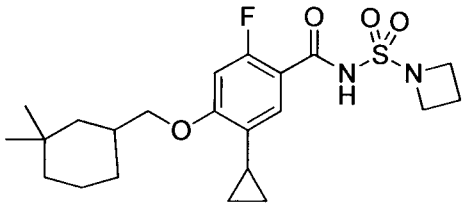
[01118] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((4,4-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



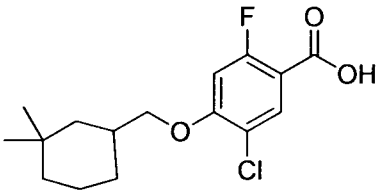
[01119] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 5-cyclopropyl-4-((4,4-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.16 g, 51%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.58 (m, 1H), 7.64-7.56 (m, 1H), 6.64-6.52 (m, 1H), 4.34-4.18 (m, 4H), 3.92-3.80 (m, 2H), 2.36-2.18 (m, 2H), 2.12-1.97 (m, 1H), 1.87-1.66 (m, 3H), 1.51-1.19 (m, 6H), 1.01-0.84 (m, 8H), 0.74-0.62 (m, 2H); MS (ES +) *m/z* 439.2 (M +1).

[01120] EXAMPLE 198

[01121] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((3,3-dimethylcyclohexyl)methoxy)-2-fluorobenzamide

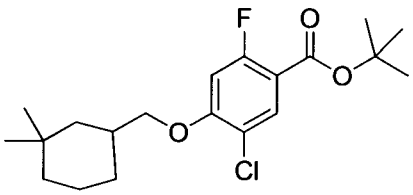


[01122] Step 1. Preparation of 5-chloro-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid



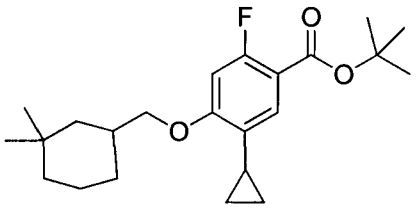
[01123] Following the procedure as described in Example 158 step 1 and making variations as required to replace (1-(trifluoromethyl)cyclohexyl)methanol with (3,3-dimethylcyclohexyl)methanol (*Jpn. Kokai Tokkyo Koho*, 61158943, 1986), the title compound was obtained as a pale yellow oil (2.74 g, 100 %) containing *o*-substituted regioisomer, which was used for next step without further purification: MS (ES-) *m/z* 313.2 (M - 1).

[01124] Step 2. *tert*-butyl 5-chloro-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate



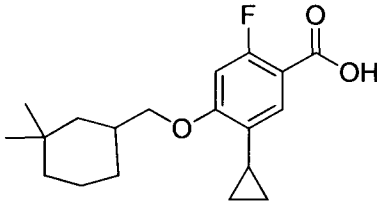
[01125] Following the procedure as described in Example 158 step 2 and making variations as required to replace 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)benzoic acid with 5-chloro-4-((3,3-dimethylcyclohexyl)methoxy)-2-fluorobenzoic acid, the title compound was obtained as pale yellow oil (3.20 g, 99 %): MS (ES-) *m/z* 316.9 (M - 54).

[01126] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate



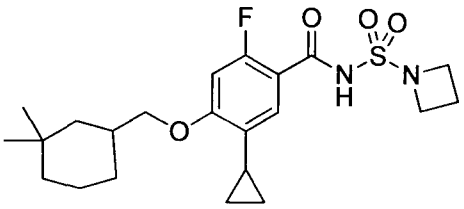
[01127] Following the procedure as described in Example 158 step 3 and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-chloro-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate, the title compound was obtained as colorless oil (2.45 g, 75 %): MS (ES+) *m/z* 399.2 (M + 23).

[01128] Step 4. Preparation of 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid



[01129] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate, the title compound was obtained as a colorless solid (0.46 g, 22 %): MS (ES-) *m/z* 319.3 (M - 1).

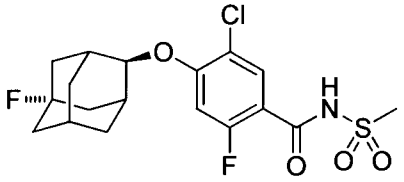
[01130] Step 5. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((3,3-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



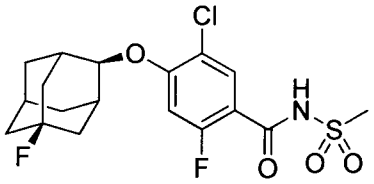
[01131] Following the procedure as described in Example 158 step 5 and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.12 g, 41%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.59 (m, 1H), 7.63-7.55 (m, 1H), 6.61-6.51 (m, 1H), 4.34-4.16 (m, 4H), 3.86-3.70 (m, 2H), 2.34-2.20 (m, 2H), 2.13-2.00 (m, 2H), 1.97-1.86 (m, 1H), 1.70-1.38 (m, 4H), 1.20-0.90 (m, 11H), 0.72-0.63 (m, 2H); MS (ES +) *m/z* 439.2 (M +1).

[01132] EXAMPLE 199/200

[01133] Synthesis of *trans*-5-chloro-2-fluoro-4-((-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide



[01134] and *cis*-5-chloro-2-fluoro-4-((-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide

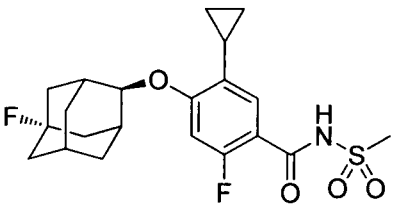


[01135] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with 5-fluoroadamantan-2-ol (*J. Am. Chem. Soc.* **1986**, *108*, 1598;), two diastereomers were obtained by silica gel chromatography: Data for the first diastereomer, *trans*-5-chloro-2-fluoro-4-((-5-fluoroadamantan-2- yl)oxy)-*N*-(methylsulfonyl)benzamide: a colorless solid (0.041 g, 2%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.61 (m, 1H), 8.17-8.08 (m, 1H), 6.74-6.65 (m, 1H), 4.57-4.50 (m, 1H), 3.43 (s, 3H), 2.43 (s, 2H), 2.30 (s, 1H), 2.19-2.07 (m, 2H), 2.06-1.92 (m, 6H), 1.57-1.41 (m, 2H);

[01136] MS (ES -) *m/z* 418.2 (M -1), 420.2 (M - 1). Data for the second diastereomer, *cis*-5-chloro-2-fluoro-4-((-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide: a colorless solid (0.0044 g, 0.2%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73-8.60 (m, 1H), 8.18-8.11 (m, 1H), 6.74-6.63 (m, 1H), 4.43-4.34 (m, 1H), 3.43 (s, 3H), 2.53 (s, 2H), 2.41-2.25 (m, 3H), 1.98-1.65 (m, 8H); MS (ES -) *m/z* 418.2 (M -1), 420.2 (M – 1).

[01137] EXAMPLE 201

[01138] Synthesis of 5-cyclopropyl-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide

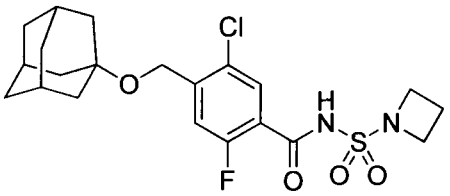


[01139] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2-fluoro-4-((-5-fluoroadamantan-2-yl)oxy)-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.008 g, 5%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.63 (m, 1H),

7.66-7.58 (m, 1H), 6.61-6.50 (m, 1H), 4.55-4.44 (m, 1H), 3.42 (s, 3H), 2.45 (s, 2H), 2.36-2.25 (m, 1H), 2.17-1.92 (m, 9H), 1.54-1.43 (m, 2H), 1.02-0.88 (m, 2H), 0.72-0.59 (m, 2H); MS (ES +) *m/z* 426.1 (M +1).

[01140] EXAMPLE 202

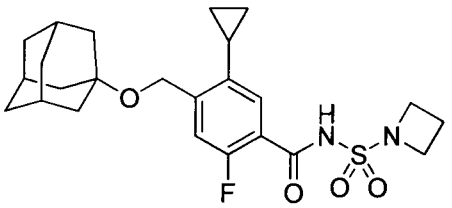
[01141] Synthesis of : 4-((adamantan-1-yloxy)methyl)-*N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluorobenzamide



[01142] Following the procedure as described in Example 47 step 5 and making variations as required to replace mathanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.04 g, 8%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78-8.66 (m, 1H), 8.09-8.03 (m, 1H), 7.56-7.47 (m, 1H), 4.60 (s, 2H), 4.32-4.20 (m, 4H), 2.36-2.15 (m, 5H), 1.87-1.82 (m, 6H), 1.75-1.59 (m, 6H); MS (ES +) *m/z* 457.1 (M +1).

[01143] EXAMPLE 203 (

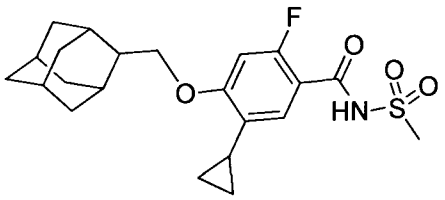
[01144] Synthesis of 4-((adamantan-1-yloxy)methyl)-*N*-(azetidin-1-ylsulfonyl)- 5-cyclopropyl-2-fluorobenzamide



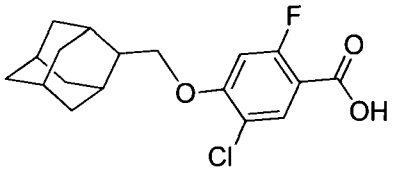
[01145] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide with 4-((adamantan-1-yloxy)methyl)-*N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluorobenzamide, the title compound was obtained as a colorless solid (0.135 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82-8.68 (m, 1H), 7.76-7.68 (m, 1H), 7.44-7.34 (m, 1H), 4.72 (s, 2H), 4.33-4.18 (m, 4H), 2.35-2.15 (m, 5H), 1.90-1.60 (m, 13H), 1.02-0.89 (m, 2H), 0.73-0.62 (m, 2H); MS (ES +) *m/z* 463.2 (M +1).

[01146] EXAMPLE 204

[01147] Synthesis of 4-(adamantan-2-ylmethoxy)-5-cyclopropyl- 2-fluoro-*N*-(methylsulfonyl)benzamide

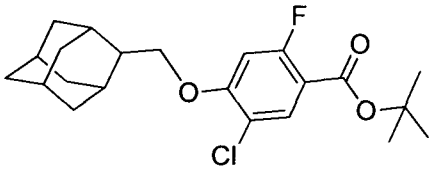


[01148] Step 1. Preparation of 4-(adamantan-2-ylmethoxy)-5-chloro-2-fluorobenzoic acid



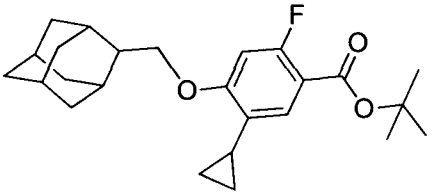
[01149] Following the procedure as described in preparation of Example 158 step 1, and making variations as required to replace (1-(trifluoromethyl)cyclohexyl)methanol with adamantan-2-ylmethanol, the title compound was obtained as a colorless solid (3.79 g, 41 %) containing *o*-substituted regioisomer, which was used for next step without further purification: MS (ES+1) *m/z* 339.1, 341.1 (M + 1).

[01150] Step 2. Preparation of *tert*-butyl 4-(adamantan-2-ylmethoxy)- 5-chloro-2-fluorobenzoate



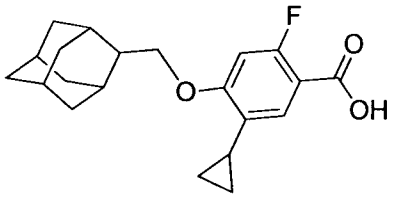
[01151] Following the procedure as described in Example 158 step 2, and making variations as required to replace 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)- methoxy)benzoic acid with 4-(adamantan-2-ylmethoxy)-5-chloro-2-fluorobenzoic acid, the title compound was obtained as a colorless oil (2.13. g, 48 %): MS (ES-) *m/z* 393.2 (M - 1).

[01152] Step 3. Preparation of *tert*-butyl 4-(adamantan-2-ylmethoxy)-5- cyclopropyl-2-fluorobenzoate



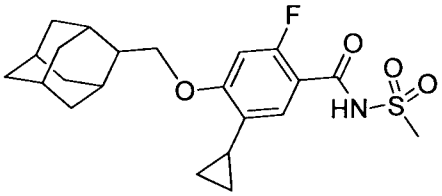
[01153] Following the procedure as described in Example 158 step 3, and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 4-(adamantan-2-ylmethoxy)-5-chloro- 2-fluorobenzoate, the title compound was obtained as colorless oil (1.99 g, 92 %): MS (E+) *m/z* 401.3 (M + 1).

[01154] Step 4. Preparation of 4-(adamantan-2-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid



[01155] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 4-(adamantan-2-ylmethoxy)-5- cyclopropyl-2-fluorobenzoate, the title compound was obtained as a colorless solid (0.79 g, 46 %): MS (ES-) *m/z* 343.3 (M - 1).

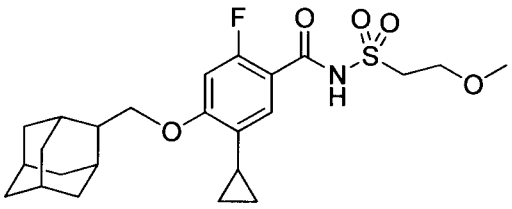
[01156] Step 5. Preparation of 4-(adamantan-2-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01157] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 4-(adamantan-2-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.16 g, 49 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78-8.66 (m, 1H), 7.60-7.51 (m, 1H), 6.70-6.57 (m, 1H), 4.16-4.06 (m, 2H), 3.42 (s, 3H), 2.36-2.25 (m, 1H), 2.12-1.73 (m, 13H), 1.69-1.60 (m, 2H), 0.98-0.89 (m, 2H), 0.70-0.60 (m, 2H); MS (ES -) *m/z* 420.3 (M -1).

[01158] EXAMPLE 205

[01159] Synthesis of 4-(adamantan-2-ylmethoxy)-5-cyclopropyl-2- fluoro-*N*-((2-methoxyethyl)-sulfonyl)benzamide

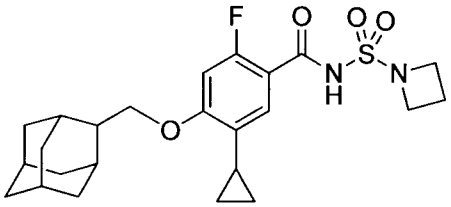


[01160] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 4-(adamantan-2-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid and to replace methanesulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained (0.16 g, 40%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73-8.59 (m, 1H), 7.60-7.48 (m, 1H), 6.69-6.56 (m, 1H), 4.15-4.06 (m, 2H),

3.90-3.75 (m, 4H), 3.31 (s, 3H), 2.35-2.24 (m, 1H), 2.10-1.73 (m, 13H), 1.69-1.59 (m, 2H), 0.98-0.87 (m, 2H), 0.68-0.60 (m, 2H); MS (ES -) *m/z* 464.3 (M -1).

[01161] EXAMPLE 206

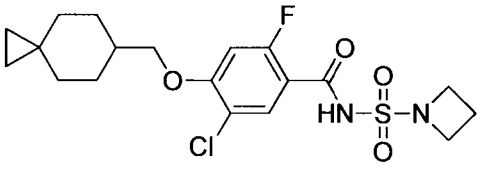
[01162] Synthesis of 4-(adamantan-2-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)- 5-cyclopropyl-2-fluorobenzamide



[01163] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 4-(adamantan-2-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.07 g, 26%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.62 (m, 1H), 7.60-7.54 (m, 1H), 6.67-6.59 (m, 1H), 4.31-4.20 (m, 4H), 4.14-4.07 (m, 2H), 2.36-2.20 (m, 3H), 2.08-1.75 (m, 13H), 1.70-1.60 (m, 2H), 0.97-0.89 (m, 2H), 0.71-0.63 (m, 2H); MS (ES -) *m/z* 461.3 (M -1).

[01164] EXAMPLE 207

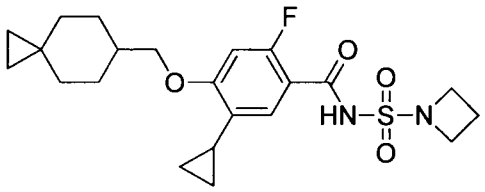
[01165] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



[01166] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2,4-difluorobenzamide and to replace adamantan-1-ylmethanol with spiro[2.5]octan-6-ylmethanol, the title compound was obtained as a colorless solid (0.61 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70-8.57 (m, 1H), 8.17-8.09 (m, 1H), 6.76-6.66 (m, 1H), 4.32-4.19 (m, 4H), 3.96-3.87 (m, 2H), 2.35-2.20 (m, 2H), 2.03-1.70 (m, 5H), 1.39-1.20 (m, 2H), 1.02-0.86 (m, 2H), 0.38-0.16 (m, 4H); MS (ES +) *m/z* 431.1 (M +1), 433.1 (M+1).

[01167] EXAMPLE 208

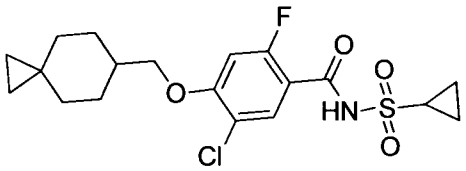
[01168] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



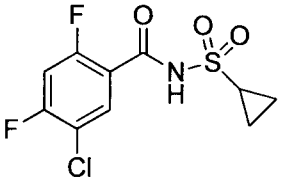
[01169] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro- *N*-(methylsulfonyl)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro- 2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide, the title compound was obtained as a colorless solid (0.39 g, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.59 (m, 1H), 7.64-7.54 (m, 1H), 6.64-6.52 (m, 1H), 4.31-4.18 (m, 4H), 3.93-3.81 (m, 2H), 2.35-2.20 (m, 2H), 2.13-2.00 (m, 1H), 1.99-1.72 (m, 5H), 1.40-1.20 (m, 2H), 1.02-0.85 (m, 4H), 0.73-0.61 (m, 2H), 0.37-0.14 (m, 4H); MS (ES + 1) *m/z* 437.2 (M +1).

[01170] EXAMPLE 209

[01171] Synthesis of 5-chloro-*N*-(cyclopropylsulfonyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide

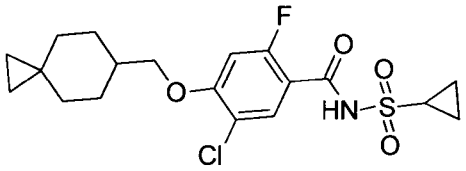


[01172] Step 1. Preparation of 5-chloro-*N*-(cyclopropylsulfonyl)-2,4-difluorobenzamide



[01173] A mixture of 5-chloro-2,4-difluorobenzoic acid (10.0 g, 51.93 mmol) and 1,1′-carbonyldiimidazole (10.11 g, 62.32 mmol) was stirred at reflux for 2 hours, cooled to ambient temperature, and cyclopropanesulfonamide (7.55 g, 62.32 mmol) was added. The reaction mixture was stirred at ambient temperature for 16 hours, diluted with ethyl acetate (300 mL), washed with 1M aqueous hydrochloric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was re-crystallized from ethyl acetate/hexanes mixture (1:2) to afford the title compound as a colorless solid (7.7 g, 56%): MS (ES -) *m/z* 294.1 (M -1).

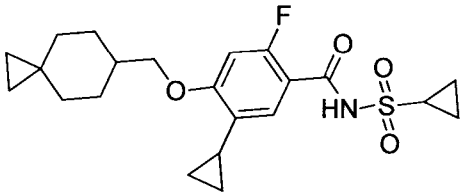
[01174] Step 2. Preparation of 5-chloro-*N*-(cyclopropylsulfonyl)-2-fluoro-4- (spiro[2.5]octan-6-ylmethoxy)benzamide



[01175] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*- (cyclopropylsulfonyl)-2,4-difluorobenzamide and to replace adamantan-1-ylmethanol with spiro[2.5]octan-6-ylmethanol, the title compound was obtained as a colorless solid (0.165 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.59 (m, 1H), 8.16-8.07 (m, 1H), 6.76-6.65 (m, 1H), 3.97-3.86 (m, 2H), 3.17-3.05 (m, 1H), 2.03-1.72 (m, 5H), 1.51-1.42 (m, 2H), 1.36-1.11 (m, 4H), 1.00-0.90 (m, 2H), 0.38-0.14 (m, 4H); MS (ES +) *m/z* 416.2, 418.2 (M +1).

[01176] EXAMPLE 210

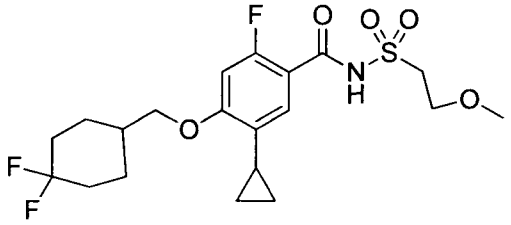
[01177] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



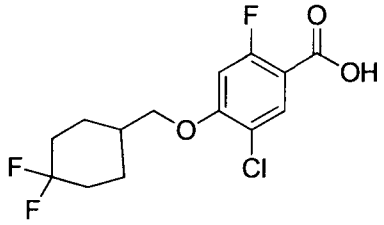
[01178] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro- *N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(cyclopropylsulfonyl)-2-fluoro-4- (spiro[2.5]octan-6-ylmethoxy)benzamide, the title compound was obtained as a colorless solid (0.024 g, 18%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76-8.62 (m, 1H), 7.63-7.54 (m, 1H), 6.63-6.53 (m, 1H), 3.96-3.78 (m, 2H), 3.20-3.02 (m, 1H), 2.12-1.72 (m, 6H), 1.50-1.41 (m, 2H), 1.40-1.22 (m, 2H), 1.20-1.10 (m, 2H), 1.02-0.88 (m, 4H), 0.72-0.61 (m, 2H), 0.38-0.15 (m, 4H); MS (ES +) *m/z* 422.2 (M +1).

[01179] EXAMPLE 211

[01180] Synthesis of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)methoxy)-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide

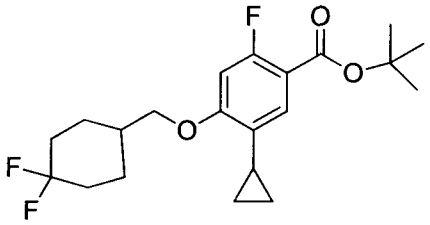


[01181] Step 1. Preparation of 5-chloro-4-((4,4-difluorocyclohexyl)methoxy)- 2-fluorobenzoic acid



[01182] Following the procedure as described in Example 158 step 1 and making variations as required to replace (1-(trifluoromethyl)cyclohexyl)methanol with (4,4-difluorocyclohexyl)methanol, the title compound was obtained as a pale yellow oil (5.28 g, 99 %) containing *o*-substituted regioisomer, which was used for next step without further purification: MS (ES-) *m/z* 321.1, 323.1 (M - 1).

[01183] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((4,4-difluoro- cyclohexyl)methoxy)-2-fluorobenzoate

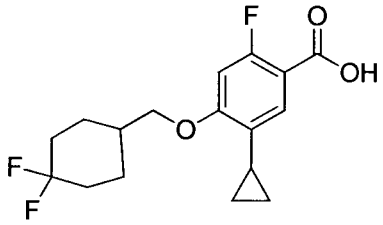


[01184] To a solution of 5-chloro-4-((4,4-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid

[01185] (5.28 g, 16.36 mmol) and *N,N*-dimethylpyridin-4-amine (0.092 g, 0.82 mmol) in *tert*-butanol (35 mL) was added di-*tert*-butyldicarbonate (7.50 g, 34.36 mmol). The reaction mixture was heated at 50 °C for 16 hours. Additional di-*tert*-butyldicarbonate (3.57 g, 16.36 mmol) was added. The reaction mixture was stirred at 50 °C for 6 hours and then concentrated in *vacuo*. The residue was purified by column chromatography eluting with a gradient of ethyl acetate in hexanes (0 -10%) to afford a pale yellow oil (5.9 g) that was dissolved in the mixture of toluene (62 mL) and water (3 mL). Cyclopropylboronic acid (2.01 g, 23.36 mmol), potassium phosphate (14.88 g, 70.11 mmol), tricyclohexylphosphine tetrafluoroborate (0.574 g, 1.56 mmol), and palladium acetate (0.175 g, 0.78 mmol) were added under a nitrogen atmosphere and the reaction mixture was stirred at 100 °C for 16 hours. The mixture was cooled to ambient temperature, water (60 mL) was added and the mixture extracted with ethyl acetate. The combined organics were

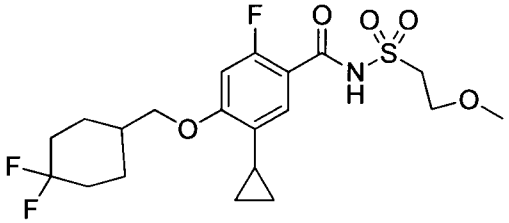
washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography eluting with a gradient of ethyl acetate in hexanes (0 - 10%) afforded the title compound (5.37 g, 86%) as a pale yellow oil: MS (ES-) *m/z* 383.0 (M - 1).

[01186] Step 3. Preparation of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid



[01187] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1- (trifluoromethyl)cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl- 4-((4,4-difluorocyclohexyl)methoxy)-2-fluorobenzoate, the title compound was obtained as a colorless solid (2.29 g, 50 %): MS (ES+) *m/z* 329.1 (M + 1).

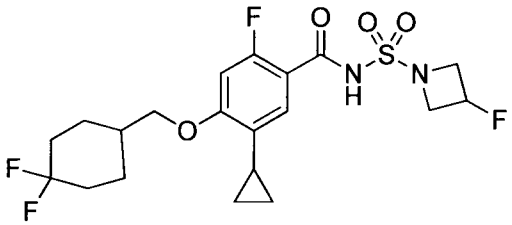
[01188] Step 4. Preparation of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide



[01189] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained (0.072 g, 26%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70-8.58 (m, 1H), 7.63-7.53 (m, 1H), 6.63-6.51 (m, 1H), 3.93-3.83 (m, 4H), 3.83-3.75 (m, 2H), 3.31 (s, 3H), 2.27-2.09 (m, 2H), 2.08-1.66 (m, 6H), 1.61-1.42 (m, 2H), 0.99-0.88 (m, 2H), 0.71-0.60 (m, 2H); MS (ES +) *m/z* 450.0 (M +1).

[01190] EXAMPLE 212

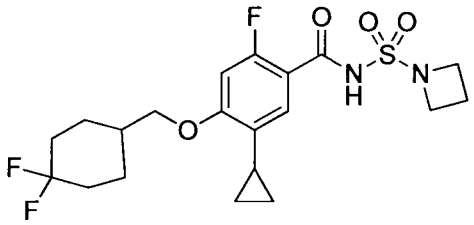
[01191] Synthesis of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)methoxy)-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01192] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.12 g, 43%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.64 (m, 1H), 7.64-7.55 (m, 1H), 6.62-6.53 (m, 1H), 5.43-5.13 (m, 1H), 4.57-4.31 (m, 4H), 3.94-3.86 (m, 2H), 2.27-2.11 (m, 2H), 2.09-1.68 (m, 6H), 1.61-1.43 (m, 2H), 0.99-0.90 (m, 2H), 0.71-0.63 (m, 2H); MS (ES +) *m/z* 465.0 (M +1).

[01193] EXAMPLE 213

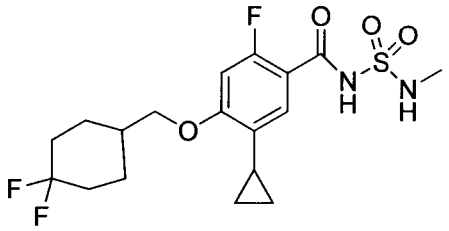
[01194] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-difluorocyclohexyl)-methoxy)-2-fluorobenzamide



[01195] Following the procedure as described in preparation of Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.14 g, 47%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.57 (m, 1H), 7.66-7.54 (m, 1H), 6.64-6.50 (m, 1H), 4.32-4.19 (m, 4H), 3.96-3.83 (m, 2H), 2.35-2.09 (m, 4H), 2.09-1.68 (m, 6H), 1.62-1.41 (m, 2H), 1.04-0.87 (m, 2H), 0.76-0.62 (m, 2H); MS (ES +) *m/z* 447.0 (M +1).

[01196] EXAMPLE 214

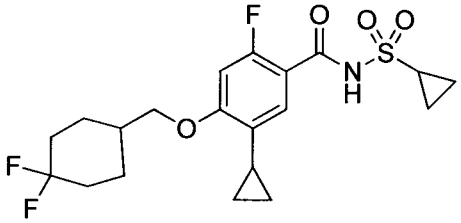
[01197] Synthesis of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)methoxy)-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[01198] Following the procedure as described in Example 158 step 5 and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with (methylsulfamoyl)amine, the title compound was obtained (0.08 g, 29%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.64 (m, 1H), 7.62-7.51 (m, 1H), 6.65-6.52 (m, 1H), 5.30-5.18 (m, 1H), 3.95-3.85 (m, 2H), 2.83-2.72 (m, 3H), 2.28-1.66 (m, 8H), 1.57-1.42 (m, 2H), 1.01-0.90 (m, 2H), 0.71-0.60 (m, 2H); MS (ES +) *m/z* 421.1 (M +1).

[01199] EXAMPLE 215

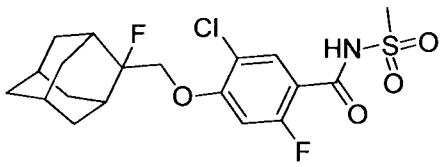
[01200] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4-((4,4-difluorocyclohexyl)-methoxy)-2-fluorobenzamide



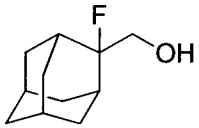
[01201] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)- methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.144 g, 46%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.63 (m, 1H), 7.64-7.56 (m, 1H), 6.61-6.52 (m, 1H), 3.93-3.84 (m, 2H), 3.16-3.04 (m, 1H), 2.26-2.08 (m, 2H), 2.08-1.66 (m, 6H), 1.60-1.42 (m, 4H), 1.20-1.10 (m, 2H), 0.99-0.89 (m, 2H), 0.70-0.61 (m, 2H); MS (ES +) *m/z* 432.0 (M +1).

[01202] EXAMPLE 216

[01203] Synthesis of 5-chloro-2-fluoro-4-((2-fluoroadamantan-2-yl)methoxy)-*N*-(methylsulfonyl)benzamide

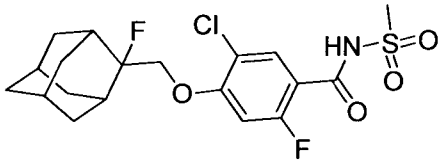


[01204] Step 1. Preparation of (2-fluoroadamantan-2-yl)methanol



[01205] To a stirred solution of methyl 2-fluoroadamantane-2-carboxylate (0.90 g, 4.20 mmol) (*Zhurnal Organicheskoi Khimii*, **1981**, *17*, 1642) in tetrahydrofuran (40 mL) was added methanol (0.24 mL, 5.90 mmol), followed by the addition of lithium borohydride solution (2.0 M in tetrahydrofuran, 5.3 mL, 10.60 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 minutes, at ambient temperature for 30 minutes and then at reflux for 1 hour. The reaction mixture was cooled to ambient temperature and poured in small portions into a cooled to 0 °C saturated ammonium chloride solution (25 mL) with stirring. The mixture was stirred at ambient temperature for 1 hour and extracted with ethyl acetate (3 x 70 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo* to afford (2-fluoroadamantan-2-yl)methanol (0.69 g, 88%) as colorless solid: MS (ES +) *m/z* 223.2 (M + 39).

[01206] Step 2. Preparation of 5-chloro-2-fluoro-4-((2-fluoroadamantan-2-yl)methoxy)-*N*-(methylsulfonyl)benzamide

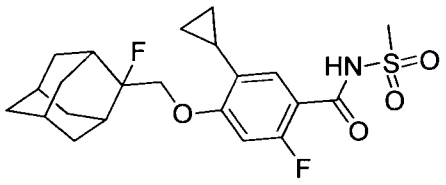


[01207]

[01208] Following the procedure as described in Example 8 and making variations as required to replace adamantan-1-ylmethanol with (2-fluoroadamantan-2-yl)methanol, the title compound was obtained as a colorless solid (0.23 g, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74-8.63 (m, 1H), 8.16-8.07 (m, 1H), 6.83-6.73 (m, 1H), 4.36 (d, *J* = 24.60 Hz, 2H), 3.43 (s, 3H), 2.36-2.15 (m, 4H), 1.98-1.84 (m, 4H), 1.82-1.62 (m, 6H); MS (ES -) *m/z* 432.1 (M -1).

[01209] EXAMPLE 217

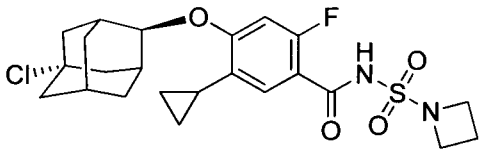
[01210] Synthesis of 5-cyclopropyl-2-fluoro-4-((2-fluoroadamantan-2-yl)methoxy)-*N*-(methylsulfonyl)benzamide



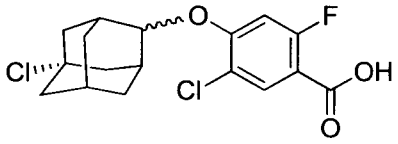
[01211] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-2-fluoro-4-((2-fluoroadamantan-2-yl)methoxy)-*N*-(methylsulfonyl)benzamide, the title compound was obtained as a colorless solid (0.24 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77-8.65 (m, 1H), 7.63-7.56 (m, 1H), 6.68-6.58 (m, 1H), 4.30 (d, J = 24.85 Hz, 2H), 3.42 (s, 3H), 2.34-2.16 (m, 4H), 2.14-2.01 (m, 1H), 1.97-1.85 (m, 4H), 1.84-1.72 (m, 4H), 1.72-1.62 (m, 2H), 1.00-0.90 (m, 2H), 0.70-0.61 (m, 2H); MS (ES -) *m/z* 438.1 (M -1).

[01212] EXAMPLE 218

[01213] Synthesis of *trans*-*N*-(azetidin-1-ylsulfonyl)-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzamide

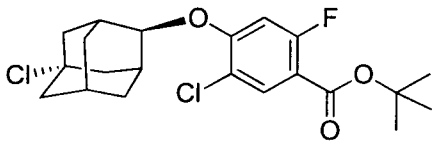


[01214] Step 1. Preparation of 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoic acid

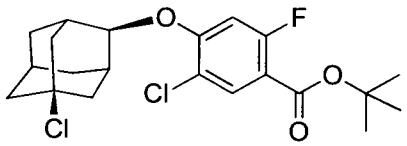


[01215] To a solution of 5-chloroadamantan-2-ol (2.00 g, 10.70 mmol) in anhydrous dimethylsulfoxide (50 ml) was added potassium *tert*-butoxide (3.01g, 26.80 mmol) and the reaction mixture was stirred at ambient temperature for 30 minutes. 5-chloro-2,4-difluorobenzoic acid (2.06 g, 10.70 mmol) was added to the reaction mixture, stirring was continued for 2 hours. The reaction mixture was acidified to pH = 1 with 5% aqueous hydrochloric acid solution and diluted with water (100 mL), the white precipitate was filtered, washed with water and dried to afforded the title compound as colorless solid (3.30 g, 86%), containing *o*-substituted regioisomer, which was used for next step without further purification: MS(ES+) *m/z* 359.2, 361.2 (M + 1), MS(ES-) *m/z* 357.1, 359.1 (M - 1).

[01216] Step 2. Preparation of *trans-tert*-butyl 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoate

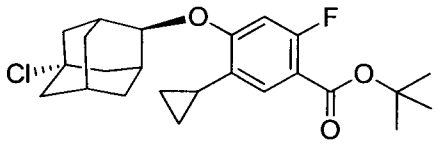


[01217] And *cis-tert*-butyl 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoate



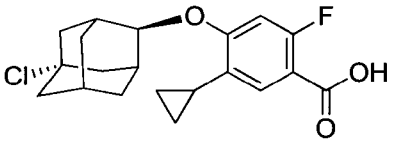
[01218] To a solution of 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoic acid (3.0 g, 8.35 mmol) and *N,N*-dimethylpyridin-4-amine (0.10 g, 0.82 mmol) in *tert*-butanol (25 mL) was added *di-tert*-butyldicarbonate (3.65 g, 16.70 mmol). The reaction mixture was heated at 50 °C for 16 hours, and concentrated *in vacuo*. The crude product was purified by column chromatography (0-15% ethyl acetate in hexanes) to afford two diastereomers. The first fraction as *trans-tert*-butyl 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoate (1.48 g, 43%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 13.0 Hz, 1H), 4.89 (t, J = 3.3 Hz, 1H), 2.33-2.13 (m, 9H), 1.99-1.94 (m, 2H), 1.52-1.48 (m, 11H); MS(ES+) *m/z* 359.1, 361.1 (M - 55). The second fraction as *cis-tert*-butyl 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoate (0.50 g, 14%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 13.0 Hz, 1H), 4.75 (t, J = 3.0 Hz, 1H), 2.40-2.32 (m, 4H), 2.09 (br s, 3H), 1.96-1.92 (m, 2H), 1.79-1.73 (m, 4H), 1.92 (s, 9H);

[01219] Step 3. Preparation of *trans-tert*-butyl 4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoate



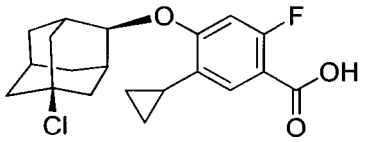
[01220] To a solution of *trans-tert*-butyl 5-chloro-4-((5-chloroadamantan-2- yl)oxy)-2-fluorobenzoate (0.94 g, 2.19 mmol), cyclopropylboronic acid (0.28 g, 3.29 mmol), potassium phosphate (2.09 g, 9.85 mmol) and tricyclohexylphosphine tetrafluoroborate (0.08 g, 0.22 mmol) in toluene (20 mL) and water (1 mL) under a nitrogen atmosphere was added palladium acetate (0.03 g, 0.11 mmol). The reaction mixture was heated at 100 °C for 18 hours and then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate, the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded the title compound (0.70 g, 76%): MS (ES+) *m/z* 421.2, 423.2 (M + 1).

[01221] Step 4. Preparation of *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid



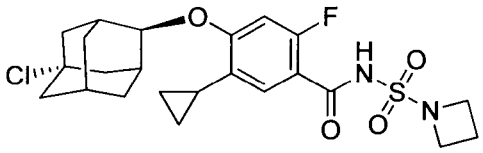
[01222] To a solution of *trans-tert*-butyl 4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoate (0.70 g, 1.67 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*. The residue was purified by column chromatography (5% to 60% ethyl acetate contains 0.2% acetic acid in hexanes) afforded the title compound as colorless solid (0.17 g, 29%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 12.4 Hz, 1H), 4.79 (t, J = 2.8Hz, 1H), 2.35-2.27 (m, 4H), 2.17-1.97 (m, 8H), 1.53-1.49 (m, 2H), 0.93-0.87 (m, 2H), 0.63-0.56 (m, 2H); MS (ES+) m/z 365.1, 367.1 (M + 1); MS (ES-) *m/z* 363.2, 365.2 (M - 1).

[01223] Preparation of *cis*-4-((5-chloroadamantan-2-yl)oxy)-5- cyclopropyl-2-fluorobenzoic acid



[01224] To a solution of *cis-tert*-butyl 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoate (3.94 g, 9.49 mmol), cyclopropylboronic acid (1.22 g, 14.2 mmol), potassium phosphate (3.02 g, 14.2 mmol) and tricyclohexylphosphine tetrafluoroborate (0.50 g, 0.95 mmol) in toluene (100 mL) and water (5 mL) under a nitrogen atmosphere was added palladium acetate (0.21 g, 0.95 mmol). The reaction mixture was heated to 100 °C for 18 hours and then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate, the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*., the crude product *cis-tert*-butyl 4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoate was in dichloromethane (30 mL) and added trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*. The residue was purified by column chromatography (5% to 60% gradient ethyl acetate contains 0.2% acetic acid in hexanes) to afford the title compound as off-white solid (2.48 g, 72%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (s, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 13.3 Hz, 1H), 4.65 (t, J = 2.8 Hz, 1H), 2.43-2.27 (m, 4H), 2.17-1.93 (m, 7H), 1.78 (s, 3H), 0.93-0.87 (m, 2H), 0.63-0.56 (m, 2H); MS (ES+) *m/z* 365.1, 367.1 (M + 1);

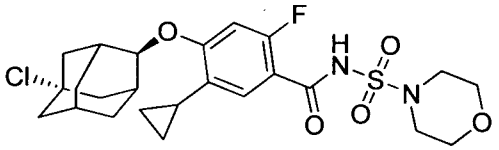
[01225] Step 5. Synthesis of *trans-N*-(azetidin-1-ylsulfonyl)-4- ((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzamide



[01226] To a mixture of *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl- 2-fluorobenzoic acid (0.17 g, 0.47 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.21 g, 1.07 mmol) and 4-dimethylaminopyridine (0.13 g, 1.07 mmol) in anhydrous dichloromethane (10 mL) was added azetidine-1-sulfonamide (0.15 g, 1.07 mmol) at ambient temperature. The resulting mixture was stirred at ambient temperature for 16 h. The mixture was quenched with hydrochloride acid (1N, 30 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the crude product was purified by silica gel column chromatography using 10-60% ethyl acetate (containing 2% acetic acid) in hexanes as an elute to afford the title compound as colorless solid (0.10 g, 42%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 7.18-7.07 (m, 2H), 4.82-4.80 (m, 1H), 4.04 (t, J = 7.7 Hz, 4H), 2.36-2.28 (m, 4H), 2.19-1.97 (m, 10H), 1.52 (d, J = 12.5 Hz, 2H), 0.94-0.87 (m, 2H), 0.71-0.66 (m, 2H); MS(ES+) m/z 483.1, 485.1 (M + 1); MS(ES-) m/z 481.2, 483.2 (M - 1).

[01227] EXAMPLE 219

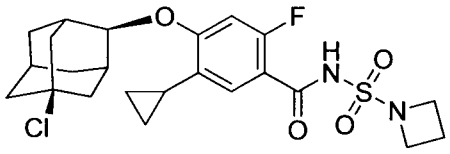
[01228] Synthesis of *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-(morpholinosulfonyl)benzamide



[01229] Following the procedure as described in Example 218 step 5 and making variations as required to replace azetidine-1-sulfonamide with morpholine-4-sulfonamide, the title compound was obtained as colorless solid (0.04 g, 18%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.14-7.06 (m, 2H), 4.82-4.80 (m, 1H), 3.65-3.62 (m, 4H), 3.27-3.24 (m, 4H), 2.36-2.27 (m, 4H), 2.18-1.85 (m, 8H), 1.53-1.49 (m, 2H), 0.93-0.87 (m, 2H), 0.71-0.65 (m, 2H); MS(ES+) m/z 513.0, 515.0 (M + 1); MS(ES-) *m/z* 511.1, 513.1 (M - 1).

[01230] EXAMPLE 220

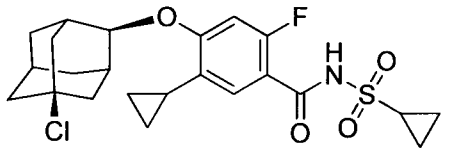
[01231] Synthesis of *cis*-*N*-(azetidin-1-ylsulfonyl)-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzamide



[01232] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as colorless solid (0.16 g, 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 13.1 Hz, 1H), 4.68 (t, J = 2.6 Hz, 1H), 4.04 (t, J = 7.70 Hz, 4H), 2.43-2.35 (m, 4H), 2.21-2.04 (m, 6H), 1.98-1.94 (m, 2H), 1.79 (br,s, 4H), 0.95-0.89 (m, 2H), 0.73-0.68 (m, 2H); MS(ES+) *m/z* 483.1, 485.1 (M + 1); MS(ES-) *m/z* 481.2, 483.2 (M - 1).

[01233] EXAMPLE 221

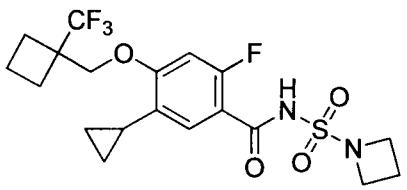
[01234] Synthesis of *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide



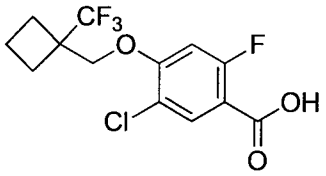
[01235] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.17 g, 53%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 13.2 Hz, 1H), 4.67 (t, J = 2.6 Hz, 1H), 3.12-3.03 (m, 1H), 2.43-2.35 (m, 4H), 2.10-2.02 (m, 4H), 1.95 (d, J = 11.7 Hz, 2H), 1.79 (br,s, 4H), 1.13-1.09 (m, 4H), 0.95-0.89 (m, 2H), 0.72-0.67 (m, 2H); MS(ES+) *m/z* 468.1, 470.1 (M + 1); MS(ES-) *m/z* 466.2, 468.2 (M - 1).

[01236] EXAMPLE 222

[01237] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide

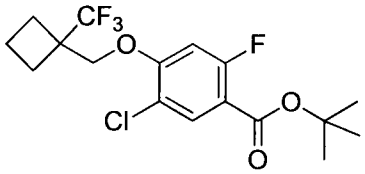


[01238] Step1. Preparation of 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid



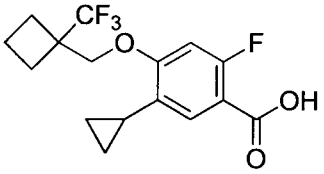
[01239] Following the procedure as described in Example 218 step 1 and making variations as required to replace 5-chloroadamantan-2-ol with (1-(trifluoromethyl)cyclobutyl)methanol, the title compound was obtained as beige color solid (2.10 g, 99%): MS (ES-) *m/z* 325.1, 327.1 (M - 1);

[01240] Step 2. Preparation of tert-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzoate



[01241] Following the procedure as described in Example 218 step 2 and making variations as required to replace 5-chloro-4-((5-chloroadamantan-2-yl)oxy)-2-fluorobenzoic acid with 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid, the title compound was obtained as clear liquid (2.41 g, 99%): MS (ES+) *m/z* 327.1, 329.1 (M - 55).

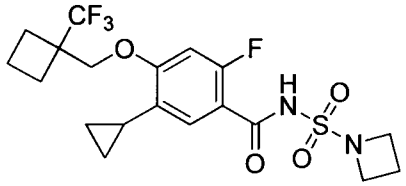
[01242] Step 3. Preparation of 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzoic acid



[01243] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)-methoxy)benzoate (2.11 g, 5.5 mmol), cyclopropylboronic acid (0.94 g, 11.0 mmol), potassium phosphate (5.25 g, 24.8 mmol) and tricyclohexylphosphine tetrafluoroborate (0.4 g, 1.10 mmol) in toluene (60 mL) and water (3 mL) under a nitrogen atmosphere was added palladium acetate (0.25 g, 1.10 mmol). The reaction mixture was heated to 110 °C for 18 hours and then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate, the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*., the crude product *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)- methoxy)benzoate was dissolved in dichloromethane (30 mL) and added trifluoroacetic acid (10 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*. The residue was purified by column chromatography (5% to 60% ethyl acetate contains 0.2% acetic acid in hexanes) afforded the title

compound was obtained as colorless solid (0.50, 27%): MS (ES+) m/z 333.1 (M + 1); MS (ES-) *m/z* 331.2 (M - 1).

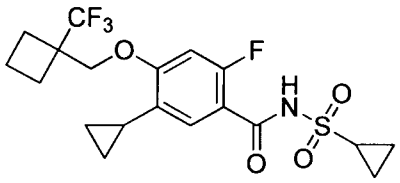
[01244] Step 4. Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro- 4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide



[01245] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid, the title compound was obtained as colorless solid (0.11 g, 55%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.67 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 12.8 Hz, 1H), 4.34 (s, 2H), 4.05 (t, J = 7.7 Hz, 4H), 2.38-2.27 (m, 2H), 2.22-2.11 (m, 5H), 2.01-1.93 (m, 2H), 0.91-0.84 (m, 2H), 0.71-0.65 (m, 2H); MS(ES+) *m/z* 451.1 (M + 1); MS(ES-) *m/z* 449.2 (M - 1).

[01246] EXAMPLE 223

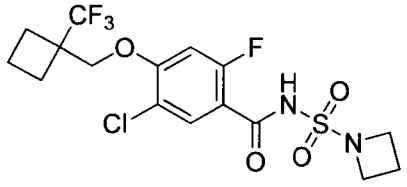
[01247] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro- 4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide



[01248] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.09 g, 47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.17-7.09 (m, 2H), 4.34 (s, 2H), 3.12-3.04 (m, 1H), 2.38-2.27 (m, 2H), 2.19-2.09 (m, 3H), 2.03-1.94 (m, 2H), 1.14-1.10 (m, 4H), 0.90-0.84 (m, 2H), 0.70-0.64 (m, 2H); MS(ES+) *m/z* 436.1 (M + 1); MS(ES-) *m/z* 434.2 (M - 1).

[01249] EXAMPLE 224

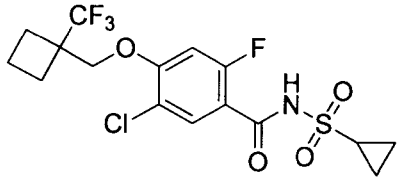
[01250] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide



[01251] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid, the title compound was obtained as colorless solid (0.08 g, 55%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 12.2 Hz, 1H), 4.42 (s, 2H), 4.06 (t, J = 7.7 Hz, 4H), 2.37-2.27 (m, 2H), 2.23-2.09 (m, 5H), 2.02-1.92 (m, 1H); MS(ES+) *m/z* 445.0, 447.0 (M + 1); MS(ES-) *m/z* 443.1, 445.1(M - 1).

[01252] EXAMPLE 225

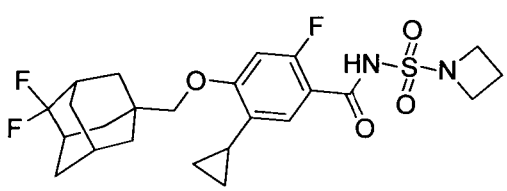
[01253] Synthesis of 5-chloro-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((1-(trifluoromethyl)-cyclobutyl)methoxy)benzamide



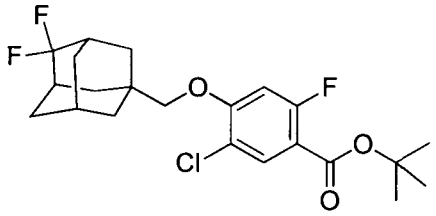
[01254] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclobutyl)methoxy)benzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.04 g, 47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 12.4 Hz, 1H), 4.41 (s, 2H), 3.12-3.03 (m, 1H), 2.37-2.27 (m, 2H), 2.18-2.09 (m, 3H), 2.01-1.92 (m, 1H), 1.15-1.11 (m, 4H); MS(ES+) *m/z* 430.0, 432.0 (M + 1); MS(ES-) *m/z* 428.1, 430.1(M - 1).

[01255] EXAMPLE 226

[01256] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((4,4-difluoroadamantan-1-yl)-methoxy)-2-fluorobenzamide

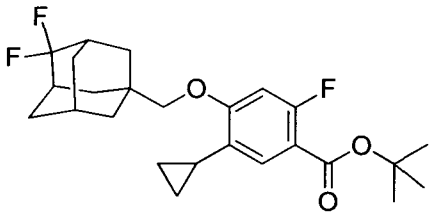


[01257] Step 1. Preparation of *tert*-butyl 5-chloro-4-((4,4-difluoroadamantan-1-yl)- methoxy)-2-fluorobenzoate



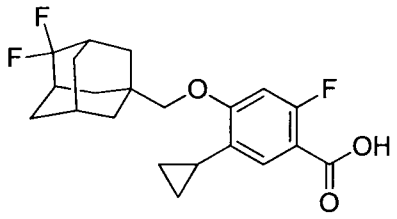
[01258] To a solution of (4,4-difluoroadamantan-1-yl)methanol (1.00 g, 4.90 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (1.84 g, 7.40 mmol) in anhydrous dimethylsulfoxide (20 mL) was added cesium carbonate (3.22 g, 9.90 mmol). The mixture was stirred at 70°C for 16 hours. The mixture was then cooled to ambient temperature, and mixed with water (50 mL). The white solid was filtered and washed with hexanes and dried by air give the title compound as colorless solid (1.70 g, 80%): MS(ES+) *m/z* 431.1, 433.1 (M + 1); 375.0, 377.0 (M – 55).

[01259] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)- methoxy)-2-fluorobenzoate



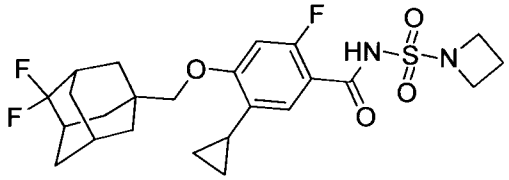
[01260] To a solution of *tert*-butyl 5-chloro-4-((4,4-difluoroadamantan-1-yl)methoxy)- 2-fluorobenzoate (1.50 g, 3.48 mmol), cyclopropylboronic acid (0.45 g, 5.22 mmol), potassium phosphate (3.33 g, 15.7 mmol) and tricyclohexylphosphine tetrafluoroborate (0.13 g, 0.35 mmol) in toluene (60 mL) and water (3 mL) under a nitrogen atmosphere was added palladium acetate (0.08 g, 0.35 mmol). The reaction mixture was heated to 100 °C for 18 hours and then cooled to ambient temperature. Water (20 mL) was added and the mixture was filtered through a pad of diatomaceous earth and the solid was washed with ethyl acetate (150 mL). The organics were washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by crystallization (ethyl acetate and hexanes) afforded the title compound as colorless solid (1.00 g, 66%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 12.6 Hz, 1H), 3.57 (s, 2H), 2.29 (br s, 2H), 2.02-1.95 (m, 6H), 1.75-1.68 (m, 6H), 1.57 (s, 9H), 0.93-0.87 (m, 2H), 0.65-0.60 (m, 2H); MS(ES+) m/z 459.2 (M + 23).

[01261] Step 3. Preparation of 5-cyclopropyl-4-((4,4-difluoroadamantan- 1-yl)methoxy)-2-fluorobenzoic acid



[01262] To a solution of *tert*-butyl 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)- methoxy)-2-fluorobenzoate (1.0 g, 2.29 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (15 ml). The reaction mixture was stirred at ambient temperature for 2 hours and then concentrated *in vacuo*. The residue was triturated in mixture of dichloromethane and hexanes afforded the title compound as colorless solid (0.82 g, 94%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 13.1 Hz, 1H), 3.57 (s, 2H), 2.24 (br s, 2H), 2.04-1.95 (m, 2H), 1.87-1.68 (m, 10H), 0.93-0.87 (m, 2H), 0.65-0.56 (m, 2H); MS(ES+) *m/z* 381.1 (M + 1); MS(ES-) *m/z* 379.2 (M - 1).

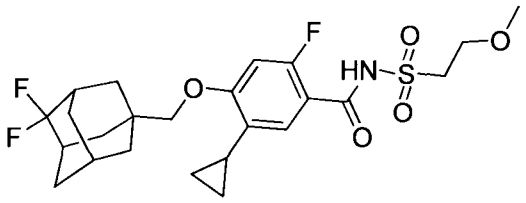
[01263] Step 4. Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluorobenzamide



[01264] To a mixture of 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)- methoxy)-2-fluorobenzoic acid (0.25 g, 0.66 mmol), 1-ethyl-3-(3- dimethylaminopropyl)carbodiimide (0.29 g, 1.51 mmol) and 4-dimethylaminopyridine (0.19 g, 1.51 mmol) in anhydrous dichloromethane (10 mL) was added azetidine-1-sulfonamide (0.13 g, 0.99 mmol) at ambient temperature. The resulting mixture was stirred at ambient temperature for 16 hours. The mixture was quenched with 1N hydrochloride acid (30 mL), followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the crude product was crystallized from ethyl acetate and hexanes and recrystallized from acetonitrile and water to afford the title compound as colorless solid (0.24 g, 73%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.72 (s, 2H), 2.25-1.98 (m, 6H), 1.88-1.69 (m, 10H), 0.94-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 499.1 (M + 1); MS(ES-) m/z 497.2 (M - 1).

[01265] EXAMPLE 227

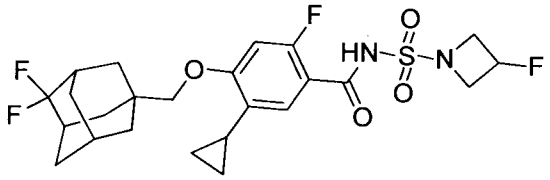
[01266] Synthesis of 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide



[01267] Following the procedure as described in Example 226 step 4 and making variations as required to replace azetidine-1-sulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained as colorless solid (0.17 g, 70%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 12.9 Hz, 1H), 3.72-3.71 (m, 6H), 3.21 (s, 3H), 2.25 (br s, 2H), 2.05-1.96 (m, 2H), 1.87-1.68 (m, 10H), 0.94-0.87 (m, 2H), 0.69-0.63 (m, 2H); MS(ES+) *m/z* 502.1 (M + 1); MS(ES-) *m/z* 500.2 (M - 1).

[01268] EXAMPLE 228

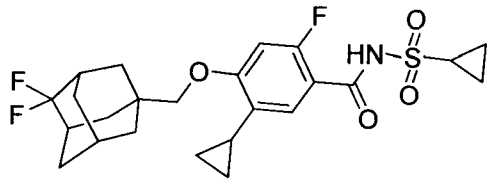
[01269] Synthesis of 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluoro-N-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01270] Following the procedure as described in Example 226 step 4, and making variations as required to replace azetidine-1-sulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.24 g, 70%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.9 Hz, 1H), 5.48-5.42 (m, 0.5H), 5.29-5.23 (m, 0.5H), 4.43-4.30 (m, 2H), 4.25-4.12 (m, 2H), 3.72 (s, 2H), 2.25 (bs, 2H), 2.05-1.96 (m, 2H), 1.87-1.68 (m, 10H), 0.94-0.87 (m, 2H), 0.69-0.64 (m, 2H); MS(ES+) *m/z* 517.1 (M + 1); MS(ES-) *m/z* 515.2 (M - 1).

[01271] EXAMPLE 229

[01272] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4-((4,4-difluoroadamantan-1-yl)-methoxy)-2-fluorobenzamide

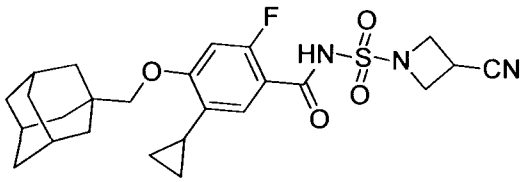


[01273] Following the procedure as described in Example 226 Step 4 and making variations as required to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as

colorless solid (0.27 g, 85%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 3.72 (s, 2H), 3.49 (br s, 1H), 2.25 (br s, 2H), 2.05-1.96 (m, 2H), 1.87-1.68 (m, 10H), 1.13-1.09 (m, 4H), 0.94-0.87 (m, 2H), 0.69-0.64 (m, 2H); MS(ES+) *m/z* 484.1 (M + 1); MS(ES-) *m/z* 482.2 (M - 1).

[01274] EXAMPLE 230

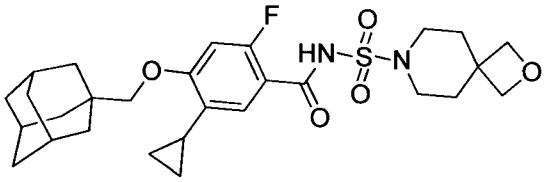
[01275] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-((3-cyanoazetidin-1-yl)sulfonyl)-5-cyclopropyl-2-fluorobenzamide



[01276] To a mixture of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid (0.20 g, 0.60 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.26 g, 1.38 mmol) and 4-dimethylaminopyridine (0.17 g, 1.38 mmol) in anhydrous dichloromethane (10 mL) was added 3-cyanoazetidine-1-sulfonamide (0.22 g, 1.38 mmol) at ambient temperature. The resulting mixture was stirred at ambient temperature for 16 hours. The mixture was quenched with 1 M aqueous hydrochloride acid (30 mL) followed by extraction with ethyl acetate (100 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo,* the residue was purified by silica gel column chromatography using 10-60% ethyl acetate (containing 2% acetic acid) in hexanes as an elute to afford the title compound as colorless solid (0.23 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 13.0 Hz, 1H), 4.35-4.22 (m, 4H), 3.84-3.74 (m, 1H), 3.65 (s, 2H), 2.09-1.99 (m, 4H), 1.75-1.67 (m, 12H), 0.95-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) *m/z* 488.2 (M + 1); MS(ES-) *m/z* 486.3 (M - 1).

[01277] EXAMPLE 231

[01278] Synthesis of *N*-(2-oxa-7-azaspiro[3.5]nonan-7-ylsulfonyl)- 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide

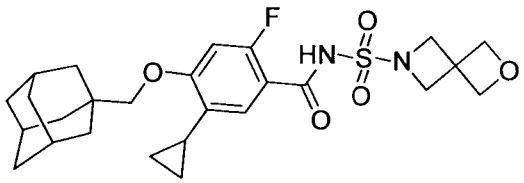


[01279] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with 2-oxa-7-azaspiro[3.5]nonane- 7-sulfonamide, the title compound was obtained as colorless solid (0.01 g, 14%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 12.9 Hz, 1H), 4.29 (s, 4H), 3.63 (s, 2H), 3.21-3.17 (m, 4H), 2.05-1.99 (m, 4H),

1.85-1.82 (m, 4H), 1.75-1.66 (m, 12H), 0.93-0.87 (m, 2H), 0.67-0.62 (m, 2H); MS(ES+) m/z 533.1 (M + 1); MS(ES-) m/z 531.2 (M - 1).

[01280] EXAMPLE 232

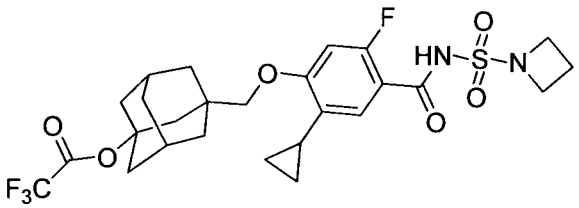
[01281] Synthesis of *N*-(2-oxa-6-azaspiro[3.3]heptan-6-ylsulfonyl)- 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide



[01282] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with 2-oxa-6-azaspiro[3.3]heptane-6- sulfonamide, the title compound was obtained as colorless solid (0.11 g, 17%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 12.9 Hz, 1H), 4.63 (s, 4H), 4.24 (s, 4H), 3.64 (s, 2H), 2.05-1.99 (m, 4H), 1.75-1.66 (m, 12H), 0.94-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 505.1 (M + 1); MS(ES-) *m/z* 503.2 (M - 1).

[01283] EXAMPLE 233

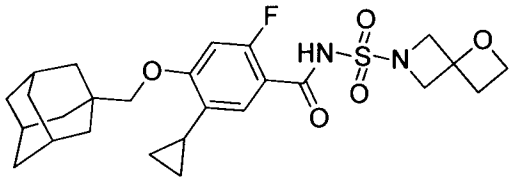
[01284] Synthesis of 3-((4-((azetidin-1-ylsulfonyl)carbamoyl)-2- cyclopropyl-5-fluorophenoxy)-methyl)adamantan-1-yl 2,2,2-trifluoroacetate



[01285] Following the procedure as described in Example 230 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((3-(2,2,2-trifluoroacetoxy)adamantan-1-yl)methoxy)benzoic acid and to replace 3-cyanoazetidine-1-sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.22 g, 47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.9 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.79 (s, 2H), 2.32 (br s, 2H), 2.19-2.14 (m, 8H), 2.06-2.00 (m, 1H), 1.70-1.59 (m, 6H), 0.95-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) *m/z* 575.1 (M + 1); MS(ES-) *m/z* 573.1 (M - 1).

[01286] EXAMPLE 234

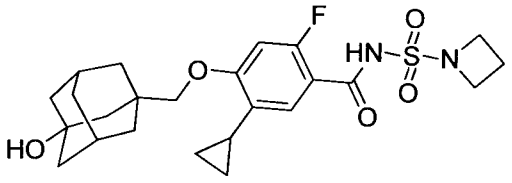
[01287] Synthesis of *N*-(1-oxa-6-azaspiro[3.3]heptan-6-ylsulfonyl)-4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide



[01288] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with 1-oxa-6-azaspiro[3.3]heptane- 6-sulfonamide, the title compound was obtained as colorless solid (0.20 g, 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 4.37 (t, J = 7.5 Hz, 2H), 4.23 (dd, J = 10.2 Hz, 22.3 Hz, 4H), 3.64 (s, 2H), 2.80 (t, J = 7.5 Hz, 2H), 2.08-1.99 (m, 4H), 1.85-1.82 (m, 4H), 1.75-1.66 (m, 12H), 0.94-0.88 (m, 2H), 0.69-0.64 (m, 2H); MS(ES+) m/z 505.1 (M + 1); MS(ES-) m/z 503.2 (M - 1).

[01289] EXAMPLE 235

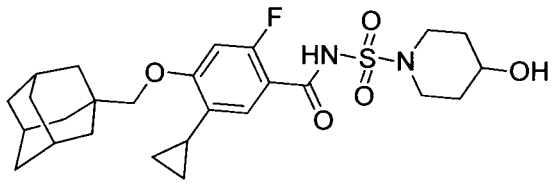
[01290] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 2-fluoro-4-((3-hydroxyadamantan-1-yl)methoxy)benzamide



[01291] Following the procedure as described in Example 230 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((3-hydroxyadamantan-1-yl)methoxy)benzoic acid and to replace 3-cyanoazetidine-1-sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.08 g, 65%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 4.47 (s, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.70 (s, 2H), 2.21-2.11 (m, 4H), 2.07-1.98 (m, 1H), 1.58-1.53 (m, 12H), 0.95-0.88 (m, 2H), 0.71-0.66 (m, 2H); MS(ES+) *m/z* 479.1 (M + 1); MS(ES-) *m/z* 477.2 (M - 1).

[01292] EXAMPLE 236

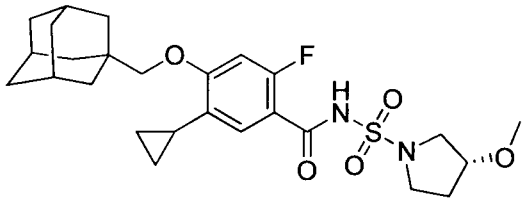
[01293] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluoro-*N*-((4-hydroxypiperidin-1-yl)sulfonyl)benzamide



[01294] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with 4-hydroxypiperidine-1-sulfonamide, the title compound was obtained as colorless solid (0.01 g, 14%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 12.9 Hz, 1H), 4.76 (d, J = 3.9 Hz, 1H), 3.63-3.47 (m, 5H), 3.12-3.04 (m, 2H), 2.07-1.99 (m, 4H), 1.79-1.66 (m, 14H), 1.48-1.37 (m, 2H), 0.93-0.87 (m, 2H), 0.68-0.63 (m, 2H); MS(ES+) *m/z* 507.2 (M + 1); MS(ES-) *m/z* 505.3 (M - 1).

[01295] EXAMPLE 237

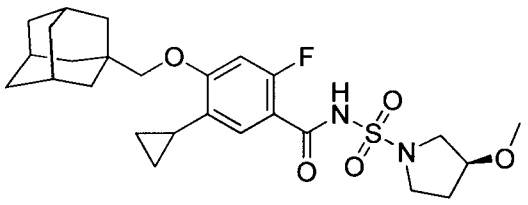
[01296] Synthesis of (*R*)-4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluoro-*N*-((3-methoxypyrrolidin-1-yl)sulfonyl)benzamide



[01297] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with (*R*)-3-methoxypyrrolidine- 1-sulfonamide, the title compound was obtained as colorless solid (0.34 g, 87%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 12.9 Hz, 1H), 4.00-3.95 (m, 1H), 3.63 (s, 2H), 3.56-3.40 (m, 4H), 3.19 (s, 3H), 2.05-1.87 (m, 6H), 1.75-1.66 (m, 12H), 0.93-0.85 (m, 2H), 0.68-0.63 (m, 2H); MS(ES+) *m/z* 507.2 (M + 1); MS(ES-) *m/z* 505.3 (M - 1).

[01298] EXAMPLE 238

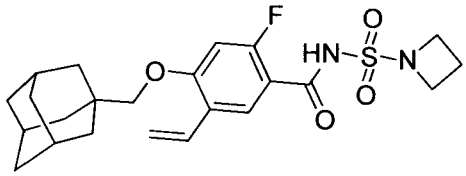
[01299] Synthesis of (*S*)-4-(adamantan-1-ylmethoxy)-5-cyclopropyl- 2-fluoro-*N*-((3-methoxypyrrolidin-1-yl)sulfonyl)benzamide



[01300] Following the procedure as described in Example 230 and making variations as required to replace 3-cyanoazetidine-1-sulfonamide with (*S*)-3-methoxypyrrolidine-1- sulfonamide, the title compound was obtained as colorless solid (0.20 g, 98%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 12.9 Hz, 1H), 3.98-3.95 (m, 1H), 3.63 (s, 2H), 3.56-3.40 (m, 4H), 3.19 (s, 3H), 2.07-1.87 (m, 6H), 1.75-1.66 (m, 12H), 0.93-0.87 (m, 2H), 0.68-0.63 (m, 2H); MS(ES+) *m/z* 507.2 (M + 1); MS(ES-) *m/z* 505.3 (M - 1).

[01301] EXAMPLE 239

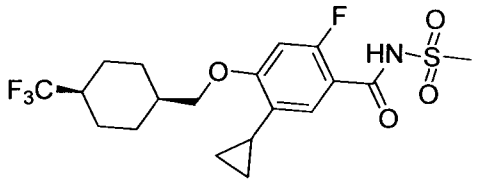
[01302] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)- 2-fluoro-5-vinylbenzamide



[01303] Following the procedure as described in Example 230 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoic acid and 3-cyanoazetidine-1-sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as colorless solid (0.13 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 12.9 Hz, 1H), 6.91 (dd, J = 11.3 Hz, 17.8 Hz, 1H), 5.93 (dd, J = 1.0 Hz, 17.8 Hz, 1H), 5.37 (dd, J = 1.0 Hz, 11.3 Hz, 1H), 4.06 (t, J = 7.7Hz, 4H), 3.67 (s, 2H), 2.23-2.12 (m, 2H), 2.00-1.99 (m, 3H), 1.75-1.64 (m, 12H); MS(ES+) *m/z* 449.1 (M + 1); MS(ES-) *m/z* 447.3 (M - 1).

[01304] EXAMPLE 240

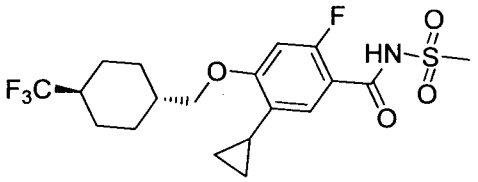
[01305] Synthesis of *cis*-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)- 4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



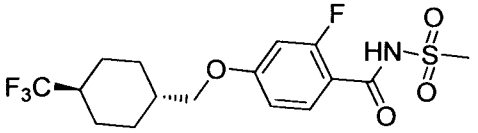
[01306] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide with *cis*-5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4- (trifluoromethyl)cyclohexyl)methoxy)benzamide, the title compound was obtained as colorless solid (0.12 g, 24%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 13.1 Hz, 1H), 4.06 (d, J = 7.1 Hz, 2H), 3.34 (s, 3H), 2.36-2.28 (m, 1H), 2.13-1.97 (m, 2H), 1.74-1.56 (m, 8H), 0.91-0.85 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) *m/z* 438.1 (M + 1); MS(ES-) *m/z* 436.2 (M - 1).

[01307] EXAMPLE 241/242

[01308] Synthesis of *trans*-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)- 4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[01309] And synthesis of *trans*-2-fluoro-*N*-(methylsulfonyl)-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



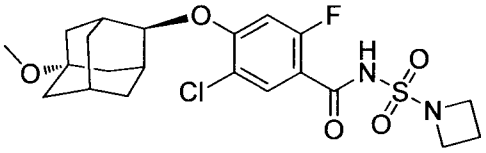
[01310] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro-*N*- (methylsulfonyl)benzamide with *trans*-5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-((4- (trifluoromethyl)cyclohexyl)methoxy)benzamide, the title compound was obtained as colorless solid (0.06 g, 47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 13.0 Hz, 1H), 3.92 (d, J = 6.1 Hz, 2H), 3.33 (s, 3H), 2.30-2.20 (m, 1H), 2.08-1.81 (m, 6H), 1.38-1.12 (m, 4H), 0.93-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 438.1 (M + 1); MS(ES-) m/z 436.2 (M - 1).

[01311] *trans*-2-fluoro-*N*-(methylsulfonyl)-4-((4-(trifluoromethyl)cyclohexyl)methoxy)benzamide was also obtained as colorless solid (0.03 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.63 (t, J =

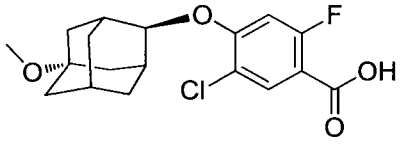
8.7 Hz, 1H), 6.97-6.85 (m, 2H), 3.89 (d, J = 6.4 Hz, 2H), 3.32 (s, 3H), 2.30-2.20 (m, 1H), 1.93-189 (m, 4H), 1.80-173. (m, 1H), 1.35-1.06 (m, 4H); MS(ES+) *m/z* 398.1 (M + 1); MS(ES-) *m/z* 396.2 (M - 1).

[01312] EXAMPLE 243

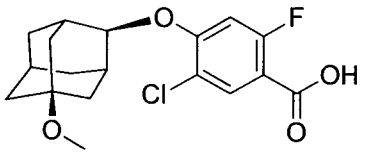
[01313] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((*trans*- 5-methoxyadamantan-2-yl)oxy)benzamide



[01314] Step 1. Preparation of 5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan- 2-yl)oxy)benzoic acid

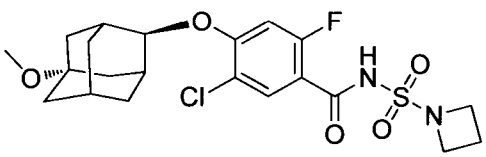


[01315] And 5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan-2-yl)oxy)benzoic acid



[01316] To a solution of 5-methoxyadamantan-2-ol (6.50 g, 35.67 mmol) in anhydrous dimethylsulfoxide (60 ml) was added potassium *tert*-butoxide (10.00 g, 89.11 mmol) and the reaction mixture was stirred at ambient temperature for 30 minutes. 5-chloro-2,4-difluorobenzoic acid (6.86 g, 35.62 mmol) was added to the reaction mixture, stirring was continued for 2 hours. The reaction mixture was acidified to pH = 1 with 5% aqueous hydrochloric acid solution and diluted with water (100 mL); extracted with ethyl acetate (100 mL x 3). The combined organic extracts was washed with water and dried and concentrated *in vacuo*. The residue was purified by column chromatography (10-50% ethyl acetate in hexanes) to afford two diastereomers. The first fraction as 5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan-2-yl)oxy)benzoic acid (1.20 g, 9%): MS(ES-) *m/z* 353.2, 351.2 (M - 1). The second fraction as 5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan- 2-yl)oxy)benzoic acid (0.8 g, 6%): MS(ES-) *m/z* 53.2, 351.2 (M - 1).

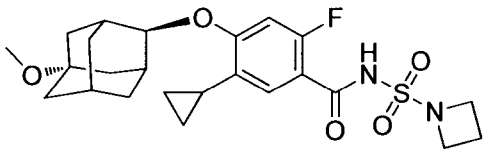
[01317] Step 2. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan- 2-yl)oxy)benzamide



[01318] To a stirred solution of 5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan-2-yl)- oxy)benzoic acid (1.20 g, 3.38 mmol) in dichloromethane (100 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.97 g, 5.05 mmol), and 4-dimethylaminopyridine (0.94 g, 7.69 mmol). The reaction stirred at ambient temperature for 10 minutes, azetidine-1-sulfonamide (0.69 g, 5.07 mmol) was added and the stirring continued at ambient temperature for 17 hours. 5% aqueous hydrochloric acid solution (10 mL) were added and diluted with ethyl acetate (300 mL), washed with water and brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (30% ethyl acetate in hexanes) afforded the title compound (1.08 g, 67%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J = 15.3 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 13.8 Hz, 1H), 4.42-4.34 (m, 1H), 4.23 (t, J = 7.5 Hz, 4H), 3.24 (s, 3H), 2.43 (br s, 2H), 2.32-2.17 (m, 5H), 1.85-1.62 (m, 6H), 1.57-1.50 (m, 2H); MS(ES+) *m/z* 473.1, 475.1 (M + 1); MS(ES-) *m/z* 471.2, 473.2 (M - 1).

[01319] EXAMPLE 244

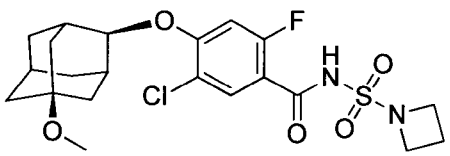
[01320] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4- ((*trans*-5-methoxyadamantan-2-yl)oxy)benzamide



[01321] Following the procedure as described in Example 165 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((1-(trifluoro- methyl)cyclopentyl)- methoxy)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2- fluoro-4-((*trans*-5-methoxyadamantan-2-yl)oxy)benzamide, the title compound was obtained (0.31 g, 64%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, J = 16.2 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 6.54 (d, J = 14.7 Hz, 1H), 4.37-4.32 (m, 1H), 4.22 (t, J = 7.8 Hz, 4H), 3.22 (s, 3H), 2.44 (br s, 2H), 2.29-2.03 (m, 6H), 1.85-1.64 (m, 6H), 1.59-1.52 (m, 2H), 0.96-0.88 (m, 2H), 0.68-0.62 (m, 2H); MS(ES+) *m/z* 479.2 (M + 1). MS(ES-) *m/z* 477.2 (M - 1).

[01322] EXAMPLE 245

[01323] Synthesis *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4- ((*cis*-5-methoxyadamantan-2-yl)oxy)benzamide

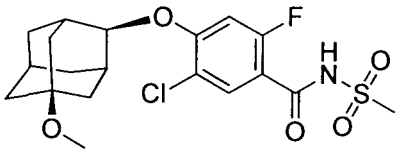


[01324] Following the procedure as described in Example 243 step 2, and making variations as required to replace 5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan-2- yl)oxy)benzoic acid with

5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan-2-yl)oxy)benzoic acid, the title compound was obtained (0.27 g, 50%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 15.3 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 13.8 Hz, 1H), 4.53-4.46 (m, 1H), 4.23 (t, J = 7.8 Hz, 4H), 3.24 (s, 3H), 2.38-2.07 (m, 7H), 1.88-1.74 (m, 6H), 1.49-1.40 (m, 2H); MS(ES+) *m/z* 475.1, 473.1 (M + 1); MS(ES-) *m/z* 473.2, 471.2 (M - 1).

[01325] EXAMPLE 246

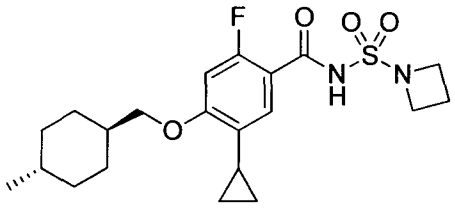
[01326] Synthesis of 5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan-2-yl)oxy)-N-(methylsulfonyl)benzamide



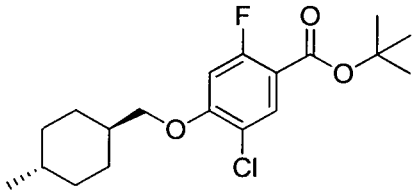
[01327] Following the procedure as described in Example 243 step 2 and making variations as required to replace 5-chloro-2-fluoro-4-((*trans*-5-methoxyadamantan-2-yl)oxy)benzoic acid with 5-chloro-2-fluoro-4-((*cis*-5-methoxyadamantan-2-yl)oxy)benzoic acid and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained (0.14 g, 38%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 15.3 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 14.1 Hz, 1H), 4.48-4.52 (m, 1H), 3.40 (s, 3H), 3.24 (s, 3H), 2.40-2.32 (m, 2H), 2.25-2.08 (m, 3H), 1.92-1.78 (m, 6H), 1.49-1.40 (m, 2H); MS(ES+) *m/z* 434.0, 432.0 (M + 1); MS(ES-) *m/z* 432.1, 430.1 (M - 1).

[01328] EXAMPLE 247

[01329] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro- 4-((*trans*-4-methylcyclohexyl)-methoxy)benzamide

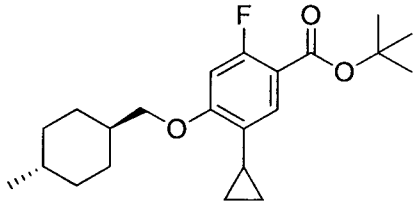


[01330] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((*trans*-4-methylcyclohexyl)-methoxy)benzoate



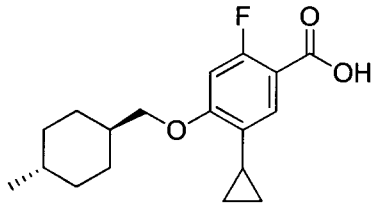
[01331] To a solution of *trans*-(4-methylcyclohexyl)methanol (3.00 g, 23.4 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (6.43 g, 25.90 mmol) in anhydrous dimethylsulfoxide (40 mL) was added cesium carbonate (16.11 g, 49.44 mmol). The mixture was heated at 70 °C for 96 hours, and then cooled to ambient temperature; diluted with water (300 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 10% ethyl acetate in hexanes gradient) to give the title compound (6.48 g 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 12.3 Hz, 1H), 3.82 (d, J = 6.2 Hz, 2H), 1.91-1.73 (m, 8H), 1.56 (s, 9H), 1.17-0.96 (m, 5H).

[01332] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*trans*-4-methyl-cyclohexyl)-methoxy)benzoate



[01333] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((*trans*-4-methylcyclohexyl)- methoxy)-benzoate (6.48 g, 18.16 mmol) in toluene-water (40 mL, v/v 20:1) was added cyclopropylboronic acid (2.34 g, 27.26 mmol) and tribasic potassium phosphate (17.37, 81.84 mmol). The reaction mixture was sparged with argon for 10 minutes and then charged with tricyclohexylphosphine tetrafluoroborate (1.35 g, 3.67 mmol) and palladium acetate (0.41 g, 1.82 mmol). The mixture was heated at 110 °C for 72 hours, then cooled to ambient temperature; filtered through a pad of diatomaceous earth and washed with ethyl acetate. The filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography (0% to 10% ethyl acetate) to give the title compound (5.95 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 12.8 Hz, 1H), 3.78 (d, J = 6.1 Hz, 2H), 1.91-1.70 (m, 8H), 1.56 (s, 9H), 1.41-129 (m, 2H), 1.14-0.95 (m, 6H), 0.65-0.60 (m, 2H).

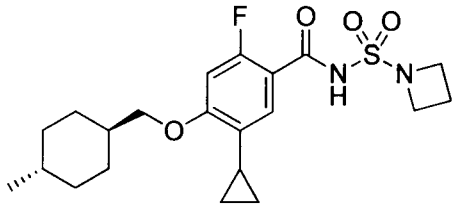
[01334] Step 3. Preparation of 5-cyclopropyl-2-fluoro-4-((*trans*-4-methylcyclohexyl)- methoxy)benzoic acid



[01335] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*trans*-4-methyl-cyclohexyl)methoxy)benzoate (5.95 g, 16.41 mmol) in anhydrous dichloromethane (28 mL) was added trifluoroacetic acid (14 mL). The mixture was stirred for 1 hour at ambient temperature, and then

concentrated *in vacuo*. The solid was triturated with methanol to give the title compound (2.42 g, 48%):): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.8 (br s, 1H), 7.30 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 13.1 Hz, 1H), 3.89 (d, J = 6.1 Hz, 2H), 2.05-1.96 (m, 1H), 1.85-1.68 (m, 5H), 1.39-1.25 (m, 1H), 1.17-0.86 (m, 9H), 0.61-0.56 (m, 2H).

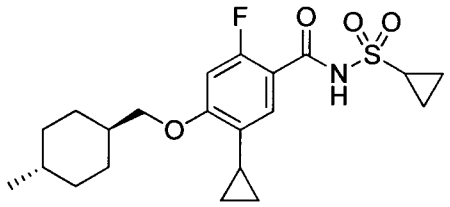
[01336] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*trans*-4-methylcyclohexyl)methoxy)benzamide



[01337] To a mixture of 5-cyclopropyl-2-fluoro-4-((*trans*-4-methylcyclohexyl)- methoxy)benzoic acid (0.255 g, 0.83 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.242 g, 1.26 mmol) and 4-dimethylaminopyridine (0.242 g, 1.98 mmol) in anhydrous dichloromethane (22 mL) was added azetidine-1-sulfonamide (0.173 g, 1.27 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The mixture was poured into 5% aqueous hydrochloric acid (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0% to 40% ethyl acetate in hexanes) to afford the title compound (0.114 g, 33%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 16.7 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 14.5 Hz, 1H), 4.25 (t, J = 7.7 Hz, 4H), 3.83 (d, J = 6.1 Hz, 2H), 2.27 (q, J = 7.7 Hz, 1H), 2.11-2.02 (m, 1H), 1.92-1.75 (m, 5H), 1.41-1.29 (m, 1H), 1.25-0.90 (m, 10H), 0.70-0.64 (m, 2H); MS (ES-) *m/z* 423.26 (M - 1).

[01338] EXAMPLE 248

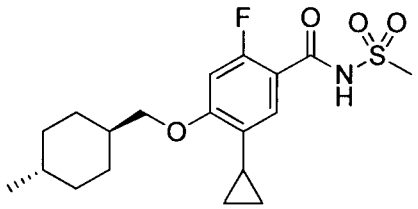
[01339] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((*trans*-4-methylcyclohexyl)methoxy)benzamide



[01340] Following the procedure as described in Example 247 step 4 and making variations as required to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as a colorless solid (0.254 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 16.3 Hz, 1H), 7.56 (d, J = 9.1 Hz, 1H), 6.55 (d, J = 14.5 Hz, 1H), 3.81 (d, J = 6.1 Hz, 2H), 3.12-3.04 (m, 1H), 2.08-1.99 (m, 1H), 1.89-1.73 (m, 5H), 1.46-0.83 (m, 14H), 0.67-0.61 (m, 2H); MS (ES-) *m/z* 408.2 (M - 1).

[01341] EXAMPLE 249

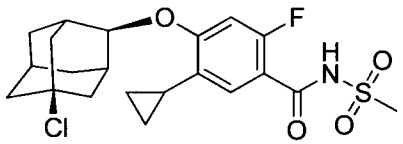
[01342] Synthesis of 5-cyclopropyl-2-fluoro-4-((*trans*-4-methylcyclohexyl)methoxy)-*N*-(methylsulfonyl)benzamide



[01343] Following the procedure as described in Example 247 step 4 and making variations as required to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained (0.188 g, 69%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 16.2 Hz, 1H), 7.56 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 14.6 Hz, 1H), 3.81 (d, J = 6.1 Hz, 2H), 3.41 (s, 3H), 2.10-2.00 (m, 1H), 1.91-1.75 (m, 5H), 1.44-1.28 (m, 1H), 1.20-0.90 (m, 9H), 0.68-0.63 (m, 2H); MS (ES-) *m/z* 382.2 (M - 1)

[01344] EXAMPLE 250

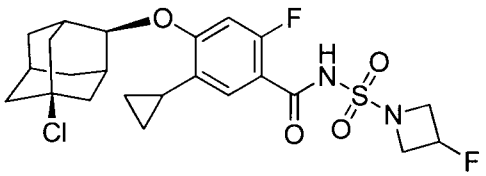
[01345] Synthesis of *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01346] Following the procedure as described in Example 218 step 5 and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid with *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained (0.18 g, 57%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 13.2 Hz, 1H), 4.67 (t, J = 3.0 Hz, 1H), 3.34 (s, 3H), 2.43-2.34 (m, 4H), 2.10-2.02 (m, 4H), 1.97-1.93 (m, 2H), 1.79 (s, 4H), 0.95-0.89 (m, 2H), 0.72-0.67 (m, 2H); MS(ES+) *m/z* 444.1, 442.1, (M + 1); MS(ES-) *m/z* 442.2, 440.2 (M - 1).

[01347] EXAMPLE 251

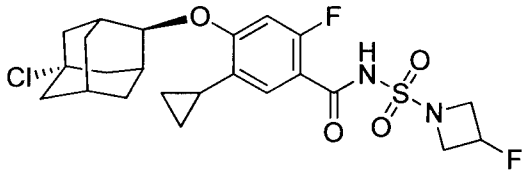
[01348] Synthesis of *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01349] Following the procedure as described in Example 218 step 5, and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl- 2-fluorobenzoic acid with *cis*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.23 g, 65%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 13.1 Hz, 1H), 5.48-5.23 (m, 1H), 4.68 (t, J = 2.8 Hz, 1H), 4.43-4.31 (m, 2H), 4.25-4.12 (m, 2H), 2.43-2.35 (m, 4H), 2.11-2.02 (m, 4H), 1.95 (d, J = 11.6 Hz, 2H), 1.79 (br s, 4H), 0.96-0.89 (m, 2H), 0.72-0.67 (m, 2H); MS(ES+) m/z 503.1, 501.1 (M + 1); MS(ES-) m/z 501.1, 499.1 (M - 1).

[01350] EXAMPLE 252

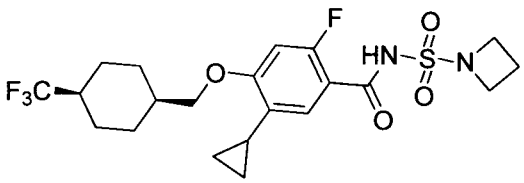
[01351] Synthesis of *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01352] Following the procedure as described in Example 218 step 5, and making variations as required to replace azetidine-1-sulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained (0.03 g, 69%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 13.1 Hz, 1H), 5.48-5.42 (m, 0.5H), 5.29-5.23 (m, 0.5H), 4.82 (t, J = 2.7 Hz, 1H), 4.42-4.30 (m, 2H), 4.24-4.11 (m, 2H), 2.36-2.28 (m, 4H), 2.19-1.97 (m, 8H), 1.52 (d, J = 12.5 Hz, 2H), 0.94-0.88 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 503.1, 501.1, (M + 1); MS(ES-) m/z 501.1, 499.1 (M - 1).

[01353] EXAMPLE 253

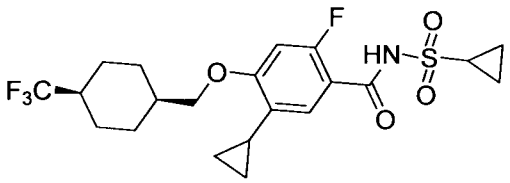
[01354] Synthesis of *cis*-*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((4-(trifluoromethyl)cyclohexyl)methoxy)benzamide



[01355] Following the procedure as described in Example 218 step 5, and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl- 2-fluorobenzoic acid with *cis*-5-cyclopropyl-2-fluoro-4-((4-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid, the title compound was obtained (0.10 g, 66%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 13.0 Hz, 1H), 4.07-4.02 (m, 6H), 2.39-2.27 (m, 1H), 2.21-2.11 (m, 3H), 2.06-1.97 (m, 1H), 1.74-1.56 (m, 8H), 0.91-0.85 (m, 2H), 0.71-0.65 (m, 2H); MS(ES+) m/z 479.1 (M + 1); MS(ES-) m/z 477.2 (M - 1).

[01356] EXAMPLE 254

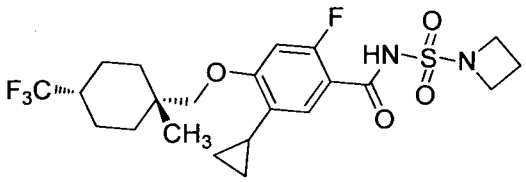
[01357] Synthesis of *cis*-5-cyclopropyl-*N*-(cyclopropylsulfonyl)- 2-fluoro-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



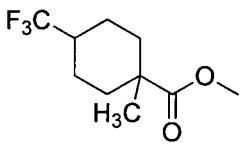
[01358] Following the procedure as described in Example 218 step 5, and making variations as required to replace *trans*-4-((5-chloroadamantan-2-yl)oxy)-5-cyclopropyl- 2-fluorobenzoic acid with *cis*-5-cyclopropyl-2-fluoro-4-((4-(trifluoromethyl)cyclohexyl)- methoxy)benzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained as colorless solid (0.11 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 13.1 Hz, 1H), 4.06 (d, J = 7.1 Hz, 2H), 3.11-3.03 (m, 1H), 2.42-2.26 (m, 1H), 2.14 (brs, 1H), 2.06-1.97 (m, 1H), 1.74-1.56 (m, 8H), 1.13-1.09 (m, 4H), 0.91-0.85 (m, 2H), 0.69-0.64 (m, 2H); MS(ES+) *m/z* 464.1 (M + 1); MS(ES-) *m/z* 462.2 (M - 1).

[01359] EXAMPLE 255

[01360] Synthesis of *cis*-*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)methoxy)benzamide

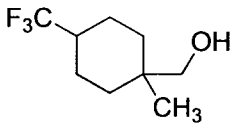


[01361] Step 1. Preparation of methyl 1-methyl-4-(trifluoromethyl)cyclohexanecarboxylate



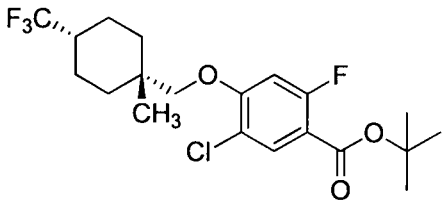
[01362] To a solution of diisopropylamine (22.0 mL, 124.0 mmol) in tetrahydrofuran (60 mL) was added *n*-BuLi (2.0 M solution in hexane, 59.0 mL, 95.0 mmol) at 0 °C and the reaction mixture was allowed to stir at same temperature for 20 minutes before cooled to -78°C. Methyl 4-(trifluoromethyl)cyclohexanecarboxylate (10.0 g, 48.0 mmol) in tetrahydrofuran (60 mL) was added dropwise at -78 °C. The reaction mixture was stirred at same temperature for 2 hours and then neat methyl iodide (4.5 mL, 72.0 mmol) was added dropwise. After stirring at -78°C for 1 hour, the reaction mixture was warmed to ambient temperature and stirred for 16 hours, before quenched with 25% aqueous ammonium chloride solution (100 mL) at 0 °C and extracted with ethyl acetate. The organic layer was washed with brine; dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound (11.2 g, 99%) as a brown colored oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.32-2.28 (m, 2H), 2.01-1.80 (m, 3H), 1.42-1.08 (m, 7H).

[01363] Step 2. Preparation of (1-methyl-4-(trifluoromethyl)cyclohexyl)methanol



[01364] To a solution of 1-methyl-4-(trifluoromethyl)cyclohexanecarboxylate (11.0 g, 49.00 mmol) in tetrahydrafuran (600 mL) was slowly added lithium borohydride solution (4.0 M in tetrahydrofuran, 37.0 mL, 147.00 mmol) and methanol (6.0 mL, 147.00 mmol) at 0 °C. After stirring at 0 °C for 15 minutes, the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was cooled to 0 °C and quenched with 25% aqueous ammonium chloride solution (100 mL), and extracted with ethyl acetate. The combined organic layers were washed with brine; dried over anhydrous magnesium sulfate; filtered and concentrated *in vacuo.* Purification of the residue by column chromatography (0 to 5% gradient ethyl acetate in hexanes) afforded the title compound (6.80 g, 72%) as a colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (s, 2H), 2.02-1.91 (m, 1H), 1.75-1.72 (m, 4H), 1.49-1.35 (m, 3H), 1.19-1.09 (m, 2H), 0.94 (s, 3H).

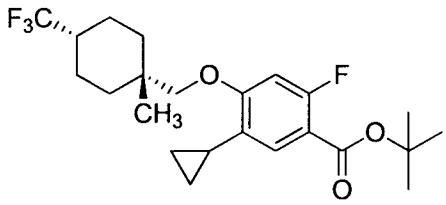
[01365] Step 3. Preparation of *cis-tert*-butyl 5-chloro-2-fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)- methoxy)benzoate



[01366] Following the procedure as described in Example 226 step 1, and making variations as required to replace (4,4-difluoroadamantan-1-yl)methanol with (1-methyl-4-(trifluoromethyl)cyclohexyl)- methanol, the title compound was obtained (6.20 g, 95 %) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* =

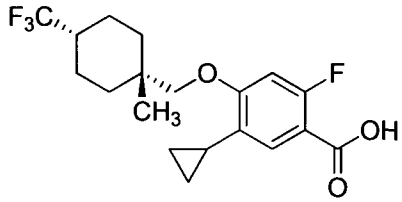
7.7 Hz, 1H), 6.65 (d, J = 12.0 Hz, 1H), 3.85 (s, 2H), 1.96-1.93 (m, 2H), 1.85-1.79 (m, 2H), 1.58 (s, 9H), 1.53-1.39 (m, 3H), 1.34-1.23 (m, 2H), 1.11 (s, 3H),

[01367] Step 4. Preparation of *cis*-tert-butyl 5-chloro-2-fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)methoxy)benzoate



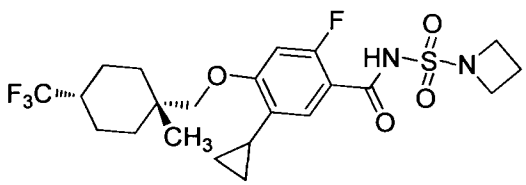
[01368] Following the procedure as described in Example 226 step 2, and making variations as required to replace *tert*-butyl 5-chloro-4-((4,4-difluoroadamantan-1-yl)methoxy)-2-fluorobenzoate with *cis-tert*-butyl 5-chloro-2-fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)methoxy)benzoate, the title compound was obtained (1.66 g, 96 %) as a pale yellow oil: 1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 12.6 Hz, 1H), 3.81 (s, 2H), 2.00-1.95 (m, 3H), 1.84-1.79 (m, 2H), 1.57 (s, 9H), 1.55-1.41 (m, 2H), 1.33-1.22 (m, 2H), 1.11 (s, 3H), 0.91-0.85 (m, 2H), 0.64-0.59 (m, 2H).

[01369] Step 5. Preparation of *cis*-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)-cyclohexyl)methoxy)benzoic acid



[01370] Following the procedure as described in Example 226 step 3, and making variations as required to replace *tert-butyl* 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)- methoxy)-2-fluorobenzoate with *cis-tert*-butyl 5-chloro-2-fluoro-4-((1-methyl-4- (trifluoromethyl)cyclohexyl)- methoxy)benzoate, the title compound was obtained as light yellow gummy solid (1.30 g, 81 %): 1H NMR (300 MHz, DMSO-d_6) □ 12.84 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 13.2 Hz, 1H), 3.92 (s, 2H), 2.26-2.20 (m, 1H), 2.04-1.95 (m, 1H), 1.87-1.83 (m, 2H), 1.72-1.67 (m, 2H), 1.54-1.41 (m, 2H), 1.34-1.23 (m, 2H), 1.05 (s, 3H), 0.91-0.85 (m, 2H), 0.60-0.55 (m, 2H); MS(ES-) m/z 373.2 (M - 1).

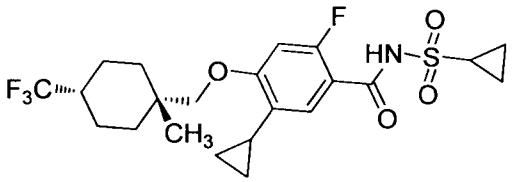
[01371] Step 6. Preparation of *cis-N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2- fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)methoxy)benzamide



[01372] Following the procedure as described in Example 226 step 4, and making variations as required to replace 5-cyclopropyl-4-((4,4-difluoroadamantan-1- yl)methoxy)-2-fluorobenzoic with *cis*-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid, the title compound was obtained as (0.13 g, 64%) a colorless solid: 1H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 13.0 Hz, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.93 (s, 2H), 2.31-2.11 (m, 3H), 2.06-1.97 (m, 1H), 1.88-1.83 (m, 2H), 1.73-1.68 (m, 2H), 1.54-1.41 (m, 2H), 1.35-1.25 (m, 2H), 1.06 (s, 3H), 0.92-0.86 (m, 2H), 0.70-0.64 (m, 2H); MS(ES+) *m/z* 493.2 (M + 1); MS(ES-) *m/z* 491.3 (M - 1).

[01373] EXAMPLE 256

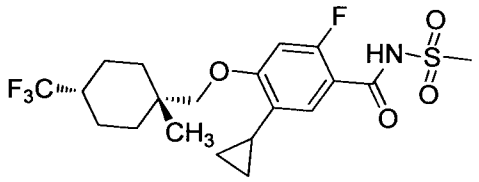
[01374] Synthesis of cis-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((1-methyl-4-(trifluoromethyl)cyclohexyl)methoxy)benzamide



[01375] Following the procedure as described in Example 226 step 4, and making variations as required to replace 5-cyclopropyl-4-((4,4-difluoroadamantan-1- yl)methoxy)-2-fluorobenzoic with *cis*-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.11 g, 61%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 13.1 Hz, 1H), 3.93 (s, 2H), 3.12-3.03 (m, 1H), 2.30-2.20 (m, 1H), 2.05-1.96 (m, 1H), 1.87-1.83 (m, 2H), 1.73-1.68 (m, 2H), 1.54-1.41 (m, 2H), 1.34-1.24 (m, 2H), 1.13-1.08 (m, 4H), 1.05 (s, 3H), 0.92-0.85 (m, 2H), 0.69-0.63 (m, 2H); MS(ES+) *m/z* 478.1 (M + 1); MS(ES-) *m/z* 476.2 (M - 1).

[01376] EXAMPLE 257

[01377] Synthesis of *cis*-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)-cyclohexyl)methoxy)-*N*-(methylsulfonyl)benzamide

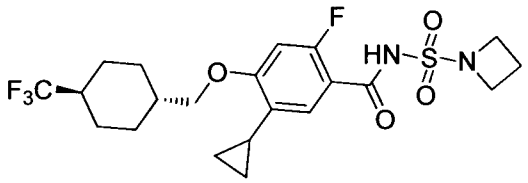


[01378] Following the procedure as described in Example 226 step 4, and making variations as required to replace 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)- 2-fluorobenzoic with *cis*-5-cyclopropyl-2-fluoro-4-((1-methyl-4-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid, and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained (0.11 g, 58%)

as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 13.1 Hz, 1H), 3.93 (s, 2H), 3.33 (s, 3H), 2.30-2.20 (m, 1H), 2.06-1.96 (m, 1H), 1.87-1.83 (m, 2H), 1.73-1.68 (m, 2H), 1.54-1.41 (m, 2H), 1.34-1.24 (m, 2H), 1.05 (s, 3H), 0.92-0.85 (m, 2H), 0.69-0.64 (m, 2H); MS(ES+) *m/z* 452.1 (M + 1); MS(ES-) *m/z* 450.2 (M - 1).

[01379] EXAMPLE 258

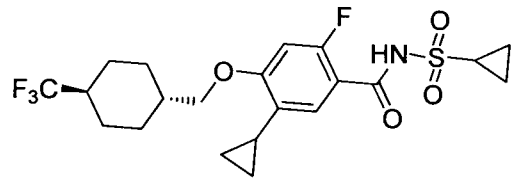
[01380] Synthesis of *trans*-*N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2- fluoro-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[01381] Following the procedure as described in Example 226 step 4, and making variations as required to replace 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)- 2-fluorobenzoic with *trans*-5-cyclopropyl-2-fluoro-4-((4-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid, the title compound was obtained (0.15 g, 78%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 13.0 Hz, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.92 (d, J = 6.1 Hz, 2H), 2.30-1.78 (m, 8H), 1.38-1.12 (m, 5H), 0.93-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) m/z 479.1 (M + 1); MS(ES-) m/z 477.2 (M - 1).

[01382] EXAMPLE 259

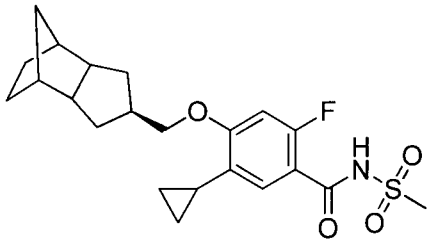
[01383] Synthesis of *trans*-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2- fluoro-4-((4-(trifluoromethyl)-cyclohexyl)methoxy)benzamide



[01384] Following the procedure as described in Example 226 step 4, and making variations as required to replace 5-cyclopropyl-4-((4,4-difluoroadamantan-1-yl)methoxy)- 2-fluorobenzoic with trans-5-cyclopropyl-2-fluoro-4-((4-(trifluoromethyl)cyclohexyl)- methoxy)benzoic acid and to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.15 g, 81%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 13.0 Hz, 1H), 3.92 (d, J = 6.0 Hz, 2H), 3.12-3.03 (m, 1H), 2.08-1.78 (m, 6H), 1.38-1.10 (m, 9H), 0.93-0.87 (m, 2H), 0.70-0.65 (m, 2H); MS(ES+) *m/z* 464.1 (M + 1); MS(ES-) *m/z* 462.2 (M - 1).

[01385] EXAMPLE 260

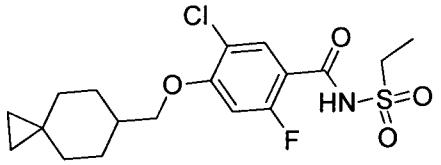
[01386] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(((2s,3aR,4S,7R,7aS)-octahydro-1*H*-4,7-methanoinden-2-yl)methoxy)benzamide



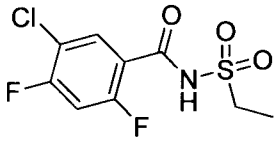
[01387] Following the procedure as described in Example 49 and making variations as required to replace 4-((adamantan-2-yloxy)methyl)-5-chloro-2-fluoro- *N*-(methylsulfonyl)benzamide with 5-chloro-2-fluoro-*N*-(methylsulfonyl)-4-(((2s,3aR,4S,7R,7aS)-octahydro-1*H*-4,7-methanoinden-2-yl)methoxy)benzamide, the title compound was obtained (0.06 g, 59%) as a colorless solid: 1H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.15-7.12 (m, 1H), 6.96-6.90 (m, 1H), 3.95-3.79 (m, 2H), 3.32 (s, 3H), 2.43-2.36 (m, 2H), 2.18-1.96 (m, 4H), 1.70-1.23 (m, 9H), 1.06-0.99 (m, 1H), 0.90-0.87 (m, 2H), 0.70-0.66 (m, 2H); MS(ES+) *m/z* 422.2 (M + 1); MS(ES-) *m/z* 420.3 (M - 1).

[01388] EXAMPLE 261

[01389] Synthesis of 5-chloro-*N*-(ethylsulfonyl)-2-fluoro-4-(spiro[2.5]octan- 6-ylmethoxy)benzamide

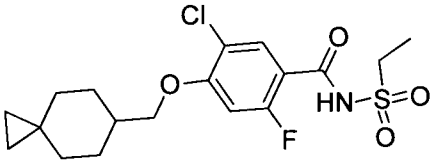


[01390] Step 1. Preparation of 5-chloro-*N*-(ethylsulfonyl)-2,4-difluorobenzamide



[01391] Following the procedure as described in preparation of Example 209 step 1, and making variations as required to replace cyclopropanesulfonamide with ethanesulfonamide, the title compound was obtained (3.8 g, 70%) as a colorless solid: MS (ES +) *m/z* 284.0, 286.0 (M +1).

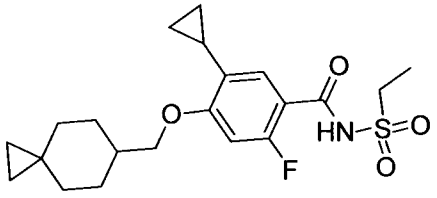
[01392] Step 2. Synthesis of 5-chloro-*N*-(ethylsulfonyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



[01393] Following the procedure as described in Example 8 and making variations as required to replace 5-chloro-2,4-difluoro-*N*-(methylsulfonyl)benzamide with 5-chloro-*N*-(ethylsulfonyl)-2,4-difluorobenzamide and to replace adamantan-1-ylmethanol with spiro[2.5]octan-6-ylmethanol, the title compound was obtained as a colorless solid (0.378 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59-8.47 (m, 1H), 8.13-8.05 (m, 1H), 6.75-6.66 (m, 1H), 3.97-3.86 (m, 2H), 3.66-3.55 (m, 2H), 2.02-1.72 (m, 5H), 1.48-1.40 (m, 3H), 1.35-1.22 (m, 2H), 1.01-0.89 (m, 2H), 0.37-0.15 (m, 4H); MS (ES +) *m/z* 404.1, 406.1 (M +1).

[01394] EXAMPLE 262

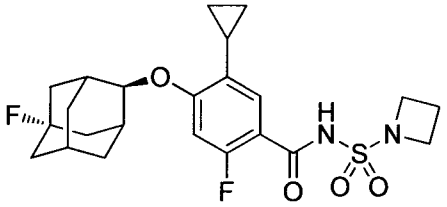
[01395] Synthesis of 5-cyclopropyl-*N*-(ethylsulfonyl)-2-fluoro-4-(spiro[2.5]octan-6-ylmethoxy)benzamide



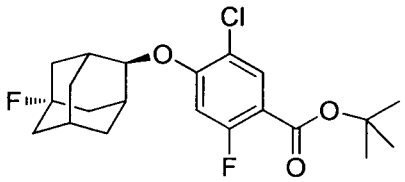
[01396] A mixture of 5-cyclopropyl-*N*-(ethylsulfonyl)-2-fluoro-4-(spiro[2.5]octan -6-ylmethoxy)benzamide (0.055 g, 0.14 mmol), cyclopropylboronic acid (0.036 g, 0.41 mmol), and potassium phosphate (0.297 g, 1.40 mmol) in toluene (3 mL) and water (0.3 mL) was sparged with nitrogen for 10 minutes. Tricyclohexylphosphine tetrafluoroborate (0.031 g, 0.084 mmol) and palladium acetate (0.0095 g, 0.042 mmol) were added and the reaction mixture was heated at 150 °C for 1 hour under microwave irradiation. The mixture was cooled to ambient temperature, diluted with ethyl acetate (100 mL) and 1M aqueous hydrochloric acid (20 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography with a gradient of ethyl acetate in hexanes (0 - 70%) afforded the title compound (0.036 g, 63%) as colorless solid: (0.036 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61-8.50 (m, 1H), 7.60-7.51 (m, 1H), 6.63-6.54 (m, 1H), 3.93-3.83 (m, 2H), 3.67-3.51 (m, 2H), 2.14-1.98 (m, 1H), 1.99-1.72 (m, 5H), 1.50-1.40 (m, 3H), 1.37-1.22 (m, 2H), 1.02-0.88 (m, 4H), 0.72-0.60 (m, 2H), 0.38-0.15 (m, 4H); MS(ES+) *m/z* 410.2 (M +1).

[01397] EXAMPLE 263

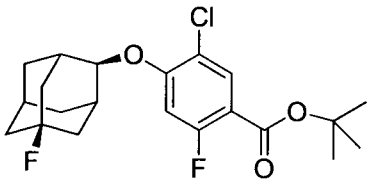
[01398] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro- 4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzamide



[01399] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzoate



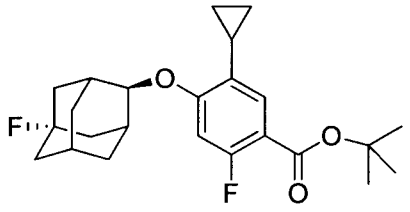
[01400] And *tert*-butyl 5-chloro-2-fluoro-4-((*cis*-5-fluoroadamantan-2-yl)oxy)benzoate



[01401] Following the procedure as described in preparation of Example 178 step 1, and making variations as required to replace (4,4-difluoro-1-methylcyclohexyl)methanol with 5-fluoroadamantan-2-ol (*J. Am. Chem. Soc.* **1986**, *108*, 1598), the crude product was purified by column chromatography with a gradient of ethyl acetate in hexanes (0 - 5%) to afford two diastereomers. The first fraction, *tert*-butyl 5-chloro-2-fluoro-4-((*trans*-5-fluoroadamantan- 2-yl)oxy)benzoate (1.44 g, 19%) as colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.86 (m, 1H), 6.67-6.58 (m, 1H), 4.55-4.45 (m, 1H), 2.41 (s, 2H), 2.28 (s, 1H), 2.20-1.92 (m, 8H), 1.60-1.56 (m, 9H), 1.52-1.39 (m, 2H); MS (ES +) *m/z* 399.1, 401.2 (M +1);

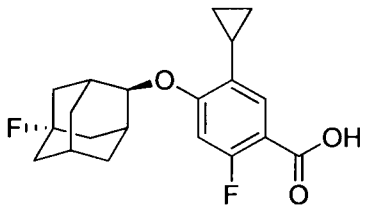
[01402] The second fraction, *tert*-butyl 5-chloro-2-fluoro-4-((*cis*-5-fluoroadamantan- 2-yl)oxy)benzoate (0.81 g, 11%) as colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.86 (m, 1H), 6.67-6.59 (m, 1H), 4.38-4.29 (m, 1H), 2.57-2.46 (m, 2H), 2.44-2.21 (m, 3H), 1.96-1.87 (m, 2H), 1.87-1.62 (m, 6H), 1.60-1.56 (m, 9H); MS (ES +) *m/z* 399.2 (M +1).

[01403] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzoate

1. 

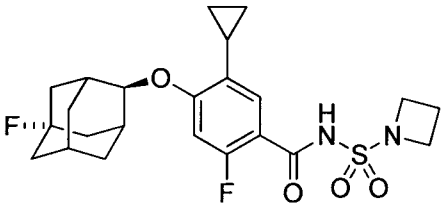
[01404] Following the procedure as described in preparation of Example 158 step 3, and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)- methoxy)benzoate with *tert*-butyl 5-chloro-2-fluoro-4-((*trans*-5-fluoroadamantan- 2-yl)oxy)benzoate, the title compound was obtained as colorless solid (1.43 g, 100 %): MS (ES +) *m/z* 427.1 (M +23).

[01405] Step 3. Preparation of 5-cyclopropyl-2-fluoro-4-((*trans*-5- fluoroadamantan-2-yl)oxy)benzoic acid



[01406] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*trans*-5- fluoroadamantan-2-yl)oxy)benzoate, the title compound was obtained as a colorless solid (1.01 g, 89 %): MS (ES+) *m/z* 349.1 (M + 1).

[01407] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzamide

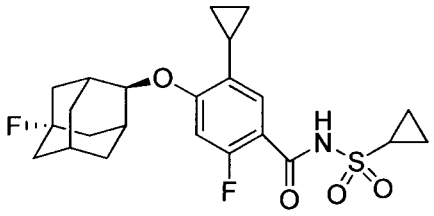


[01408] Following the procedure as described in Example 158 step 5, and making variations as required to to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 5-cyclopropyl-2-fluoro-4-((*trans*-5- fluoroadamantan-2-yl)oxy)benzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.149 g, 51%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72-8.58 (m, 1H), 7.68-7.59 (m, 1H), 6.60-6.50 (m, 1H),

4.56-4.46 (m, 1H), 4.33-4.19 (m, 4H), 2.51-2.39 (m, 2H), 2.35-2.20 (m, 3H), 2.17-1.93 (m, 9H), 1.54-1.43 (m, 2H), 1.00-0.89 (m, 2H), 0.75-0.61 (m, 2H); MS (ES +) *m/z* 467.1 (M +1).

[01409] EXAMPLE 264

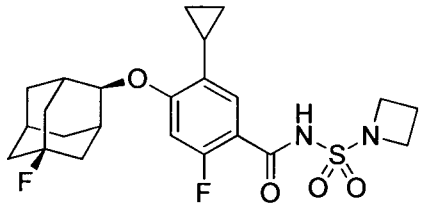
[01410] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((*trans*-5-fluoroadamantan-2-yl)oxy)benzamide



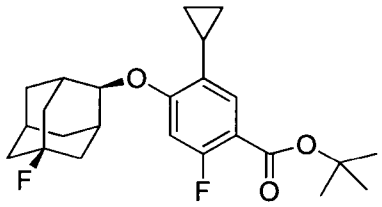
[01411] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoic acid with 5-cyclopropyl-2-fluoro-4-((*trans*-5- fluoroadamantan-2-yl)oxy)benzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.149 g, 52%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.60 (m, 1H), 7.68-7.58 (m, 1H), 6.60-6.47 (m, 1H), 4.54-4.46 (m, 1H), 3.17-3.02 (m, 1H), 2.51-2.39 (m, 2H), 2.35-2.24 (m, 1H), 2.17-1.91 (m, 9H), 1.63-1.41 (m, 4H), 1.21-1.07 (m, 2H), 1.00-0.88 (m, 2H), 0.73-0.60 (m, 2H);MS (ES +) *m/z* 452.1 (M + 1).

[01412] EXAMPLE 265

[01413] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 2-fluoro-4-((*cis*-5-fluoroadamantan-2-yl)oxy)benzamide



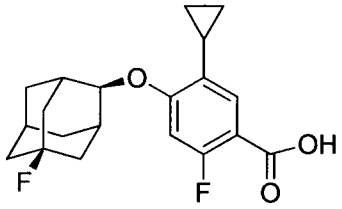
[01414] Step 1. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*cis*-5- fluoroadamantan-2-yl)oxy)benzoate



[01415] Following the procedure as described in preparation of Example 158 step 3, and making variations as required to replace *tert*-butyl 5-chloro-2-fluoro-4-((1-(trifluoromethyl)cyclohexyl)methoxy)benzoate

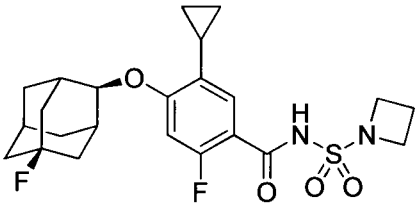
with *tert*-butyl 5-chloro-2-fluoro-4-((*cis*-5-fluoroadamantan-2-yl)oxy)benzoate, the title compound was obtained as colorless solid (0.28 g, 34 %): MS (ES +) *m/z* 405.2 (M + 1).

[01416] Step 2. Preparation of 5-cyclopropyl-2-fluoro-4-((*cis*-5- fluoroadamantan-2-yl)oxy)benzoic acid



[01417] Following the procedure as described in Example 158 step 4, and making variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)benzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-((*cis*-5- fluoroadamantan-2-yl)oxy)benzoate, the title compound was obtained as a colorless solid (0.200 g, 83 %): MS (ES+) m/z 349.1 (M + 1).

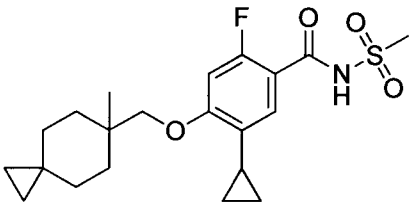
[01418] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((*cis*-5-fluoroadamantan-2-yl)oxy)benzamide



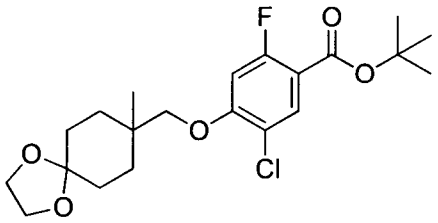
[01419] Following the procedure as described in Example 158 step 5, and making variations as required to replace 5-cyclopropyl-2-fluoro-4-((1-(trifluoromethyl)- cyclohexyl)methoxy)-benzoic acid with 5-cyclopropyl-2-fluoro-4-((*trans*-5- fluoroadamantan-2-yl)oxy)benzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.137 g, 52%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71-8.55 (m, 1H), 7.69-7.59 (m, 1H), 6.63-6.49 (m, 1H), 4.40-4.31 (m, 1H), 4.32-4.18 (m, 4H), 2.62-2.48 (m, 2H), 2.39-2.19 (m, 5H), 2.15-2.01 (m, 1H), 1.98-1.89 (m, 2H), 1.89-1.66 (m, 6H), 1.04-0.90 (m, 2H), 0.72-0.61 (m, 2H); MS (ES +) *m/z* 467.1 (M +1).

[01420] EXAMPLE 266

[01421] Synthesis of 5-cyclopropyl-2-fluoro-4-((6-methylspiro[2.5]octan-6-yl)methoxy)-N-(methylsulfonyl)benzamide

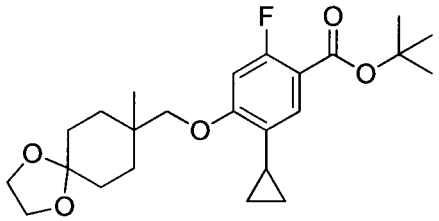


[01422] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((8-methyl- 1,4-dioxaspiro[4.5]decan-8-yl)methoxy)benzoate



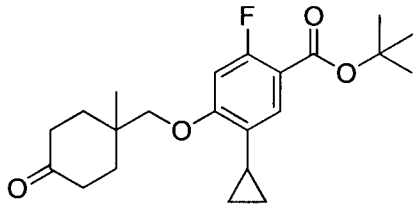
[01423] To a solution of (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (4.30 g, 23 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (10.66 g, 30 mmol) in anhydrous dimethylsulfoxide (37 mL) was added cesium carbonate (14.99 g, 46 mmol). The reaction mixture was heated to 70 °C and stirred for 4 days. At this point, HPLC and TLC analysis indicated remaining starting material, but the reaction was not progressing any further. The reaction mixture was cooled to ambient temperature, filtered through a pad of diatomaceous earth and rinsed with ethyl acetate (100 mL). The filtrate was washed with 1N aqueous hydrochloric acid solution (100 mL). The organic layer was separated, washed with brine (40 ml), dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 20% ethyl acetate in hexanes) afforded the title compound (5.13 g, 54%) as a colorless oil: MS (ES+) *m/z* 359.1 (M - 55).

[01424] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((8-methyl-1,4- dioxaspiro[4.5] decan-8-yl)methoxy)benzoate



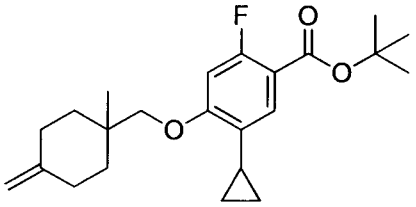
[01425] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methoxy)benzoate (3.09 g, 7.45 mmol), cyclopropylboronic acid (0.96 g, 11.17 mmol), potassium phosphate (7.12 g, 33.53 mmol) and tricyclohexylphosphine tetrafluoroborate (0.28 g, 0.75 mmol) in toluene (50 mL) and water (2.5 mL). The resulting suspension was sparged with Argon for 15 minutes before the addition of palladium acetate (0.083 g, 0.37 mmol). The reaction mixture was heated at 100 °C for 18 hours and then cooled to ambient temperature; filtered through a pad of diatomaceous earth and rinsed with ethyl acetate. The filtrate was diluted with additional water (20 mL). The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was filtered through a plug of silica gel (100% ethyl acetate) to afford the title compound (2.59 g, 83%) as a colorless oil: MS(ES+) *m/z* 365.2 (M - 55).

[01426] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4- oxocyclohexyl) methoxy)benzoate



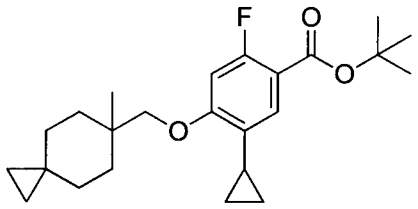
[01427] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((8-methyl-1,4- dioxaspiro[4.5]decan-8-yl)methoxy)benzoate (2.59 g, 6.16 mmol) in tetrahydrofuran (6 mL) and water (4.3 mL) was added trifluoroacetic acid (2.2 mL, 27.72 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction was quenched with 2 M aqueous sodium hydroxide solution (5 mL) before being diluted with saturated aqueous sodium bicarbonate (20 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 15% ethyl acetate in hexanes) afforded the title compound (2.09 g, 90%) as a colorless oil: MS (ES+) *m/z* 321.2 (M - 55).

[01428] Step 4. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4- methylenecyclohexyl) methoxy)benzoate



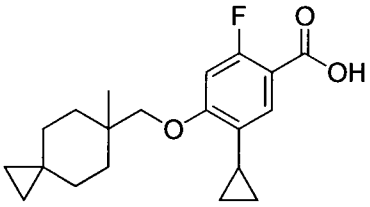
[01429] To a cooled (-20 °C) suspension of methyltriphenylphosphonium bromide (1.44 g, 4.02 mmol) in tetrahydrofuran (12 mL) was added lithium hexamethyldisilazide (1M solution in tetrahydrofuran, 4.0 mL, 4.00 mmol). After 90 minutes, a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4-oxocyclohexyl)methoxy)benzoate (1.00 g, 2.68 mmol) in tetrahydrofuran (6 mL) was added. The reaction mixture was slowly warmed to ambient temperature and stirred for 12 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (20 mL) and diluted with ethyl acetate (100 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 30 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 5% ethyl acetate in hexanes) afforded the title compound (0.83 g, 82%) as a colourless oil: MS(ES+) *m/z* 319.1 (M - 55).

[01430] Step 5. Preparation of *tert*-butyl-5-cyclopropyl-2-fluoro-4- ((6-methylspiro[2.5]octan-6-yl)methoxy)benzoate



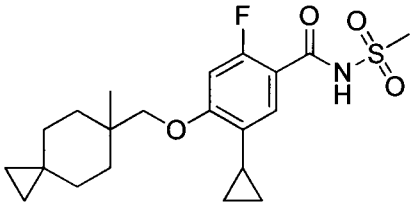
[01431] To a cooled (0 °C) solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4-methylenecyclohexyl)methoxy)benzoate (0.30 g, 0.804 mmol) in 1,2-dichloroethane (2 mL), was added chloroiodomethane (0.21 mL, 2.65 mmol), followed by diethylzinc (1M solution in hexanes, 1.33 mL, 1.33 mmol). The reaction mixture was stirred at 0 °C for 2 hours and then quenched with 1N aqueous hydrochloric acid solution. The aqueous layer was separated and extracted with dichloromethane (3 x 30 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by column chromatography (0% to 5% ethyl acetate in hexanes) afforded the title compound (0.29 g, 93%) as a colorless oil: MS (ES+) *m/z* 333.2 (M - 55).

[01432] Step 6. Preparation of 5-cyclopropyl-2-fluoro-4-((6- methylspiro[2.5]octan-6-yl)methoxy)benzoic acid



[01433] To a cooled (0 °C) solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((6-methylspiro[2.5]octan-6-yl)methoxy)benzoate (0.277 g, 0.713 mmol) and anisole (0.11 mL, 1.07 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (0.75 mL, 9.61 mmol). The reaction mixture was stirred at 0 °C for 4 hours before being quenched with water (5 mL). The reaction was diluted with dichloromethane (20 mL) and washed with water (4 x 10mL) until the last wash was neutral as monitored by pH paper. The organic layer was dried over anhydrous sodium sulfate and concentrated in *vacuo* to afford the title compound (0.213 g, 90%) as a white solid: MS(ES-) *m/z* 331.3 (M - 1).

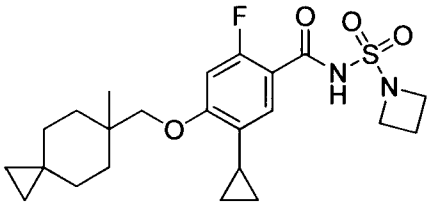
[01434] Step 7. Preparation of 5-cyclopropyl-2-fluoro-4-((6- methylspiro[2.5]octan-6-yl)methoxy)-*N*-(methylsulfonyl)benzamide



[01435] To a stirred solution of 5-cyclopropyl-2-fluoro-4-((6-methylspiro[2.5]octan-6-yl)methoxy)benzoic acid (0.085 g, 0.256 mmol) in dichloromethane (7 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.076 g, 0.384 mmol) and 4-dimethylaminopyridine (0.072 g, 0.589 mmol). The reaction mixture was stirred at ambient temperature for 10 minutes; methanesulfonamide (0.039 g, 0.41 mmol) was added and the stirring continued at ambient temperature for 17 hours. The reaction mixture was concentrated, diluted with ethyl acetate (20 mL) and washed with 5% aqueous hydrochloric acid solution (10 mL). The organic layer was separated and washed with water and brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 30% ethyl acetate in hexanes) afforded the title compound (0.058 g, 55%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 16.5 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 6.58 (d, J = 14.6 Hz, 1H), 3.74 (s, 2H), 3.40 (s, 3H), 2.09-1.95 (m, 1H), 1.69-1.42 (m, 6H), 1.29-1.02 (m, 5H), 0.96-0.87 (m, 2H), 0.67-0.60 (m, 2H), 0.31-0.16 (m, 4H); MS(ES-) *m/z* 408.3 (M - 1).

[01436] EXAMPLE 267

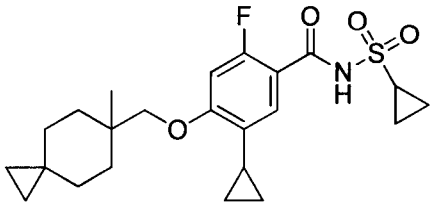
[01437] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((6-methylspiro[2.5]octan-6-yl)methoxy)benzamide



[01438] Following the procedure as described in Example 266 step 7, and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.074 g, 39%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J =16.5 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 6.58 (d, J = 14.5 Hz, 1H), 4.23 (t, J = 7.7 Hz, 4H), 3.74 (s, 2H), 2.32-2.18 (m, 2H), 2.08-1.94 (m, 1H), 1.67-1.40 (m, 6H), 1.26-1.03 (m, 5H), 0.98-0.79 (m, 2H), 0.67-0.61 (m, 2H), 0.30-0.16 (m, 4H); MS(ES-) *m/z* 449.3 (M - 1).

[01439] EXAMPLE 268

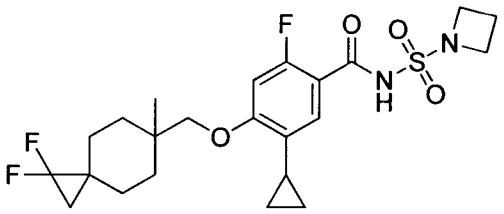
[01440] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)- 2-fluoro-4-((6-methylspiro[2.5]octan-6-yl)methoxy)benzamide



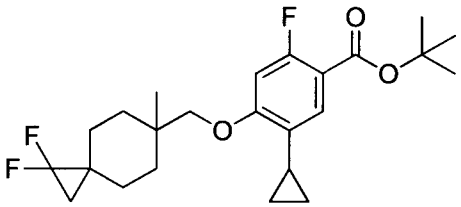
[01441] Following the procedure as described in Example 266 step 7 and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.046 g, 41%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 16.3 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 14.5 Hz, 1H), 3.74 (s, 2H), 3.14-3.04 (m, 1H), 2.07-1.93 (m, 1H), 1.67-1.38 (m, 7H), 1.26-1.00 (m, 7H), 0.96-0.77 (m, 3H), 0.67-0.60 (m, 2H), 0.30-0.16 (m, 4H); MS(ES-) *m/z* 434.3 (M - 1).

[01442] EXAMPLE 269

[01443] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((1,1-difluoro-6-methylspiro[2.5]octan-6-yl)methoxy)-2-fluorobenzamide



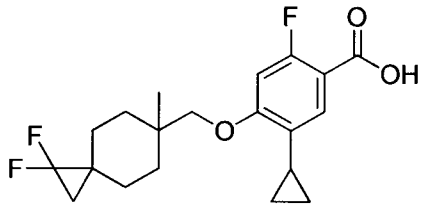
[01444] Step 1. Preparation of *tert*-butyl 5-cyclopropyl-4-((1,1-difluoro-6- methylspiro[2.5]octan-6-yl)methoxy)-2-fluorobenzoate



[01445] To a 10 mL microwave tube charged with *tert*-butyl 5-cyclopropyl-2- fluoro-4-((1-methyl-4-methylenecyclohexyl)methoxy)benzoate (0.475 g, 1.27 mmol) and tetrahydrofuran (4 mL) was added trimethyl(trifluoromethyl)silane (0.375 mL, 2.54 mmol) and sodium iodide (0.42 g, 2.79 mmol). The reaction mixture was heated at 115 °C for 1 hour. After cooling to ambient temperature, additional trimethyl(trifluoromethyl)silane (0.375 mL, 2.54 mmol) and sodium iodide (0.42 mg, 2.79 mmol) were added. The reaction was heated at 115 °C for another 1 hour. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water. The aqueous layer was

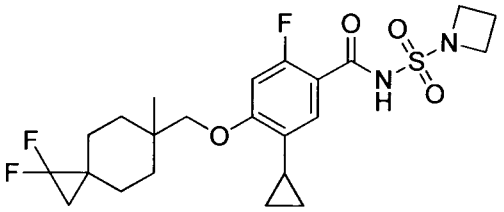
separated and extracted with ethyl acetate (3 x 30 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 5% ethyl acetate in hexanes) afforded the title compound (0.426 g, 79%) as a colorless oil: MS (ES+) *m/z* 369.1 (M - 55).

[01446] Step 2. Preparation of 5-cyclopropyl-4-((1,1-difluoro-6-methylspiro[2.5]- octan-6-yl)-methoxy)-2-fluorobenzoic acid



[01447] To a cooled (0 °C) solution of *tert*-butyl 5-cyclopropyl-4-((1,1-difluoro-6- methylspiro[2.5]octan-6-yl)methoxy)-2-fluorobenzoate (0.426 g, 1.00 mmol) and anisole (0.155 mL, 1.50 mmol) in dichloromethane (4.5 mL) was added trifluoroacetic acid (1.06 mL, 13.5 mmol). The reaction mixture was stirred at 0 °C for 3 hours before being quenched with water (5 mL). The reaction was diluted with dichloromethane (20 mL) and washed with water (4 x 10mL) until the last wash was neutral as monitored by pH paper. The organic layer was dried over anhydrous sodium sulfate and concentrated in *vacuo* to afford the title compound (0.353 g, 95%) as a white solid: MS(ES-) *m/z* 367.3 (M - 1).

[01448] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((1,1-difluoro-6-methylspiro[2.5]octan-6-yl)methoxy)-2-fluorobenzamide

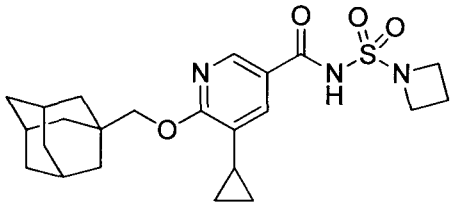


[01449] To a stirred solution of 5-cyclopropyl-4-((1,1-difluoro-6-methylspiro[2.5]-octan-6-yl)methoxy)-2-fluorobenzoic acid (0.039 g, 0.106 mmol) in dichloromethane (3 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)- carbodiimide hydrochloride (0.031g, 0.159 mmol) and 4-dimethylaminopyridine (0.030 g, 0.244 mmol). The reaction was stirred at ambient temperature for 10 minutes, azetidine-1-sulfonamide (0.023 g, 0.17 mmol) was added and the stirring was continued at ambient temperature for 17 hours. The reaction was concentrated, diluted with ethyl acetate (10 mL) and washed with 5% aqueous hydrochloric acid solution (5 mL). The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (0% to 30% ethyl acetate in hexanes) afforded the title compound (0.043 g, 83%) as a white solid [mixture of *cis/trans* diastereomers]: ^{1}H NMR (300 MHz, $CDCl_3$) [*second*

diastereomer peaks in italics] δ 8.64 (d, *J* = 16.5 Hz, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 6.58[*6.56*] (d, *J* = 14.0 Hz, 1H), 4.24 (t, *J* = 7.7 Hz, 4H), 3.77[*3.72*] (s, 2H), 2.32-2.19 (m, 2H), 2.06-1.94 (m, 1H), 1.82-1.37 (m, 6H), 1.29-1.10 (m, 5H),1.08-0.83 (m, 4H), 0.70-0.60 (m, 2H); MS(ES-) *m/z* 485.3 (M - 1).

[01450] EXAMPLE **270**

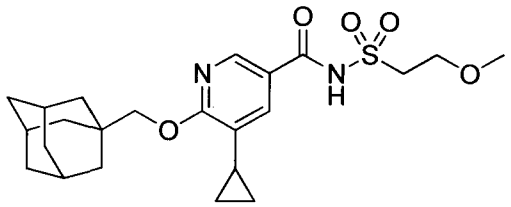
[01451] Synthesis of 6-(adamantan-1-ylmethoxy)-*N*-(azetidin-1- ylsulfonyl)-5-cyclopropylnicotinamide



[01452] Following the procedure as described in Example 150, step 5 and making variations as required to replace methyl sulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.03 g, 6%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 4.02 (t, *J* = 7.6 Hz, 4H), 3.94 (s, 2H), 2.17-2.07 (m, 2H), 2.06-1.99 (m, 1H), 1.98-1.91 (m, 3H), 1.73-1.58 (m, 12H), 0.99-0.90 (m, 2H), 0.78-0.72 (m, 2H); MS (ES+) *m/z* 446.2 (M+1).

[01453] EXAMPLE **271**

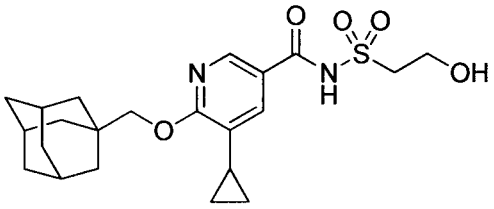
[01454] Synthesis of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((2-methoxyethyl)-sulfonyl)nicotinamide



[01455] A mixture of 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid (0.24 g, 0.73 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.35 g, 1.83 mmol), 4-dimethylaminopyridine (0.22 g, 1.83 mmol), and 2-methoxyethanesulfonamide (0.13 g, 0.95 mmol) in dichloromethane (10 mL) was stirred at ambient temperature for 3 days. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 1 M aqueous hydrochloric acid solution (2 x 30 mL), brine (30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) to provide the title compound (0.25 g, 76%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (br s, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 2H), 3.75-3.65 (m, 4H), 3.14 (s, 3H), 2.07-1.98 (m, 1H), 1.98-1.91 (m, 3H), 1.73-1.58 (m, 12H)0.99-0.91 (m, 2H), 0.76-0.70 (m, 2H); MS (ES+) *m/z* 449.2 (M+1).

[01456] EXAMPLE **272**

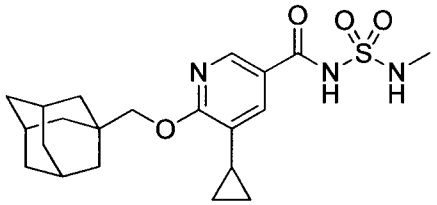
[01457] Synthesis of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((2-hydroxyethyl)sulfonyl)nicotinamide



[01458] A solution of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl-*N*-((2-methoxyethyl)-sulfonyl)nicotinamide (0.19 g, 0.42 mmol) in anhydrous dichloromethane (10 mL) at 0 °C was treated with boron tribromide (0.079 mL, 0.84 mmol) under nitrogen. The reaction mixture was stirred for 25 minutes and then diluted with ethyl acetate (50 mL). The mixture was washed with 1 M aqueous hydrochloric acid solution (2 x 30 mL), brine (30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo* to provide the title compound (0.18 g, quant.): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (br s, 1H), 8.45 (d, J = 2.3 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 4.95 (br s, 1H), 3.93 (s, 2H), 3.80-3.73 (m, 2H), 3.65-3.58 (m, 2H), 2.07-1.98 (m, 1H), 1.98-1.90 (m, 3H), 1.73-1.57 (m, 12H), 0.98-0.90 (m, 2H), 0.76-0.70 (m, 2H); MS (ES+) *m/z* 435.2 (M+1).

[01459] EXAMPLE **273**

[01460] Synthesis of 6-(adamantan-1-ylmethoxy)-5-cyclopropyl- *N*-(*N*-methylsulfamoyl)nicotinamide

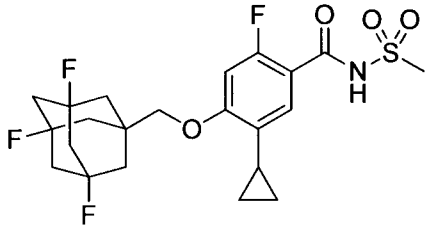


[01461] A solution of *tert*-butyl 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinate (0.50 g, 1.30 mmol) in dichloromethane (20 mL) was treated with trifluoroacetic acid (5.0 mL). The resulting mixture was stirred for 30 minutes and then concentrated *in vacuo*. The residue was treated with methanol (20 mL) and concentrated *in vacuo*. The residue was dissolved in anhydrous tetrahydrofuran (20 mL), treated with carbonyl diimidazole (0.42 g, 2.60 mmol), and refluxed under nitrogen for 30 min. The reaction mixture was cooled to ambient temperature and added (methylsulfamoyl)amine (0.43 g, 3.90 mmol) and 1,8-diazabicycloundec-7-ene (0.58 mL, 3.90 mmol). The reaction mixture was refluxed under nitrogen for 30 minutes. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 mL), washed with 1 M aqueous hydrochloric acid solution (2 x 30 mL) and brine (30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) to provide the title compound (0.12 g,

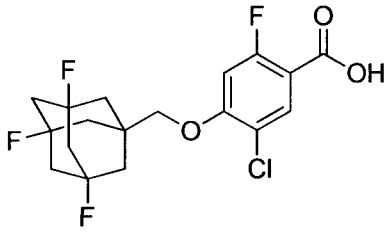
22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.58-7.51 (m, 1H), 3.92 (s, 2H), 2.52-2.48 (m, 3H), 2.07-1.98 (m, 1H), 1.97-1.90 (m, 3H), 1.72-1.55 (m, 12H), 0.98-0.90 (m, 2H), 0.77-0.70 (m, 2H); MS (ES+) *m/z* 420.2 (M+1).

[01462] EXAMPLE **274**

[01463] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)- 4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzamide

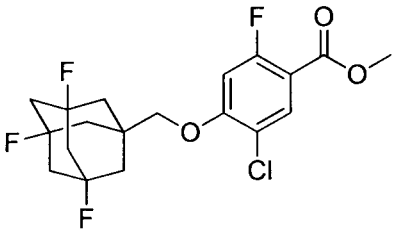


[01464] Step 1. Preparation of 5-chloro-2-fluoro-4-((3,5,7-trifluoroadamantan- 1-yl)methoxy)benzoic acid



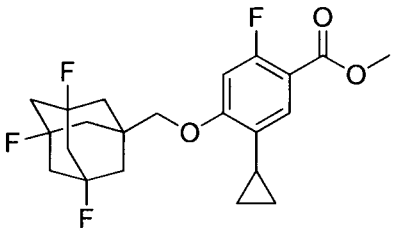
[01465] A mixture of (3,5,7-trifluoroadamantan-1-yl)methanol (1.37 g, 6.22 mmol) and potassium *tert*-butoxide (0.91 g, 8.09 mmol) in anhydrous dimethylsulfoxide (20 mL) was stirred under nitrogen for 20 minutes. The reaction mixture was treated with a mixture of 5-chloro-2,4-difluorobenzoic acid (1.20 g, 6.22 mmol) and potassium *tert*-butoxide (0.70 g, 6.22 mmol) in anhydrous dimethylsulfoxide (10 mL) that had been stirred for 10 min. The resulting mixture was stirred under nitrogen at ambient temperature for 20 hours, diluted with ethyl acetate (120 mL), water (20 mL) and 1 M aqueous hydrochloric acid solution (50 mL). The separated organic layer was washed with 1 M aqueous hydrochloric acid solution (50 mL) and brine; dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) to provide the title compound (0.98 g, 40%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.13 (br s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 12.6 Hz, 1H), 4.00 (s, 2H), 2.25-2.14 (m, 3H), 2.06-1.96 (m, 3H), 1.81-1.73 (m, 6H); MS (ES-) *m/z* 391.2, 393.2 (M-1).

[01466] Step 2. Preparation of methyl 5-chloro-2-fluoro-4-((3,5,7-trifluoroadamantan- 1-yl)-methoxy)benzoate



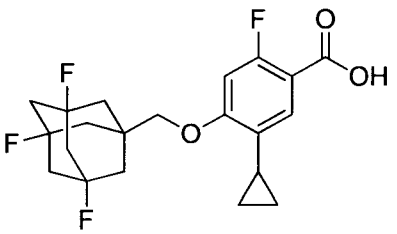
[01467] Following the procedure as described in Example 150 step 2 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-chloronicotinic acid with 5-chloro- 2-fluoro-4-((-3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid, the title compound was obtained as a colorless solid (0.90 g, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 12.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 2H), 2.24-2.05 (m, 6H), 1.87-1.78 (m, 6H); MS (ES+) *m/z* 407.3, 409.1 (M+1).

[01468] Step 3. Preparation of methyl 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoate



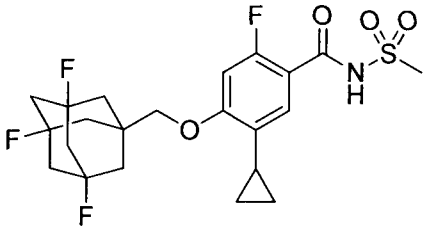
[01469] Following the procedure as described in Example 150 step 3 and making variations as required to replace methyl 6-(adamantan-1-ylmethoxy)-5-chloronicotinate with methyl 5-chloro-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoate. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless solid (0.57 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 12.6 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 2H), 2.24-2.14 (m, 3H), 2.14-2.04 (m, 3H), 1.99-1.88 (m, 1H), 1.86-1.79 (m, 6H), 0.96-0.88 (m, 2H), 0.66-0.58 (m, 2H); MS (ES+) *m/z* 413.2 (M+1).

[01470] Step 4. Preparation of 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid



[01471] Following the procedure as described in Example 150 step 4 and making variations as required to replace methyl 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinate with methyl 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoate, the title compound was obtained as a colorless solid (0.48 g, quant.): MS (ES-) *m/z* 397.2 (M-1).

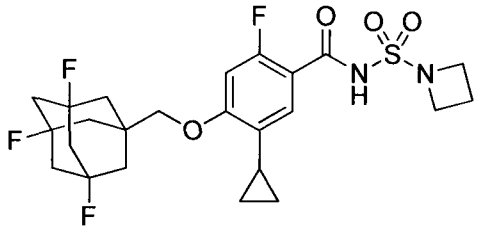
[01472] Step 5. Preparation of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)- 4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzamide



[01473] Following the procedure as described in Example 150 step 5 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)), gave the title compound as a colorless solid (0.14 g, 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (br s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 3.93 (s, 2H), 3.31 (s, 3H), 2.25-2.14 (m, 3H), 2.10-1.98 (m, 4H), 1.83-1.75 (m, 6H), 0.93-0.85 (m, 2H), 0.66-0.59 (m, 2H); MS (ES-) *m/z* 474.2 (M-1).

[01474] EXAMPLE **275**

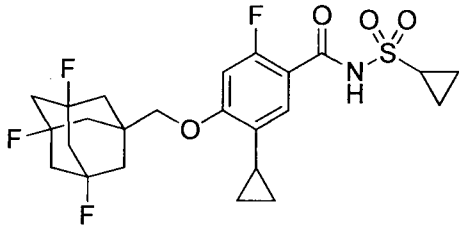
[01475] Synthesis of *N*-(Azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzamide



[01476] Following the procedure as described in Example 150 step 5 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid and to replace methyl sulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.10 g, 47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (br s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.7 Hz, 1H), 4.01 (t, J = 7.6 Hz, 4H), 3.93 (s, 2H), 2.25-1.99 (m, 9H), 1.80 (s, 6H), 0.93-0.85 (m, 2H), 0.67-0.60 (m, 2H); MS (ES-) *m/z* 515.1 (M-1).

[01477] EXAMPLE **276**

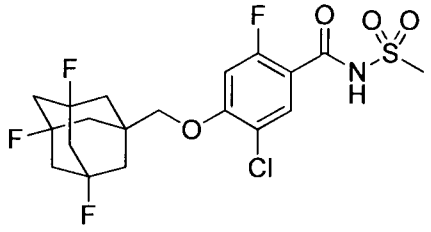
[01478] Synthesis of 5-Cyclopropyl-*N*-(cyclopropylsulfonyl)-2- fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzamide



[01479] Following the procedure as described in Example 150 step 5 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-cyclopropyl-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid and to replace methyl sulfonamide with cyclopropanesulfonamide. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.10 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 7.12 (d, J = 8.33 Hz, 1H), 6.94 (d, J = 12.86 Hz, 1H), 3.93 (s, 2H), 3.09-2.99 (m, 1H), 2.25-2.13 (m, 3H), 2.10-1.98 (m, 4H), 1.85-1.75 (m, 6H), 1.12-1.01 (m, 4H), 0.93-0.84 (m, 2H), 0.66-0.59 (m, 2H); MS (ES+) *m/z* 502.1 (M+1).

[01480] EXAMPLE **277**

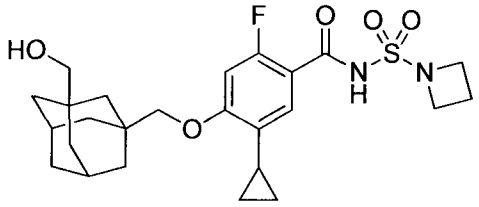
[01481] Synthesis of 5-Chloro-2-fluoro-*N*-(methylsulfonyl)-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzamide



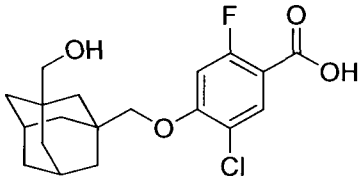
[01482] Following the procedure as described in Example 150 step 5 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-2-fluoro-4-((3,5,7-trifluoroadamantan-1-yl)methoxy)benzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide, the title compound was obtained as a colorless solid (0.035 g, 28%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 12.28 Hz, 1H), 4.00 (s, 2H), 3.22 (s, 3H), 2.26-2.15 (m, 3H), 2.07-1.97 (m, 3H), 1.82-1.74 (m, 6H); MS (ES-) *m/z* 468.21, 470.20 (M-1).

[01483] EXAMPLE **278**

[01484] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide

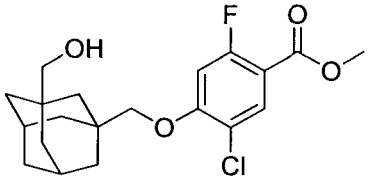


[01485] Step 1. Preparation of 5-chloro-2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzoic acid



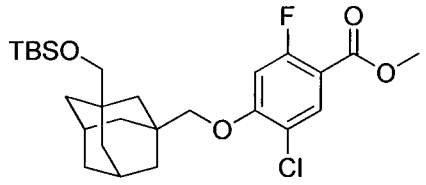
[01486] Following the procedure as described in Example 274 step 1 and making variations as required to replace (3,5,7-trifluoroadamantan-1-yl)methanol with adamantane-1,3-diyldimethanol. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (3.53 g, 42%): MS (ES-) *m/z* 367.2, 369.2 (M-1).

[01487] Step 2. Preparation of methyl 5-chloro-2-fluoro-4-((3-(hydroxymethyl)- adamantan-1-yl)methoxy)benzoate



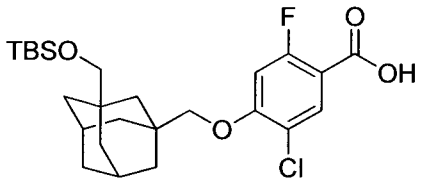
[01488] A solution of 5-chloro-2-fluoro-4-((3-(hydroxymethyl)adamantan- 1-yl)methoxy)benzoic acid (3.53 g, 9.57 mmol), 4-dimethylaminopyridine (0.23 g, 1.90 mmol), and methanol (3.87 mL, 95.70 mmol) in anhydrous dimethylformamide (50 mL) under nitrogen was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (3.67 g, 19.10 mmol). The reaction mixture was stirred for 24 hours at ambient temperature; diluted with ethyl acetate (200 mL) and washed with water (100 mL), saturated ammonium chloride (100 mL), and brine (100 mL); dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate) to provide the title compound (0.65 g, 18%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 12.6 Hz, 1H), 3.85 (s, 3H), 3.56 (s, 2H), 3.23 (s, 2H), 2.11 (br s, 1H), 1.74-1.40 (m, 14H); MS (ES+) *m/z* 383.1, 385.1 (M+1).

[01489] Step 3. Preparation of methyl 4-((3-(((*tert*-butyldimethylsilyl)oxy)methyl)- adamantan-1-yl)-methoxy)-5-chloro-2-fluorobenzoate



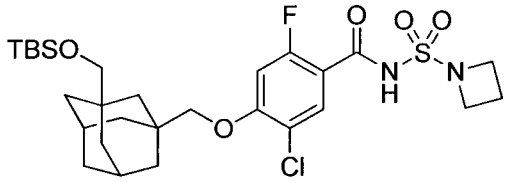
[01490] A solution of methyl 5-chloro-2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzoate (0.83 g, 2.17 mmol), *tert*-butylchlorodimethylsilane (0.36 g, 2.39 mmol), and imidazole (0.74 g, 10.90 mmol) in anhydrous dimethylformamide (12 mL) was stirred at ambient temperature under nitrogen for 16 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL), saturated ammonium chloride (2 x 50 mL) and brine (2 x 50 mL); dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (8:1 hexanes:ethyl acetate) to provide the title compound (1.10 g, quant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 12.1 Hz, 1H), 3.87 (s, 3H), 3.58 (s, 2H), 3.17 (s, 2H), 2.13-2.05 (m, 2H), 1.69-1.58 (m, 6H), 1.49-1.36 (m, 6H), 0.87 (s, 9H), -0.01 (s, 6H); MS (ES+) *m/z* 497.1, 499.1 (M+1).

[01491] Step 4. Preparation of 4-((3-(((*tert*-butyldimethylsilyl)oxy)methyl)adamantan- 1-yl)methoxy)-5-chloro-2-fluorobenzoic acid



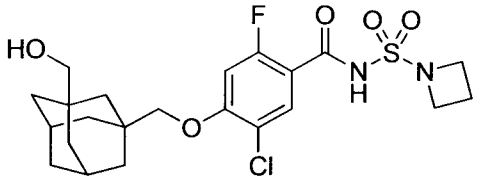
[01492] Following the procedure as described in Example 150 step 4 and making variations as required to replace methyl 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinate with methyl 4-((3-(((*tert*-butyldimethylsilyl)oxy)methyl)adamantan-1-yl)methoxy)-5- chloro-2-fluorobenzoate, the title compound was obtained as a colorless solid (1.02 g, 94%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 12.7 Hz, 1H), 3.70 (s, 2H), 3.12 (s, 2H), 2.05-1.96 (m, 2H), 1.63-1.42 (m, 6H), 1.41-1.27 (m, 6H), 0.81 (s, 9H), -0.05 (s, 6H); MS (ES+) *m/z* 483.1, 485.1 (M+1).

[01493] Step 5. Preparation of *N*-(azetidin-1-ylsulfonyl)-4-(((((*tert*-butyldimethyl-silyl)oxy)methyl)adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzamide



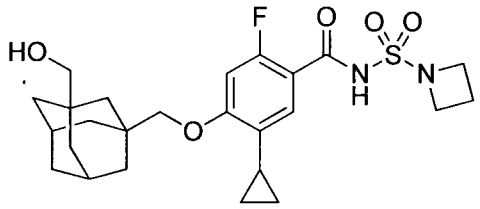
[01494] Following the procedure as described in Example 150 step 5 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((3-(((*tert*-butyldimethylsilyl)oxy)methyl)adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoic acid and to replace methyl sulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.82 g, 65%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 12.4 Hz, 1H), 4.02 (t J = 7.7 Hz, 4H), 3.72 (s, 2H), 3.15 (s, 2H), 2.14 (p, J = 7.7 Hz, 2H), 2.06-1.98 (m, 2H), 1.62-1.46 (m,6H), 1.43-1.33 (m, 6H), 0.83 (s, 9H), -0.03 (s, 6H); MS (ES+) *m/z* 601.1, 603.1 (M+1).

[01495] Step 6. Preparatio of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2- fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide



[01496] A solution of *N*-(azetidin-1-ylsulfonyl)-4-((3-(((*tert*-butyldimethylsilyl)oxy)-methyl)adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzamide (0.82 g, 1.36 mmol) in anhydrous tetrahydrofuran (24 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran, 4.1 mL, 4.1 mmol) under nitrogen. The resulting mixture was stirred for 18 hours; diluted with ethyl acetate (80 mL), washed with 1 M aqueous hydrochloric acid and brine (80 mL, v/v 1:1) and brine (2 x 50 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) to provide the title compound (0.51 g, 77%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (br s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 12.5 Hz, 1H), 4.36 (br s, 1H), 4.02 (t, J = 7.7 Hz, 4H), 3.72 (s, 2H), 2.99 (s, 2H), 2.14 (p, J = 7.7 Hz, 2H), 2.06-1.99 (m, 2H), 1.62-1.46 (m, 6H), 1.44-1.30 (m, 6H); MS (ES+) *m/z* 486.9, 488.9 (M+1).

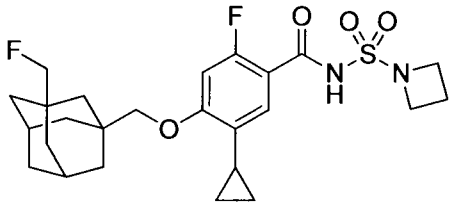
[01497] Step 7. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide



[01498] A degassed mixture of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((3-(hydroxymethyl)adamantan-1-yl)methoxy)benzamide (0.51 g, 1.04 mmol), cyclopropylboronic acid (0.89 g, 10.4 mmol), tricyclohexylphosphine tetrafluoroborate (0.23 g, 0.62 mmol), potassium phosphate (tribasic, 1.10 g, 5.20 mmol), water (3.0 mL), and tetrahydrofuran (3.0 mL) in toluene (15 mL) was added palladium (II) acetate (0.070 g, 0.31 mmol). The resulting mixture was refluxed under nitrogen for 18 hours. The reaction mixture was cooled to ambient temperature and added additional cyclopropylboronic acid (0.89 g, 10.40 mmol), tricyclohexylphosphine tetrafluoroborate (0.23 g, 0.62 mmol), and potassium phosphate (tribasic, 1.10 g, 5.20 mmol), and then refluxed under nitrogen for 10 hours. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (80 mL) and water (50 mL), acidified with 1 M aqueous hydrochloric acid solution. The organic layer was washed with 1 M aqueous hydrochloric acid solution (20 mL) and brine (2 x 50 mL); dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) to provide the title compound (0.27 g, 53%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.90 (d, J = 13.0 Hz, 1H), 4.38-4.31 (m, 1H), 4.01 (t, J = 7.5 Hz, 4H), 3.64 (s, 2H), 3.02-2.96 (m, 2H), 2.19-2.06 (m, 2H), 2.06-1.94 M, 3H), 1.64-1.47 (m, 6H), 1.45-1.32 (m, 6H), 0.92-0.83 (m, 2H), 0.96-0.61 (m, 2H); MS (ES+) *m/z* 493.2 (M+1).

[01499] EXAMPLE **279**

[01500] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((3-(fluoromethyl)adamantan-1-yl)methoxy)benzamide

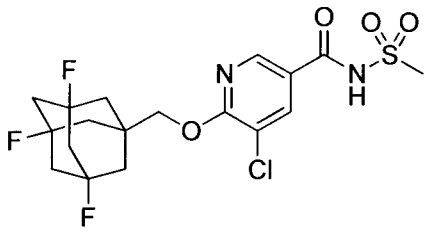


[01501] A solution of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((3-(hydroxymethyl)adamantan-1-yl)methoxy)benzamide (0.27 g, 0.55 mmol) in dichloromethane (15 mL) at °C was treated with diethylaminosulfur trifluoride (0.15 mL, 1.10 mmol) under nitrogen. The resulting

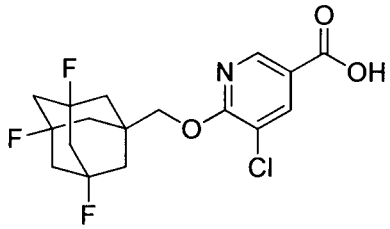
mixture was stirred for 50 minutes and quenched with water (1.0 mL). The mixture was diluted with ethyl acetate (50 mL), washed with 1 M aqueous hydrochloric acid solution (30 mL) and brine (2 x 30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) to provide the title compound (0.019 g, 7%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.91 (d, J = 12.7 Hz, 1H), 4.01 (t, J = 7.7 Hz, 4H), 3.85-3.45 (m, 4H), 2.19-2.05 (m, 3H), 2.04-1.93 (m, 3H), 1.93-1.83 (m, 3H), 1.81-1.61 (m, 4H), 1.56-1.33 (m, 4H), 0.92-0.84 (m, 2H), 0.68-0.61 (m, 2H); MS (ES-) *m/z* 493.2 (M-1).

[01502] EXAMPLE **280**

[01503] Synthesis of 5-chloro-*N*-(methylsulfonyl)-6-((3,5,7-trifluoroadamantan-1-yl)methoxy)nicotinamide

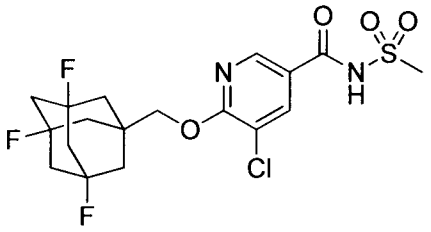


[01504] Step 1. Preparation of 5-chloro-6-((3,5,7-trifluoroadamantan- 1-yl)methoxy)nicotinic acid



[01505] Following the procedure as described in Example 274 step 1 and making variations as required to replace 5-chloro-2,4-difluorobenzoic acid with 5,6-dichloronicotinic acid. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.93 g, 87%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.33 (br s, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 4.28 (s, 2H), 2.25-2.14 (m, 3H), 2.06-1.96 (m, 3H), 1.81-1.73 (m, 6H); MS (ES+) *m/z* 376.1, 378.1 (M+1).

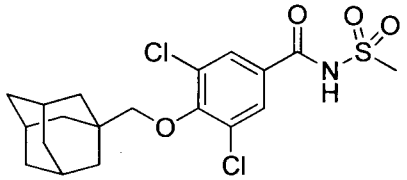
[01506] Step 2. Preparation of 5-chloro-*N*-(methylsulfonyl)-6-((3,5,7-trifluoroadamantan-1-yl)methoxy)nicotinamide



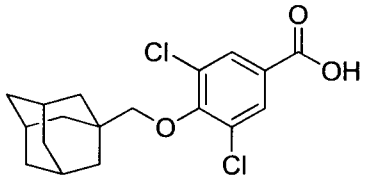
[01507] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-6-((3,5,7-trifluoroadamantan-1-yl)methoxy)nicotinic acid and to replace 2-methoxyethane- sulfonamide with methyl sulfonamide. Purification by reverse phase HPLC, the title compound was obtained as a colorless solid (0.13 g, 18%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.24 (br s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 2.2 Hz, 1H), 4.29 (s, 2H), 3.33 (s, 3H), 2.24-2.14 (m, 3H), 2.06-1.96 (m, 3H), 1.81-1.74 (m, 6H); MS (ES-) *m/z* 451.2, 453.2 (M-1).

[01508] EXAMPLE **281**

[01509] Synthesis of 4-(adamantan-1-ylmethoxy)-3,5- dichloro-*N*-(methylsulfonyl)benzamide

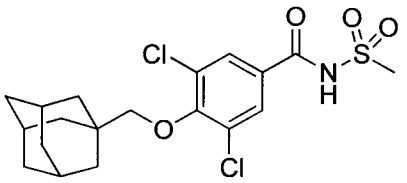


[01510] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-3,5-dichlorobenzoic acid



[01511] Following the procedure as described in Example 274 step 1 and making variations as required to replace (3,5,7-trifluoroadamantan-1-yl)methanol with adamantan-1-ylmethanol and to replace 5-chloro-2,4-difluorobenzoic acid with 3,5-dichloro-4-fluorobenzoic acid, the title compound was obtained as a colorless solid (1.73 g, quant.): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.44 (br s, 1H), 7.86 (s, 2H), 3.53 (s, 2H), 1.99-1.90 (m, 3H), 1.73-1.57 (m, 12H); MS (ES-) *m/z* 353.2, 355.2 (M-1).

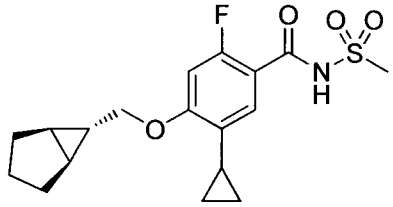
[01512] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-3,5- dichloro-*N*-(methylsulfonyl)benzamide



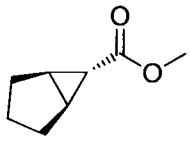
[01513] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-(adamantan-1-ylmethoxy)-3,5-dichlorobenzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+ 0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.72 g, 74%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 8.01 (s, 2H), 3.55 (s, 2H), 3.33 (s, 3H), 1.99-1.91 (m, 3H), 1.72-1.57 (m, 12H); MS (ES-) *m/z* 430.1, 432.1 (M-1).

[01514] EXAMPLE **282**

[01515] Synthesis of 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01516] Step 1. Preparation of (1*R*,5*S*,6r)-methyl bicyclo[3.1.0]hexane-6-carboxylate



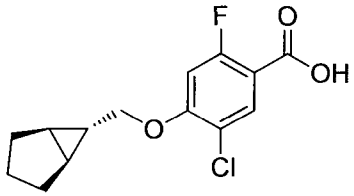
[01517] Following the procedure as described in Example 150 step 2 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-chloronicotinic acid with (1*R*,5*S*,6r)-bicyclo[3.1.0]hexane-6-carboxylic acid, the title compound was obtained as a colorless oil (0.84 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H), 1.83-1.64 (m, 6H), 1.61-1.49 (m, 1H), 1.35 (t, J = 3.1 Hz, 1H), 1.12-0.94 (m, 1H).

[01518] Step 2. Preparation of (1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethanol



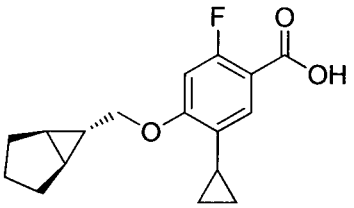
[01519] A solution of (1*R*,5*S*,6r)-methyl bicyclo[3.1.0]hexane-6-carboxylate (0.84 g, 6.00 mmol) and anhydrous methanol (0.49 mL, 12.0 mmol) in anhydrous tetrahydrofuran (35 mL) was treated with lithium borohydride (4.0 M solution in tetrahydrofuran, 3.0 mL, 12.0 mmol). The resulting mixture was refluxed under nitrogen for 6 hours. The reaction mixture was cooled to ambient temperature and quenched with water (20 mL), acidified with 3 M aqueous hydrochloric acid, and diluted with dichloromethane (100 mL). The organic layer was washed with water (20 mL) and brine (30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo* to provide the title compound (0.58 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (br s, 1H), 3.37 (d, J = 7.2 Hz, 1H), 1.85-1.45 (m, 6H), 1.14-0.98 (m, 2H), 0.90-0.81 (m, 1H).

[01520] Step 3. Preparation of 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethoxy)- 5-chloro-2-fluorobenzoic acid



[01521] Following the procedure as described in Example 274 step 1 and making variations as required to replace (3,5,7-trifluoroadamantan-1-yl)methanol with (1*R*,5*S*,6r)-bicyclo[3.1.0]hexan- 6-ylmethanol. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.53 g, 36%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 12.9 Hz, 1H), 3.94 (d, J = 7.3 Hz, 1H), 1.74-1.57 (m, 4H), 1.55-1.42 (m, 1H), 1.32-1.23 (m, 2H), 117-0.99 (m, 2H); MS (ES+) *m/z* 285.1, 287.1 (M+1).

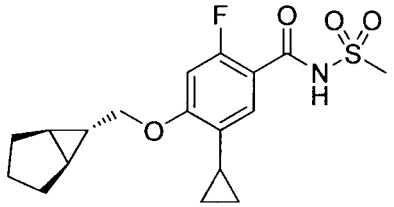
[01522] Step 4. Preparation of 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethoxy)-
5-cyclopropyl-2-fluorobenzoic acid



[01523] Following the procedure as described in Example 278 step 7 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((3-(hydroxymethyl)- adamantan-1-yl)methoxy)benzamide with 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6- ylmethoxy)-5-chloro-2-fluorobenzoic acid. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.076 g, 14%): ^{1}H NMR (300 MHz,

DMSO-d_6) δ 12.70 (br s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 13.2 Hz, 1H), 3.88 (d, J = 7.0 Hz, 2H), 2.06-1.93 (m, 1H), 1.76-1.56 (m, 4H), 1.54-1.43 (m, 1H), 1.31-0.98 (m, 4H), 0.92-0.93 (m, 2H), 0.62-0.52 (m, 2H); MS (ES-) *m/z* 289.2 (M-1).

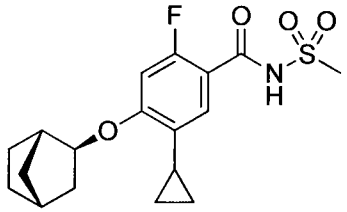
[01524] Step 5. Preparation of 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethoxy)- 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



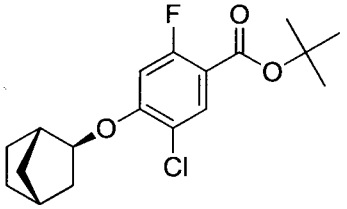
[01525] Following the procedure as described in Example **271** and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*R*,5*S*,6r)-bicyclo[3.1.0]hexan-6-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide. Purification by reverse phase HPLC to give the title compound as a colorless solid (0.025 g, 26%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.84 (br s, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 13.2 Hz, 1H), 3.88 (d, J = 7.0 Hz, 2H), 3.29 (s, 3H), 2.07-1.97 (m, 1H), 1.75-1.44 (m, 5H), 1.32-1.25 (m, 2H), 1.21-0.99 (m, 2H), 0.92-0.83 (m, 2H), 0.70-0.62 (m, 2H); MS (ES-) *m/z* 366.2 (M-1).

[01526] EXAMPLE **283**

[01527] Synthesis of 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



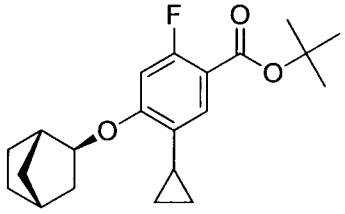
[01528] Step 1. Preparation of *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluorobenzoate



[01529] A mixture of (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-ol (1.0 g, 8.92 mmol), *tert*-butyl 5-chloro-2,4-difluorobenzoate (2.88 g, 11.60 mmol), and cesium carbonate (5.81 g, 17.84 mmol) in

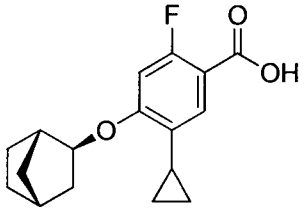
anhydrous dimethylsulfoxide (12 mL) was heated in a sealed tube at 80 °C for 18 hours, then at 115 °C for 1 hour. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (80 mL), washed with water (30 mL), saturated ammonium chloride (40 mL) and brine (40 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was triturated with methanol to provide the title compound (0.76 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 12.4 Hz, 1H), 4.22-4.17 (m, 1H), 2.51-2.46 (m, 1H), 2.38-2.31 (m, 1H), 1.83-1.67 (m, 2H), 1.66-1.58 (m, 1H), 1.56 (s, 9H), 1.52-1.42 (m, 2H), 1.26-1.09 (m, 3H); MS (ES+) *m/z* 285.0, 287.0 (M–55).

[01530] Step 2. Preparation of *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoate



[01531] Following the procedure as described in Example 278 step 7 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide with *tert*-Butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluorobenzoate. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless oil (0.77 g, quant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 1H), 6.45 (d, J = 13.0 Hz, 1H), 4.20-4.13 (m, 1H), 2.49-2.44 (m, 1H), 2.35-2.29 (m, 1H), 2.01-1.91 (m, 1H), 1.82-1.73 (m, 1H), 1.70-1.63 (m, 1H), 1.61-1.56 (m, 1H), 1.55 (s, 9H), 1.50-1.44 (m, 1H), 1.27-1.09 (m, 4H), 0.88-0.81 (m, 2H), 0.63-0.56 (m, 2H); MS (ES+) *m/z* 291.2 (M-55).

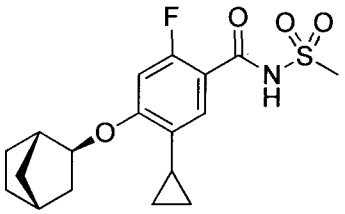
[01532] Step 3. Preparation of 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid



[01533] A solution of *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoate (0.88 g, 2.54 mmol) in dichloromethane (40 mL) was added trifluoroacetic acid (1.9 mL, 25.4 mmol). The resulting mixture was stirred for 1 hour and then concentrated *in vacuo*. The residue was triturated with methanol to provide the title compound (0.24 g, 32%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 13.2 Hz, 1H), 4.40-4.34 (m, 1H),

2.39-2.34 (m, 1H), 2.29-2.23 (m, 1H), 1.99-1.88 (m, 1H), 1.85-1.76 (m, 1H), 1.60-1.33 (m, 4H), 1.25-1.03 (m, 3H), 0.88-0.79 (m, 2H), 0.57-0.49 (m, 2H); MS (ES+) *m/z* 291.1 (M+1).

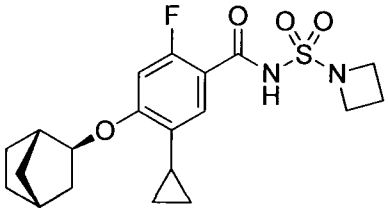
[01534] Step 4. Preparation of 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01535] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.090 g, 72%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 13.2 Hz, 1H), 4.42-4.35 (m, 1H), 3.30 (s, 3H), 2.38-2.34 (m, 1H), 2.30-2.24 (m, 1H), 2.00-1.94 (m, 1H), 1.86-1.77 (m, 1H), 1.59-1.32 (m, 4H), 1.25-1.04 (m, 3H), 0.88-0.79 (m, 2H), 0.66-0.59 (m, 2H); MS(ES-) *m/z* 368.1 (M+1).

[01536] EXAMPLE **284**

[01537] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzamide

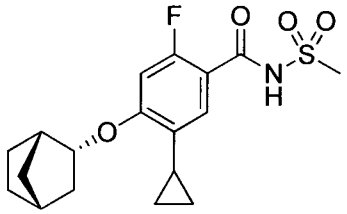


[01538] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.080 g, 56%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 13.1 Hz, 1H), 4.42-4.36 (m, 1H), 4.01 (t, J = 7.6 Hz, 4H), 2.39-2.34 (m, 1H), 2.30-2.45 (m, 1H),

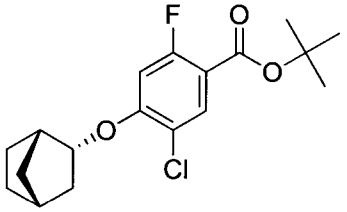
2.19-2.06 (m, 2H), 2.01-1.90 (m, 1H), 1.87-1.77 (m, 1H), 1.60-1.32 (m, 4H), 1.26-1.04 (m, 3H), 0.88-0.80 (m, 2H), 0.68-0.59 (m, 2H); MS (ES-) *m/z* 409.2 (M+1).

[01539] EXAMPLE 285

[01540] Synthesis of 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide

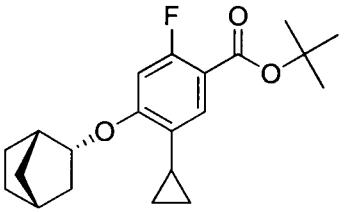


[01541] Step 1. Preparation of *tert*-butyl 4-((1*S*,2*R*,4)-bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluorobenzoate



[01542] Following the procedure as described in Example 283 step 1 and making variations as required to replace (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-ol with (1*S*,2*R*,4*R*)-bicyclo- [2.2.1]heptan-2-ol. Purification by silica gel column chromatography (R_f = 0.5 in 10:1 hexanes:ethyl acetate) gave the title compound as a colorless oil (0.98 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 1H), 6.54 (d, J = 12.4 Hz, 1H), 4.65-4.57 (m, 1H), 2.65-2.59 (m, 1H), 2.33-2.27 (m, 1H), 2.12-1.93 (m, 1H), 1.66-1.59 (m, 1H), 1.55 (s, 9H), 1.47-1.29 (m, 4H), 1.18-1.07 (m, 1H); MS (ES+) *m/z* 285.1, 287.1 (M-55).

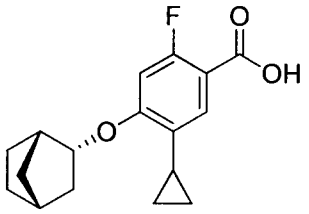
[01543] Step 2. Preparation of *tert*-butyl 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoate



[01544] Following the procedure as described in Example 278 step 7 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide with *tert*-butyl 4-((1*S*,2*R*,4)-bicyclo[2.2.1]heptan-2-yloxy)-5-chloro-2-fluorobenzoate. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless oil (1.00 g, quant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 13.0 Hz, 1H), 4.63-4.55 (m, 1H), 2.65-2.58 (m, 1H),

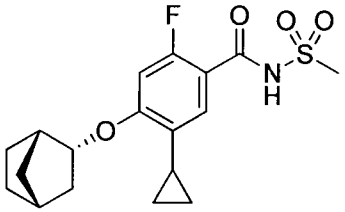
2.32-2.25 (m, 1H), 2.11-1.91 (m, 3H), 1.66-1.58 (m, 1H), 1.55 (s, 9H), 1.48-1.29 (m, 4H), 1.15-1.05 (m, 1H), 0.92-0.84 (m, 2H), 0.65-0.58 (m, 2H); MS (ES+) *m/z* 291.2 (M-55).

[01545] Step 3. Preparation of 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid



[01546] Following the procedure as described in Example 283 step 3 and making variations as required to replace *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5- cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5- cyclopropyl-2-fluorobenzoate. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.50 g, 57%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.76 (br s, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 13.2 Hz, 1H), 4.80-4.70 (m, 1H), 2.59-2.52 (m, 1H), 2.25-2.18 (m, 1H), 2.15-2.03 (m, 1H), 2.02-1.79 (m, 2H), 1.61-1.48 (m, 1H), 1.45-1.17 (m, 4H), 0.97-0.82 (m, 3H), 0.60-0.50 (m, 2H); MS (ES+) *m/z* 291.1 (M+1).

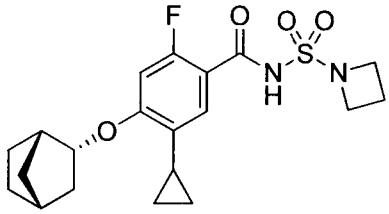
[01547] Step 4. Preparation of 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2- yloxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01548] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.080 g, 64%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 13.1 Hz, 1H), 4.81-4.72 (m, 1H), 3.29 (s, 3H), 2.59-2.54 (m, 1H), 2.25-2.19 (m, 1H), 2.17-2.05 (m, 1H), 2.04-1.92 (m, 1H), 1.91-1.78 (m, 1H),1.61-1.48 (m, 1H), 1.46-1.17 (m, 4H), 0.97-0.80 (m, 3H), 0.67-0.60 (m, 2H); MS (ES+) *m/z* 368.09 (M+1).

[01549] EXAMPLE **286**

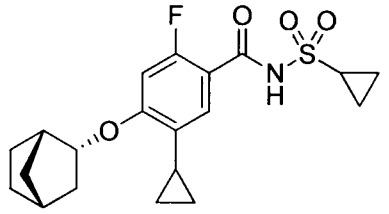
[01550] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzamide



[01551] Following the procedure as described in Example **271** and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.11 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 13.1 Hz, 1H), 4.82-4.73 (m, 1H), 4.00 (t, J = 7.6 Hz, 4H), 2.60-2.54 (m, 1H), 2.25-2.19 (m, 1H), 2.18-2.05 (m, 3H), 2.04-1.93 (m, 1H), 1.91-1.80 (m, 1H), 1.61-1.49 (m, 1H), 1.46-1.17 (m, 4H), 0.98-0.81 (m, 3H), 0.68-0.60 (m, 2H); MS (ES+) *m/z* 409.1 (M+1).

[01552] EXAMPLE 287

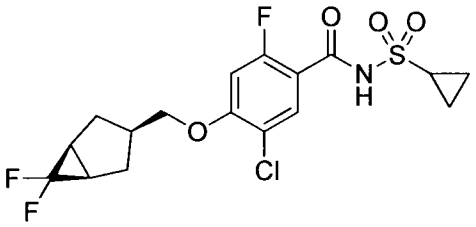
[01553] Synthesis of 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide



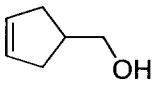
[01554] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-((1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with cyclopropanesulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.090 g, 67%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 13.1 Hz, 1H), 4.82-4.73 (m, 1H), 3.08-2.98 (m, 1H), 2.60-2.53 (m, 1H), 2.26-1.18 (m, 1H), 2.18-2.05 (m, 1H), 2.03-1.93 (m, 1H), 1.91-1.79 (m, 1H), 1.62-1.48 (m, 1H), 1.47-1.18 (m, 4H), 1.12-1.03 (m, 4H), 0.97-0.79 (m, 3H), 0.68-0.59 (m, 2H); MS (ES+) *m/z* 394.1 (M+1).

[01555] EXAMPLE 288

[01556] Synthesis of 5-chloro-*N*-(cyclopropylsulfonyl)-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzamide

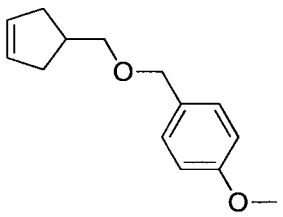


[01557] Step 1. Preparation of cyclopent-3-en-1-ylmethanol



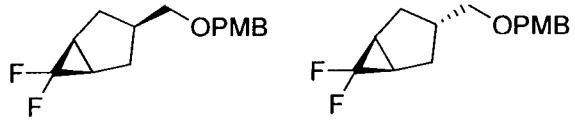
[01558] Following the procedure as described in Example 282 step 2 and making variations as required to replace (1*R*,5*S*,6r)-methyl bicyclo[3.1.0]hexane-6-carboxylate with methyl cyclopent- 3-enecarboxylate, the title compound was obtained as a colorless oil (4.50 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 2H), 3.50 (d, J = 5.7 Hz, 2H), 2.52-2.37 (m, 3H), 2.19 (br s, 1H), 2.14-1.99 (m, 2H).

[01559] Step 2. Preparation of 1-((cyclopent-3-en-1-ylmethoxy)methyl)- 4-methoxybenzene



[01560] A solution of cyclopent-3-en-1-ylmethanol (3.50 g, 35.66 mmol) in anhydrous dimethylformamide (100 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 1.71 g, 42.79 mmol) portionwise under nitrogen. The mixture was stirred at 0 °C for 1 hour and then stirred at ambient temperature for 1 hour. *para*-Methoxybenzyl chloride (5.80 mL, 42.79 mmol) was added to the reaction mixture and the resulting mixture was stirred for 2 hours. The reaction mixture was quenched with methanol (10 mL) and then water (200 mL). The mixture was extracted with ethyl acetate and the organic layer was washed with saturated ammonium chloride (2 x 200 mL) and brine (200 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (3:1 hexanes:ethyl acetate) to provide the title compound (6.15 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.67-5.60 (m, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.34 (d, J = 7.2 Hz, 2H), 2.66-2.40 (m, 3H), 2.16-2.03 (m, 2H); MS (ES+) *m/z* 241.2 (M+23).

[01561] Step 3. Preparation of (1*R*,3*r*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)-oxy)methyl)bicyclo[3.1.0]hexane and (1*R*,3*s*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)methyl)bicyclo[3.1.0]hexane



[01562] A mixture of 1-((cyclopent-3-en-1-ylmethoxy)methyl)-4-methoxybenzene (3.18 g, 14.57 mmol) and sodium iodide (4.80 g, 32.05 mmol) in anhydrous tetrahydrofuran (24 mL) was added trimethyl(trifluoromethyl)silane (4.3 mL, 29.14 mmol). The resulting mixture was heated at 115 °C under microwave irradiation in a sealed tube for 1 hour. The reaction mixture was relieved of gaseous by-products, additional trimethyl(trifluoromethyl)silane (4.3 mL, 29.14 mmol) was added, and the reaction mixture was heated at 115 °C under microwave irradiation for another 1 hour. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to provide two isomers: (1*R*,3*r*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)methyl)bicyclo[3.1.0]hexane (10:1 hexanes:ethyl acetate) (2.64 g, 68%) and (1*R*,3*s*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)methyl)-bicyclo[3.1.0]hexane (0.66 g, 17%). (Stereochemistry was arbitrarily assigned.) Analytical data for (1*R*,3*r*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)methyl)bicyclo[3.1.0]hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.30 (d, J = 6.3 Hz, 2H), 2.36-2.18 (m, 1H), 2.12-2.02 (m, 2H), 1.96-1.83 (m, 2H), 1.79-1.65 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –124.2 (d, J = 158.8 Hz, 1F), -148.0 (d, J = 158.8 Hz, 1F). Analytical data for (1*R*,3*s*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)methyl)-bicyclo[3.1.0]hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.39 (s, 2H), 3.79 (s, 3H), 3.28 (d, J = 7.2 Hz, 2H), 2.79-2.60 (m, 1H), 2.25-2.11 (m, 2H), 2.07-1.93 (m, 2H), 1.54-1.42 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ – 124.2 (d, J = 150.5 Hz, 1F), -151.7 (d, J = 150.5 Hz, 1F).

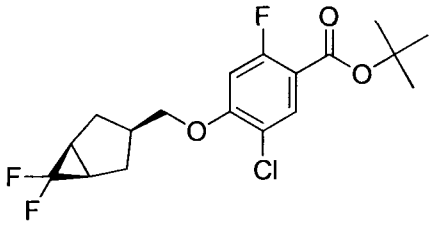
[01563] Step 4. Preparation of ((1*R*,3*r*,5*S*)-6,6-Difluorobicyclo[3.1.0]hexan-3-yl)methanol



[01564] A mixture of (1*R*,3*r*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)- methyl)bicyclo[3.1.0]hexane (2.64 g, 9.84 mmol) and water (1.0 mL) in dichloromethane (40 mL) at 0 °C was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.35 g, 14.76 mmol). The resulting mixture was stirred for 5 hours and then filtered through anhydrous sodium sulfate. The filtrate was washed with saturated sodium bicarbonate (40 mL); dried over anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue

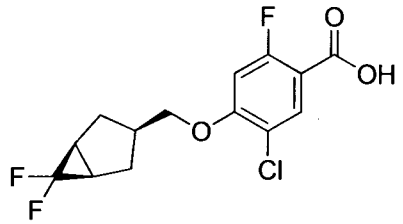
was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate) to provide the title compound (1.24 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (d, J = 6.0 Hz, 2H), 2.25-2.11 (m, 1H), 2.11-2.00 (m, 2H), 1.96-1.86 (m, 2H), 1.78-1.64 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ - 124.3 (d, J = 158.8 Hz, 1F), -148.1 (d, J = 158.8 Hz, 1F).

[01565] Step 5. Preparation of *tert*-butyl 5-chloro-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]-hexan-3-yl)methoxy)-2-fluorobenzoate



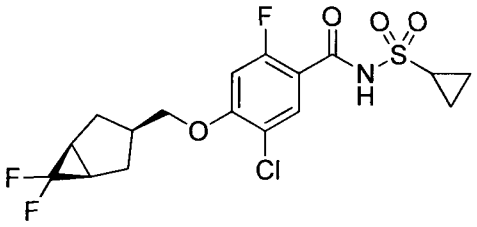
[01566] Following the procedure as described in Example 283 step 1 and making variations as required to replace (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-ol with ((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]-hexan-3-yl)methanol. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless solid (2.12 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 6.58 (d, J = 12.3 Hz, 1H), 3.90 (d, J = 6.1 Hz, 2H), 2.60-2.42 (m, 1H), 2.26-2.14 (m, 2H), 2.04-1.84 (m, 4H), 1.55 (s, 9H); MS (ES+) *m/z* 320.9, 322.9 (M-55).

[01567] Step 6. Preparation of 5-chloro-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]-hexan-3-yl)methoxy)-2-fluorobenzoic acid



[01568] Following the procedure as described in Example 283 step 3 and making variations as required to replace *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5- cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-chloro-4-(((1*R*,3*r*,5*S*)-6,6- difluorobicyclo[3.1.0]hexan- 3-yl)methoxy)-2-fluorobenzoate. Purification by titration with methanol gave the title compound as a colorless solid (0.19 g, 73%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (br s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 12.7 Hz, 1H), 4.04 (d, J = 6.2 Hz, 2H), 2.37-2.21 (m, 1H), 2.18-2.02 (m, 4H), 1.91-1.76 (m, 2H); MS (ES+) *m/z* 321.0, 323.0 (M+1).

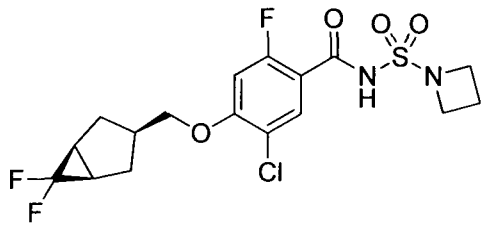
[01569] Step 7. Preparation of 5-chloro-*N*-(cyclopropylsulfonyl)-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]- hexan-3-yl)methoxy)-2-fluorobenzamide



[01570] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with cyclopropanesulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.090 g, 68%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 12.4 Hz, 1H), 4.04 (d, J = 6.3 Hz, 2H), 3.08-2.98 (m, 1H), 2.37-2.22 (m, 1H), 2.17-2.01 (m, 4H), 1.90-1.70 (m, 2H), 1.14-1.02 (m, 4H); ^{19}F NMR (282 MHz, DMSO-d$_6$) δ – 109.6 (s, 1F), -122.5 (d, J = 155.7 Hz, 1F), -145.7 (d, J = 155.7 Hz, 1F); MS (ES+) *m/z* 424.0, 426.0 (M+1).

[01571] EXAMPLE **289**

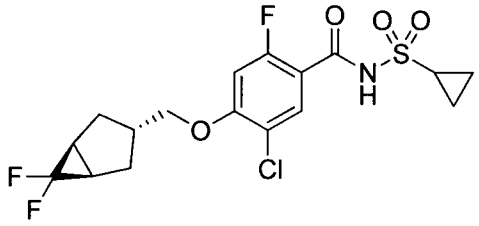
[01572] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzamide



[01573] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-4-(((1*R*,3*r*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.10 g, 79%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 12.3 Hz, 1H), 4.07-3.97 (m, 6H), 2.38-2.22 (m, 1H), 2.20-2.02 (m, 6H), 1.89-1.76 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ – 109.8 (s, 1F), -122.5 (d, J = 155.7 Hz, 1F), -145.8 (d, J = 155.7 Hz, 1F); MS (ES+) *m/z* 439.0, 441.0 (M+1).

[01574] EXAMPLE **290**

[01575] Synthesis of 5-chloro-*N*-(cyclopropylsulfonyl)-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzamide

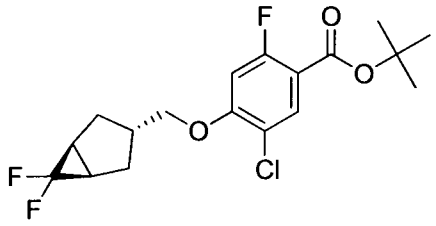


[01576] Step 1. Preparation of ((1*R*,3*s*,5*S*)-6,6-dfluorobicyclo[3.1.0]hexan-3-yl)methanol



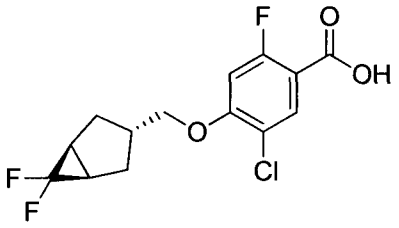
[01577] Following the procedure as described in Example 288 Step 4 and making variations as required to replace (1*R*,3*r*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)- oxy)methyl)bicyclo[3.1.0]hexane with (1*R*,3*s*,5*S*)-6,6-difluoro-3-(((4-methoxybenzyl)oxy)- methyl)bicyclo[3.1.0]hexane. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate) to give the title compound as a colorless oil (0.37 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (d, J = 7.0 Hz, 2H), 2.72-2.53 (m, 1H), 2.24-2.11 (m, 2H), 2.07-1.94 (m, 2H), 1.71 (br s, 1H), 1.55-1.44 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.4 (d, J = 151.6 Hz, 1F), -152.2 (d, J = 151.6 Hz, 1F).

[01578] Step 2. Preparation of *tert*-butyl 5-chloro-4-(((1*R*,3*s*,5*S*)-6,6- difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoate



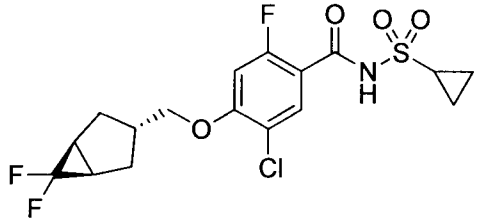
[01579] Following the procedure as described in Example 283 step 1 and making variations as required to replace (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-ol with ((1*R*,3*s*,5*S*)-6,6-Difluorobicyclo[3.1.0]hexan-3-yl)methanol. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless solid (0.37 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84, (d, J = 7.6 Hz, 1H), 6.57 (d, J = 12.1 Hz, 1H), 3.86 (d, J = 7.2 Hz, 2H), 3.06-2.86 (m, 1H), 2.40-2.26 (m, 2H), 2.15-2.00 (m, 2H), 1.76-1.60 (m, 2H), 1.55 (s, 9H); MS (ES+) *m/z* 320.94, 322.92 (M-55).

[01580] Step 3. Preparation of 5-chloro-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoic acid



[01581] Following the procedure as described in Example 283 step 3 and making variations as required to replace *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5- cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-chloro-4-(((1*R*,3*s*,5*S*)-6,6- difluorobicyclo[3.1.0]hexan- 3-yl)methoxy)-2-fluorobenzoate. Purification by titration with methanol gave the title compound as a colorless solid (0.23 g, 74%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.17 (br s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 12.7 Hz, 1H), 3.96 (d, J = 6.9 Hz, 2H), 2.92-2.76 (m, 1H), 2.30-2.14 (m, 4H), 1.57-1.43 (m, 2H); MS (ES+) *m/z* 321.0, 323.0 (M+1).

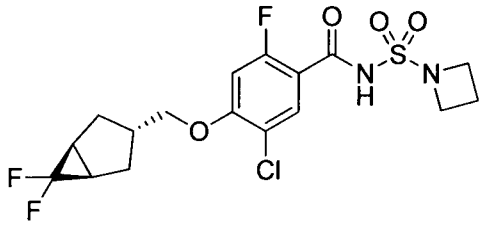
[01582] Step 4. Preparation of 5-chloro-*N*-(cyclopropylsulfonyl)-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzamide



[01583] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with cyclopropanesulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.070 g, 53%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 12.4 Hz, 1H), 3.97 (d, J = 6.9 Hz, 2H), 3.08-2.98 (m, 1H), 2.92-2.78 (m, 1H), 2.31-2.15 (m, 4H), 1.57-1.44 (m, 2H), 1.13-1.03 (m, 4H); ^{19}F NMR (282 MHz, DMSO-d_6) δ – 109.6 (s, 1F), -122.6 (d, J = 147.4 Hz, 1F), -149.5 (d, J = 147.4 Hz, 1F); MS (ES+) *m/z* 424.0, 426.0 (M+1).

[01584] EXAMPLE 291

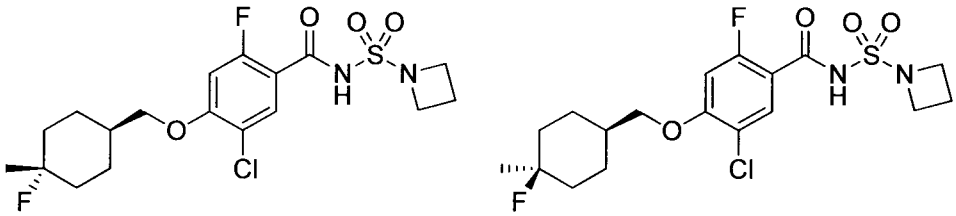
[01585] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzamide



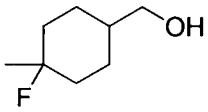
[01586] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 5-chloro-4-(((1*R*,3*s*,5*S*)-6,6-difluorobicyclo[3.1.0]hexan-3-yl)methoxy)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with azetidine-1-sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.10 g, 73%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 12.3 Hz, 1H), 4.05-3.94 (m, 6H), 2.94-2.77 (m, 1H), 2.32-2.07 (m, 6H), 1.57-1.45 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -109.8 (s, 1F), -122.6 (d, J = 147.4 Hz, 1F), -149.5 (d, J = 147.4 Hz, 1F); MS (ES+) *m/z* 439.0, 441.0 (M+1).

[01587] EXAMPLE 292/293

[01588] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*r*,4*r*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide and *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*s*,4*s*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide



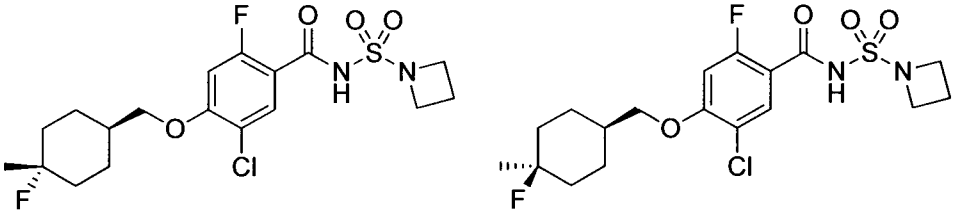
[01589] Step 1. Preparation of (4-fluoro-4-methylcyclohexyl)methanol



[01590] A solution of ethyl 4-hydroxy-4-methylcyclohexanecarboxylate (2.50 g, 13.42 mmol) in dichloromethane (35 mL) at 0 °C was added with diethylaminosulfur trifluoride (14.2 mL, 107.40 mmol) slowly under nitrogen. The resulting mixture was stirred for 24 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and poured into ice (200 g). The organic layer was washed with saturated sodium bicarbonate (3 x 100 mL) and brine (100 mL); dried with anhydrous sodium sulfate; filtered and concentrated *in vacuo* to provide the crude product as an oil; which was dissolved in anhydrous

tetrahydrofuran (60 mL) and anhydrous methanol (1.10 mL, 26.8 mmol). To the mixture was added lithium borohydride (4 M solution in tetrahydrofuran, 6.70 mL, 26.8 mmol) dropwise and the resulting mixture was refluxed under nitrogen for 4 hours. The reaction mixture was cooled to ambient temperature and quenched with water and then 3 M aqueous hydrochloric acid solution. The mixture was diluted with ethyl acetate (150 mL) and the organic layer was washed with saturated sodium bicarbonate (2 x 100 mL) and brine (100 mL); dried with anhydrous sodium sulfate; filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2:1 hexanes:ethyl acetate) to provide the title compound as a colorless oil (0.66 g, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50-3.43 (m, 2H), 1.97-1.86 (m, 1H), 1.85-1.71 (m, 2H), 1.69-1.52 (m, 4H), 1.49-1.24 (m, 5H), 1.20-1.03 (m, 1H).

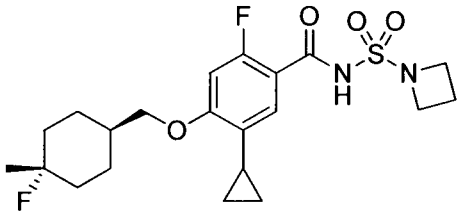
[01591] Step 2. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*r*,4*r*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide and *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*s*,4*s*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide



[01592] Following the procedure as described in Example 274 step 1 and making variations as required to replace (3,5,7-trifluoroadamantan-1-yl)methanol with (4-fluoro-4-methylcyclohexyl)methanol and to replace 5-chloro-2,4-difluorobenzoic acid with *N*-(azetidin-1-ylsulfonyl)-5-chloro- 2,4-difluorobenzamide. Purification by reverse phase HPLC afforded two isomers: *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*s*,4*s*)-4-fluoro-4- methylcyclohexyl)-methoxy)benzamide (first fraction, 0.10 g, 5%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.08-3.96 (m, 6H), 2.20-2.07 (m, 2H), 1.96-1.68 (m, 5H), 1.66-1.52 (m, 2H), 1.38-1.21 (m, 5H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -109.8 (1F), -130.4 (1F); MS (ES+) *m/z* 437.0, 439.0 (M+1). And *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*r*,4*r*)-4-fluoro-4-methylcyclohexyl)- methoxy)benzamide (second fraction, 0.20 g, 10%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.07-3.95 (m, 6H), 2.21-2.07 (m, 2H), 1.87-1.60 (m, 5H), 1.60-1.43 (m, 2H), 1.42-1.31 (m, 2H), 1.67 (d, J = 21.2 Hz, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ - 109.8 (1F), -150.0 (1F); MS (ES+) *m/z* 437.08, 439.08 (M+1).

[01593] EXAMPLE **294**

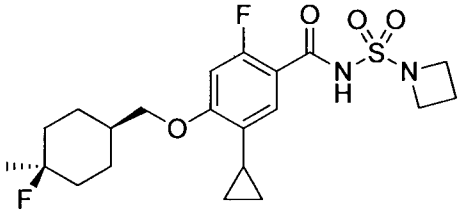
[01594] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(((1*r*,4*r*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide



[01595] Following the procedure as described in Example 278 step 7 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((-3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*r*,4*r*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide. Purification by silica gel column chromatography (1:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.035 g, 17%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (br s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 4.01 (t, J = 7.7 Hz, 4H), 3.90 (d, J = 6.2 Hz, 2H), 2.19-2.06 (m, 2H), 2.04-1.94 (m, 1H), 1.88-1.63 (m, 4H), 1.60-1.48 (m, 1H), 1.45-1.28 (m, 4H), 1.22 (d, J = 11.0 Hz, 3H), 0.90-0.80 (m, 2H), 0.68-0.61 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.5 (1F), -150.1 (1F); MS (ES+) *m/z* 443.1 (M+1).

[01596] EXAMPLE 295

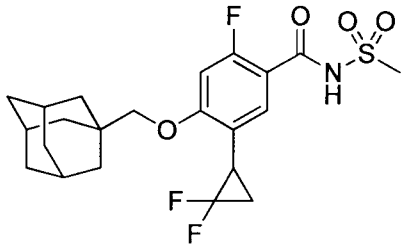
[01597] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(((1*s*,4*s*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide



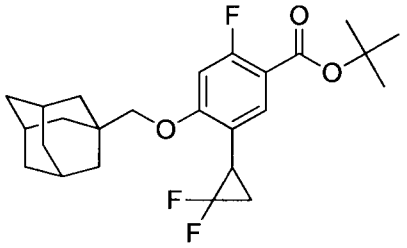
[01598] Following the procedure as described in Example 278 step 7 and making variations as required to replace *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-((3-(hydroxymethyl)-adamantan-1-yl)methoxy)benzamide with *N*-(azetidin-1-ylsulfonyl)-5-chloro-2-fluoro-4-(((1*s*,4*s*)-4-fluoro-4-methylcyclohexyl)methoxy)benzamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.018 g, 18%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (br s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 13.1 Hz, 1H), 4.05-3.92 (m, 6H), 2.19-2.06 (m, 2H), 2.03-1.95 (m, 1H), 1.92-1.70 (m, 5H), 1.68-1.53 (m, 2H), 1.38-1.18 (m, 5H), 0.90-0.81 (m, 2H), 0.68-0.61 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.5 (1F), -129.7 (1F); MS (ES+) *m/z* 443.1 (M+1).

[01599] EXAMPLE 296

[01600] Synthesis of 4-(adamantan-1-ylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluoro-N-(methylsulfonyl)benzamide

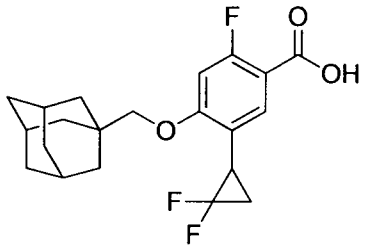


[01601] Step 1. Preparation of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-(2,2- difluorocyclopropyl)-2-fluorobenzoate



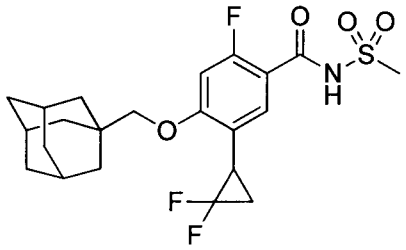
[01602] Following the procedure as described in Example 288 step 3 and making variations as required to replace 1-((cyclopent-3-en-1-ylmethoxy)methyl)-4-methoxybenzene with *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-vinylbenzoate. Purification by silica gel column chromatography (10:1 hexanes:ethyl acetate) gave the title compound as a colorless solid (0.95 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 12.7 Hz, 1H), 3.57-3.46 (m, 2H), 2.74-2.60 (m, 1H), 2.06-1.97 (m, 5H), 1.82-1.60 (m, 12H), 1.55 (s, 9H); MS (ES+) *m/z* 381.1 (M-55).

[01603] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-5-(2,2- difluorocyclopropyl)-2-fluorobenzoic acid



[01604] Following the procedure as described in Example 283 step 3 and making variations as required to replace *tert*-butyl 4-((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yloxy)-5- cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-(2,2- difluorocyclopropyl)-2-fluorobenzoate. Purification by trituration with methanol gave the title compound as a colorless solid (0.45 g, 54%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.91 (br s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 12.7 Hz, 1H), 3.68-3.56 (m, 2H), 2.84-2.70 (m, 1H), 1.99-1.90 (m, 4H), 1.89-1.78 (m, 1H), 1.71-1.56 (m, 12H); MS (ES+) *m/z* 381.2 (M+1).

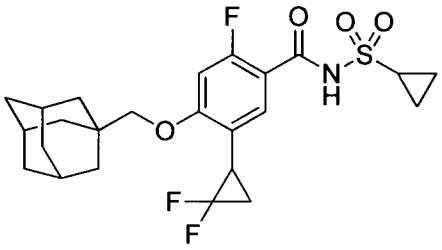
[01605] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluoro-*N*-(methylsulfonyl)benzamide



[01606] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-(adamantan-1-ylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with methyl sulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.070 g, 58%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 13.0 Hz, 1H), 3.71-3.54 (m, 2H), 3.31 (s, 3H), 2.85-2.71 (m, 1H), 2.03-1.87 (m, 5H), 1.75-.155 (m, 12H); MS (ES+) *m/z* 458.1 (M+1).

[01607] EXAMPLE 297

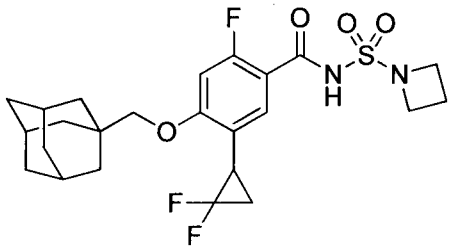
[01608] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(cyclopropylsulfonyl)- 5-(2,2-difluoro-cyclopropyl)-2-fluorobenzamide



[01609] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-(adamantan-1-ylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with cyclopropylsulfonamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.055 g, 43%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 13.0 Hz, 1H), 3.70-3.56 (m, 2H), 3.10-2.99 (m, 1H), 2.84-2.71 (m, 1H), 2.04-1.85 (m, 5H), 1.76-1.55 (m, 12H), 1.14-1.02 (m, 4H); MS (ES+) *m/z* 484.1 (M+1).

[01610] EXAMPLE 298

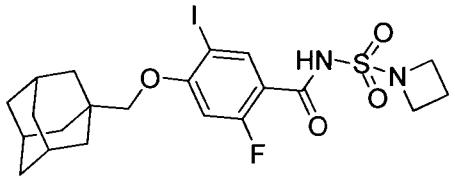
[01611] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-(2,2-difluorocyclopropyl)-2-fluorobenzamide



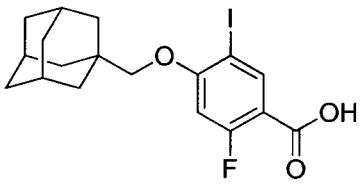
[01612] Following the procedure as described in Example 271 and making variations as required to replace 6-(adamantan-1-ylmethoxy)-5-cyclopropylnicotinic acid with 4-(adamantan-1-ylmethoxy)-5-(2,2-difluorocyclopropyl)-2-fluorobenzoic acid and to replace 2-methoxyethanesulfonamide with azetidine 1-sulfamide. Purification by silica gel column chromatography (2:1 hexanes:ethyl acetate (+0.2% acetic acid v/v)) gave the title compound as a colorless solid (0.040 g, 31%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 12.9 Hz, 1H), 4.01 (t, J = 7.7 Hz, 4H), 3.68-3.57 (m, 2H), 2.84-2.71 (m, 1H), 2.20-2.06 (m, 2H), 2.06-1.88 (m, 5H), 1.75-1.54 (m, 12H); MS (ES+) *m/z* 499.2 (M+1).

[01613] EXAMPLE 299

[01614] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)- 2-fluoro-5-iodobenzamide

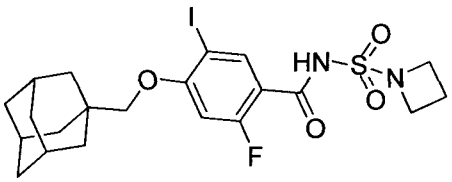


[01615] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid



[01616] To a solution of methyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoate (1.80 g, 4.05 mmol) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.85 g, 20.30 mmol) in water (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After addition of 1 N hydrochloric acid (10 mL) and ethyl acetate (150 mL), the organic phase was separated, washed with 1 N hydrochloric acid (10 mL) and brine (10 mL); dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* yielded the title compound (1.75 g, quant) as an off-white solid, which was used without further purification: MS (ES-) *m/z* 429.1 (M-1).

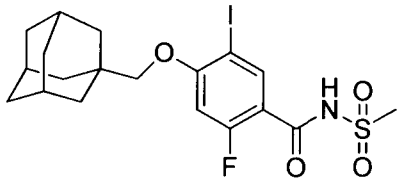
[01617] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-iodobenzamide



[01618] To a mixture of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid (1.75 g, 4.07 mmol) in anhydrous tetrahydrofuran (20 mL) was added 1,1'-carbonyldiimidazole (1.31 g, 8.10 mmol). The resulting mixture was heated at 70 °C for 30 minutes and then cooled to ambient temperature. Azetidine-1-sulfonamide (1.10 g, 8.10 mmol) was added followed by 1,8-diazabicyclo- [5.4.0]undec-7-ene (1.72 mL, 12.20 mmol) and the reaction mixture was stirred at ambient temperature for 16 hours. After addition of 1 N hydrochloric acid (5 mL) and diluting the mixture with ethyl acetate (150 mL), the organic phase was washed with 1 N hydrochloride acid (5 mL) and brine (10 mL); dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-100% ethyl acetate in hexanes as eluent to afford the title compound as an off-white solid (0.48 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 8.7 Hz, 1H), 6.56 (d, J = 13.7 Hz, 1H), 3.90 (t, J = 7.6 Hz, 4H), 3.59 (s, 2H), 2.35-2.15 (m, 2H), 2.12-1.99 (m, 3H), 1.83-1.63 (m, 12H); MS (ES-) *m/z* 547.1 (M-1).

[01619] EXAMPLE 300

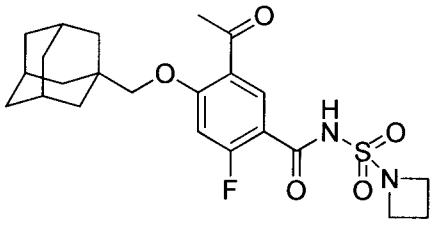
[01620] Synthesis of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodo-*N*-(methylsulfonyl)benzamide



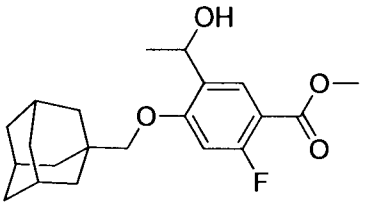
[01621] Following the procedure as described in Example 299 Step 2 and making variations as required to replace azetidine-1-sulfonamide with methanesulfonamide and purification by reverse-phase preparative HPLC, the title compound was obtained as a colorless solid (0.037 g, 5%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.08 (br s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 12.9 Hz, 1H), 3.68 (s, 2H), 3.28 (s, 3H), 2.04-1.95 (m, 3H), 1.78-1.60 (m, 12H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -108.9 (s, 1F); MS (ES-) *m/z* 506.0 (M-1).

[01622] EXAMPLE 301

[01623] Synthesis of 5-acetyl-4-(adamantan-1-ylmethoxy)-*N*- (azetidin-1-ylsulfonyl)-2-fluorobenzamide

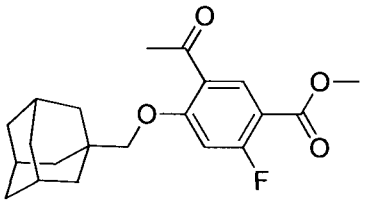


[01624] Step 1. Preparation of methyl 4-(adamantan-1-ylmethoxy)-2-fluoro- 5-(1-hydroxyethyl)benzoate



[01625] To a mixture of methyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoate (1.25 g, 2.80 mmol) in anhydrous tetrahydrofuran (10 mL) was added isopropylmagnesium chloride lithium chloride complex (1.3 M solution in tetrahydrofuran, 3.2 mL, 4.20 mmol) at -40 °C. The reaction mixture was stirred for 1 hour at -40 °C, after which acetaldehyde (0.79 mL, 14.10 mmol) was added. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 hours and then was quenched by addition of saturated ammonium chloride solution (10 mL). The mixture was extracted with ethyl acetate (2 × 50 mL) and the combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-35% ethyl acetate in hexanes as eluent to afford the title compound as an amorphous solid (0.76 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 12.7 Hz, 1H), 5.16–5.06 (m, 1H), 3.88 (s, 3H), 3.55 (d, J = 8.9 Hz, 1H), 3.52 (d, J = 9.3 Hz, 1H), 2.27 (d, J = 4.8 Hz, 1H), 2.08-1.98 (m, 3H), 1.83-1.61 (m, 12H), 1.49 (d, J = 6.5 Hz, 3H); MS (ES+) *m/z* 345.2 (M-17).

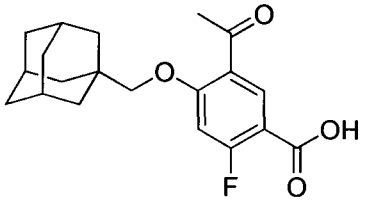
[01626] Step 2. Synthesis of methyl 5-acetyl-4-(adamantan-1-ylmethoxy)- 2-fluorobenzoate



[01627] To a mixture of methyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(1- hydroxyethyl)benzoate (0.76 g, 2.10 mmol) in dichloromethane (20 mL) was added Dess-Martin periodinane (1.34 g, 3.20 mmol). The reaction mixture was stirred for 1 hour at ambient temperature and then quenched by addition of saturated sodium bicarbonate solution (5 mL) and saturated sodium thiosulfate solution (5 mL). Dichloromethane (30 mL) was added and the mixture was stirred for 16 hours at ambient temperature. The organic phase was separated, washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of

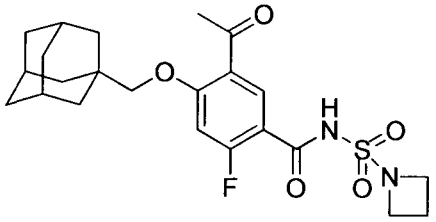
the filtrate *in vacuo* gave a residue, which re-dissolved in a mixture of diethyl ether and dichloromethane (30 mL, 1:1). Insoluble material was filtered off, and the filtrate was concentrated *in vacuo* to yield the title compound as a colorless oil (0.75 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 1H), 6.62 (d, J = 12.8 Hz, 1H), 3.78 (s, 3H), 3.55 (s, 2H), 2.55 (s, 3H), 1.97-1.90 (m, 3H), 1.72-1.53 (m, 12H).

[01628] Step 3. Preparation of 5-acetyl-4-(adamantan-1-ylmethoxy)-2-fluorobenzoic acid



[01629] To a solution of methyl 5-acetyl-4-(adamantan-1-ylmethoxy)-2-fluorobenzoate (0.75 g, 2.10 mmol) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.441 g, 10.50 mmol) in water (4 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. After adjusting the reaction mixture to pH 2 with 1 N hydrochloric acid, the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* yielded the title compound as a colorless oil (0.727 g, quant.), which was used without further purification: MS (ES-) *m/z* 345.3 (M-1).

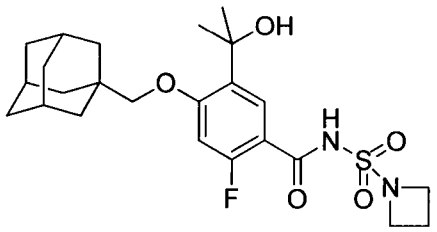
[01630] Step 4. Preparation of 5-acetyl-4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluorobenzamide



[01631] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 5-acetyl-4-(adamantan-1-ylmethoxy)-2-fluorobenzoic acid and purification by triturating in methanol, the title compound was obtained as a beige solid (0.571 g, 59%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (br s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 13.0 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.78 (s, 2H), 2.61 (s, 3H), 2.23-2.13 (m, 2H), 2.00 (s, 3H), 1.78-1.61 (m, 12H); MS (ES-) *m/z* 465.0 (M-1).

[01632] EXAMPLE 302

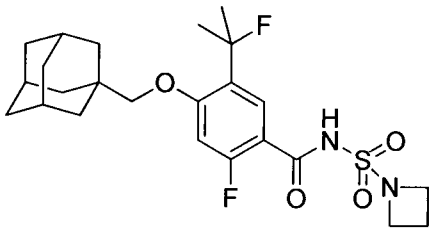
[01633] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(2-hydroxypropan-2-yl)benzamide



[01634] To a solution of 5-acetyl-4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluorobenzamide (0.200 g, 0.43 mmol) in anhydrous tetrahydrofuran (4 mL) was added methylmagnesium bromide (3.0 M solution in diethyl ether, 0.29 mL, 0.86 mmol) at -78 °C. After 1 hour at -78 °C, additional methylmagnesium bromide (3.0 M solution in diethyl ether, 0.29 mL, 0.86 mmol) was added; the reaction mixture was allowed to warm to ambient temperature, and stirred for 1 hour. After addition of 1 N hydrochloride acid (5 mL) and diluting the mixture with ethyl acetate (100 mL), the organic phase was washed with brine (5 mL) and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate *in vacuo* gave a residue which was purified by reverse-phase preparative HPLC to give the title compound as a colorless solid (0.101 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 13.0 Hz, 1H), 5.25 (s, 1H), 4.04 (t, J = 7.6 Hz, 4H), 3.65 (s, 2H), 2.22-2.10 (m, 2H), 2.01 (br s, 3H), 1.79-1.61 (m, 12H), 1.51 (s, 6H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -111.6 (s, 1F); MS (ES-) *m/z* 479.2 (M-1).

[01635] EXAMPLE 303

[01636] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(2-fluoropropan-2-yl)benzamide

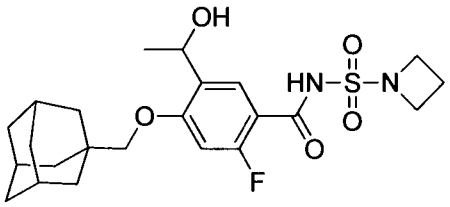


[01637] To a solution of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(2-hydroxypropan-2-yl)benzamide (0.0 67 g, 0.14 mmol) in anhydrous dichloromethane (10 mL) was added diethylaminosulfur trifluoride (22 µL, 0.17 mmol) at -78 °C. The reaction mixture was stirred for 2 hours at -78 °C and then quenched by addition of saturated sodium bicarbonate solution (5 mL). The mixture was allowed to warm to ambient temperature and diluted with dichloromethane (50 mL). The organic phase was washed with brine (5 mL), dried over anhydrous magnesium sulfate, and filtered. The residue obtained after concentration of the filtrate *in vacuo* was purified by silica gel column chromatography using 0-20% ethyl acetate in hexanes as eluent to afford a beige solid. Lyophilization from

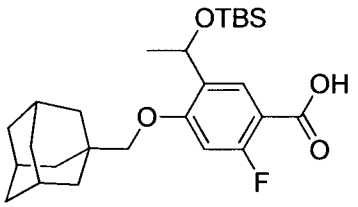
acetonitrile and water (2 mL, 1:1) gave the title compound as colorless solid (0.012 g, 18%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 12.7 Hz, 1H), 4.05 (t, J = 7.6 Hz, 4H), 3.69 (s, 2H), 2.23-2.11 (m, 2H), 2.04-1.97 (m, 3H), 1.79-1.61 (m, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.8 (s, 1F), -130.0 (s, 1F); MS (ES-) *m/z* 481.2 (M-1).

[01638] EXAMPLE 304

[01639] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxyethyl)benzamide



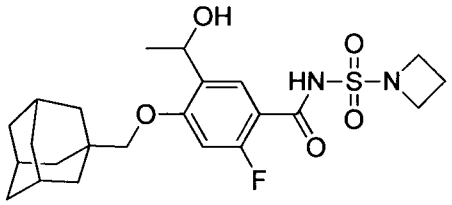
[01640] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-5-(1-((*tert*- butyldimethylsilyl)oxy)ethyl)-2-fluorobenzoic acid



[01641] To a solution of methyl-4-(adamantan-1-ylmethoxy)-2-fluoro-5-(1- hydroxyethyl)benzoate (0.26 g, 0.72 mmol) and 2,6-lutidine (0.17 mL, 1.44 mmol) in anhydrous dichloromethane (5 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.285 g, 1.08 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. After dilution with dichloromethane (100 mL), the organic phase was washed with 1 N hydrochloric acid (2 × 5 mL), brine (10 mL), and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate *in vacuo* afforded methyl 4-(adamantan-1-ylmethoxy)-5- (1-((*tert*-butyldimethylsilyl)- oxy)ethyl)-2-fluorobenzoate as a yellowish oil (0.35 g, quant.), which was used without further purification.

[01642] To a solution of methyl 4-(adamantan-1-ylmethoxy)-5-(1- ((*tert*-butyldimethylsilyl)oxy)-ethyl)-2-fluorobenzoate in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.151 g, 3.6 mmol) in water (5 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 days. After adjusting the reaction mixture to pH 5 with 1 N hydrochloric acid, the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* yielded the title compound as a yellowish oil (0.33 g, quant.), which was used without further purification: MS (ES+) *m/z* 461.4 (M-1).

[01643] Step 4. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(1-hydroxyethyl)benzamide

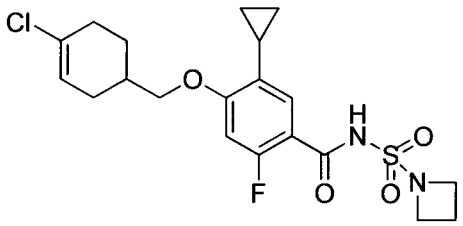


[01644] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-fluoro-benzoic acid, 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-(1-((*tert*-butyldimethylsilyl)-oxy)ethyl)-2-fluoro benzamide was obtained as an oily residue (0.42 g, quant.), which was used without further purification.

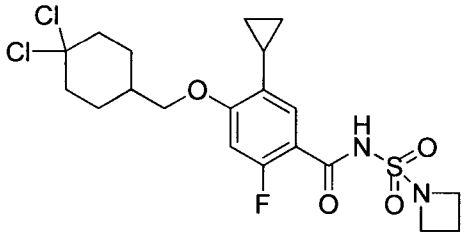
[01645] To a mixture of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-fluorobenzamide in tetrahydrofuran (5 mL) was added 1 N hydrochloric acid (10 mL) and the reaction mixture was stirred for 16 hours at ambient temperature. After diluting the mixture with dichloromethane (50 mL), the organic phase was separated, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC to afford the title compound as a colorless solid (0.073 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.66 (br s, 1H), 7.80-7.70 (m, 1H), 6.97-6.85 (m, 1H), 5.29-5.16 (m, 1H), 5.01-4.90 (m, 1H), 4.15-3.90 (m, 4H), 3.71-3.51 (m, 2H), 3.38-3.29 (m, 2H), 2.23-1.90 (m, 3H), 1.80-1.53 (m, 12H), 1.35-1.23 (m, 3H); MS (ES-) *m/z* 465.2 (M-1).

[01646] EXAMPLE 305/306

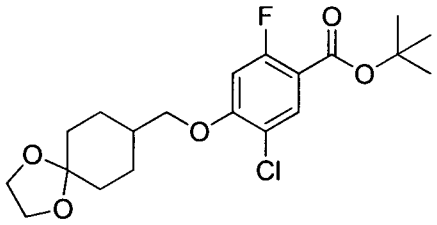
[01647] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzamide



[01648] And *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)-methoxy)-2-fluorobenzamide

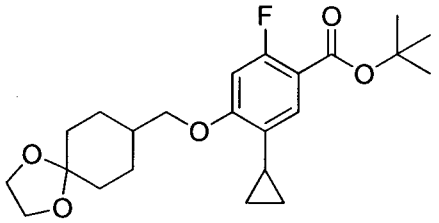


[01649] Step 1. Preparation of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-5-chloro-2-fluorobenzoate



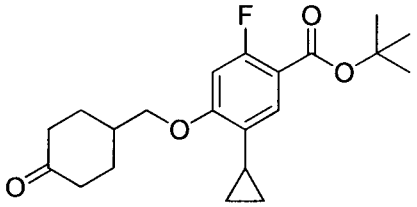
[01650] To a mixture of 1,4-dioxaspiro[4.5]decan-8-ylmethanol (5.00 g, 29.0 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (7.22 g, 29.00 mmol) in anhydrous dimethyl sulfoxide (30 mL) was added cesium carbonate (18.90 g, 58.00 mmol) and the reaction mixture was heated at 70-80 °C for 4 hours. After cooling to ambient temperature, ethyl acetate was added (200 mL) and the mixture was washed with water (4 × 15 mL), brine (2 × 15 mL); dried over anhydrous sodium sulfate, and filtered. After concentration of the filtrate *in vacuo*, the residue was purified by silica gel column chromatography using 0-30% ethyl acetate in hexanes as eluent to afford the title compound as a colorless oil (5.06 g, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 6.60 (d, J = 12.2 Hz, 1H), 3.95–3.93 (m, 4H), 3.83 (d, J = 6.3 Hz, 2H), 1.98-1.87 (m, 4H), 1.84-1.71 (m, 4H), 1.64-1.56 (m, 1H), 1.56 (s, 9H).

[01651] Step 2. Preparation of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate



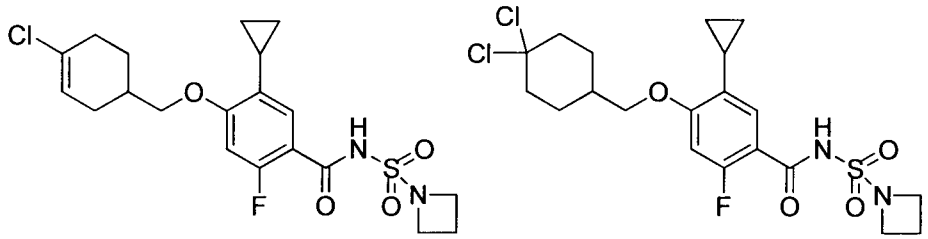
[01652] To a mixture of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-5- chloro-2-fluorobenzoate (1.20 g, 3.00 mmol) in toluene (18 mL) was added cyclopropylboronic acid (1.55 g, 18.00 mmol), potassium phosphate tribasic (1.91 g, 9.00 mmol), tricyclohexyl- phosphine tetrafluoroborate (0.884 g, 2.40 mmol), palladium acetate (0.269 g, 1.20 mmol) and water (2 mL). The reaction mixture was thoroughly degassed by passing argon through it and then heated in a microwave at 150 °C for 30 minutes. The reaction was performed 4 times as described. After cooling to ambient temperature, the reaction mixtures were combined, diluted with ethyl acetate (200 mL) and filtered over anhydrous sodium sulfate. After removing all volatiles under reduced pressure, the residue was purified by silica gel column chromatography using 0-30% ethyl acetate in hexanes as eluent to afford the title compound as a yellowish oil (3.16 g, 16%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 1H), 6.48 (d, J = 12.7 Hz, 1H), 3.95-3.92 (m, 4H), 3.80 (d, J = 6.1 Hz, 2H), 2.04-1.70 (m, 10H), 1.54 (s, 9H), 0.91-0.82 (m, 2H), 0.64-0.57 (m, 2H).

[01653] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4 -oxocyclohexyl)methoxy)benzoate



[01654] To a mixture of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate (3.16 g, 7.77 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added trifluoroacetic acid (2.7 mL) and the reaction mixture was stirred for 16 hours at ambient temperature. After diluting the reaction mixture with ethyl acetate (200 mL), the organic phase was washed with 1 N sodium hydroxide solution (2 × 15 mL), brine (15 mL), and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-40% ethyl acetate in hexanes as eluent to afford the title compound as a colorless oil (2.70 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 12.5 Hz, 1H), 3.90 (d, J = 6.0 Hz, 2H), 2.53–2.15 (m, 8H), 2.03-1.92 (m, 1H), 1.73-1.59 (m, 1H), 1.55 (s, 9H), 0.92-0.83 (m, 2H), 0.65-0.58 (m, 2H).

[01655] Step 4. Preparation of of *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en-1-yl)-methoxy)-5-cyclopropyl-2-fluorobenzamide and *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)methoxy)-2-fluorobenzamide



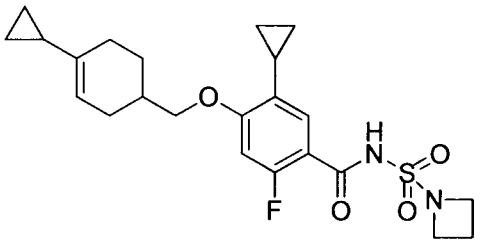
[01656] To a mixture of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-oxocyclohexyl)- methoxy)benzoate (0.300 g, 0.83 mmol) in anhydrous dichloromethane (5 mL) was added phosphorus pentachloride (0.518 g, 2.49 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 3 hours. After cooling to 0 °C, water (10 mL) was added to the reaction mixture followed by dichloromethane (100 mL). The organic phase was washed with water (10 mL), brine (10 mL); dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a mixture of 4-((4-chlorocyclohex-3-en-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-cyclopropyl-4-((4,4-dichlorocyclohexyl)methoxy)-2-fluorobenzoic acid as a colorless oil (0.38 g, quant.) which was used without further purification.

[01657] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with a mixture of

4-((4-chlorocyclohex-3-en-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-cyclopropyl-4-((4,4-dichlorocyclohexyl)methoxy)-2-fluorobenzoic acid, the title compounds were obtained as pure and separated materials after purification by reverse-phase preparative HPLC. Data for the first fraction, *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzamide, colorless solid (0.041 g, 11%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (br s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 12.9 Hz, 1H), 5.89-5.84 (m, 1H), 4.07-3.98 (m, 6H), 2.45-2.25 (m, 3H), 2.23-1.89 (m, 6H), 1.66-1.51 (m, 1H), 0.93-0.86 (m, 2H), 0.72-0.64 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.5 (s, 1F); MS (ES-) *m/z* 441.2, 443.2 (M-1). Data for second fraction, *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)methoxy)-2-fluorobenzamide), colorless solid (0.027 g, 7%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (br s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 14.2 Hz, 1H), 4.24 (t, J = 7.5 Hz, 4H), 3.89 (d, J = 5.8 Hz, 2H), 2.68–2.54 (m, 2H), 2.34–2.18 (m, 4H), 2.07–1.86 (m, 4H), 1.82–1.65 (m, 2H), 0.99–0.90 (m, 2H), 0.70–0.63 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -111.1 (s, 1F); MS (ES-) *m/z* 477.2, 479.2 (M-1).

[01658] EXAMPLE 307

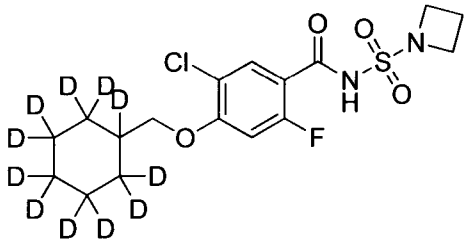
[01659] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4-cyclopropylcyclohex-3-en-1-yl)methoxy)-2-fluorobenzamide



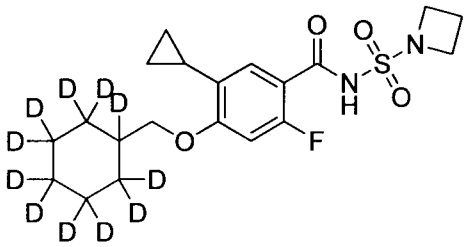
[01660] Following the procedure as described in Example 305/306, Step 2 and making variations as required to replace *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)- 5-chloro-2-fluorobenzoate with *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en- 1-yl)methoxy)-5-cyclopropyl-2-fluorobenzamide and purification by reverse-phase preparative HPLC, the title compound was obtained as a colorless solid (0.031 g, 10%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br s, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.9 Hz, 1H), 5.42 (d, J = 3.2 Hz, 1H), 4.02 (t, J = 7.7 Hz, 4H), 3.97 (d, J = 6.2 Hz, 2H), 2.24-2.08 (m, 3H), 2.08-1.93 (m, 2H), 1.93-1.78 (m, 4H), 1.45-1.27 (m, 2H), 0.93-0.84 (m, 2H), 0.71-0.63 (m, 2H), 0.54-0.46 (m, 2H), 0.45-0.36 (m, 2H); MS (ES-) *m/z* 447.2 (M-1).

[01661] EXAMPLE 308/309

[01662] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzamide



[01663] And *N*-(azetidin-1-ylsulfonyl)-4-(cyclohexyl-d_{11}-methoxy)-5- cyclopropyl-2-fluorobenzamide



[01664] Following the procedure as described in Example 305/306 Step 1 and making variations as required to replace 1,4-dioxaspiro[4.5]decan-8-ylmethanol with cyclohexyl-d_{11}-methyl alcohol, *tert*-butyl 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoate was obtained as a colorless oil (2.43 g, 86% yield).

[01665] Following the procedure as described in Example 305/306 Step 2 and making variations as required to replace *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)- 5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoate, a mixture of *tert*-butyl 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2-fluorobenzoate and *tert*-butyl 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoate was obtained as a yellowish solid (0.482 g). The mixture was used without further purification.

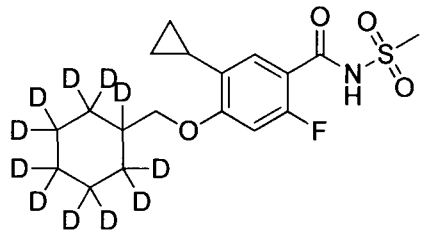
[01666] To a mixture of *tert*-butyl 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2- fluorobenzoate and *tert*-butyl 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoate (1.57 g) in dichloromethane (20 mL) was added trifluoroacetic acid (5 mL). The reaction mixture was stirred at ambient temperature for 2 hours. After evaporation of all volatiles under reduced pressure, a mixture of 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoic acid was obtained as a brownish solid (1.30 g).

[01667] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with a mixture of 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoic acid, the title compounds were obtained as pure and separated materials after purification by reverse-phase preparative HPLC. Data for the first fraction, *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzamide, colorless solid (0.039 g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (br s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.7 Hz, 1H),

4.02 (t, J = 7.0 Hz, 4H), 3.96 (s, 2H), 2.21–2.09 (m, 2H); MS (ES-) m/z 414.3 (M-1). Data for the second fraction, N-(azetidin-1-ylsulfonyl)-4-(cyclohexyl-d_{11}- methoxy)- 5-cyclopropyl-2-fluorobenzamide), colorless solid (0.050 g): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 4.02 (t, J = 7.7 Hz, 4H), 3.88 (s, 2H), 2.21-2.09 (m, 2H), 2.07-1.96 (m, 1H), 0.93-0.86 (m, 2H), 0.70-0.64 (m, 2H); MS (ES-) m/z 422.2 (M-1).

[01668] EXAMPLE 310

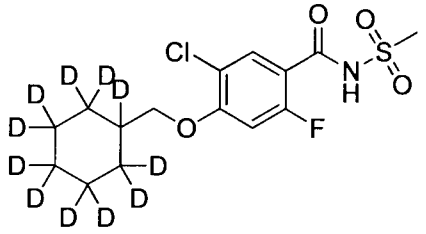
[01669] Synthesis of 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2-fluoro- N-(methylsulfonyl)benzamide



[01670] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(cyclohexyl-d_{11}-methoxy)-5-cyclopropyl-2-fluorobenzoic acid and azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (0.038 g, 6%) after purification by reverse-phase preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 11.88 (br s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 13.1 Hz, 1H), 3.88 (s, 2H), 3.32 (s, 3H), 2.08–1.95 (m, 1H), 0.93–0.85 (m, 2H), 0.70–0.63 (m, 2H); MS (ES-) m/z 379.3 (M-1).

[01671] EXAMPLE 311

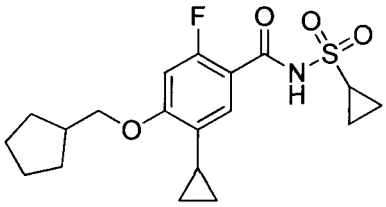
[01672] Synthesis of 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluoro -N-(methylsulfonyl)benzamide



[01673] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 5-chloro-4-(cyclohexyl-d_{11}-methoxy)-2-fluorobenzoic acid and azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (0.108 g, 26%) after purification by reverse-phase preparative HPLC: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 12.5 Hz, 1H), 3.95 (s, 2H), 3.33 (s, 3H); MS (ES-) m/z 373.3, 375.3 (M-1).

[01674] EXAMPLE 312

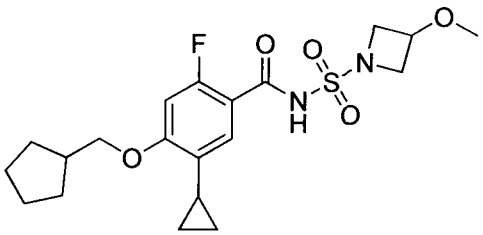
[01675] Synthesis of 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*- (cyclopropylsulfonyl)-2-fluorobenzamide



[01676] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with cyclopropane-sulfonamide, the title compound was obtained as a colorless solid (0.039 g, 12%) after trituration in diethyl ether followed by trituration in methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (br s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 13.1 Hz, 1H), 3.97 (d, J = 6.8 Hz, 2H), 3.13-3.02 (m, 1H), 2.41-2.26 (m, 1H), 2.08-1.95 (m, 1H), 1.85-1.72 (m, 2H), 1.68-1.49 (m, 4H), 1.44-1.31 (m, 2H), 1.15-1.07 (m, 4H), 0.93-0.85 (m, 2H), 0.71-0.64 (m, 2H); MS (ES-) *m/z* 380.2 (M-1).

[01677] EXAMPLE 313

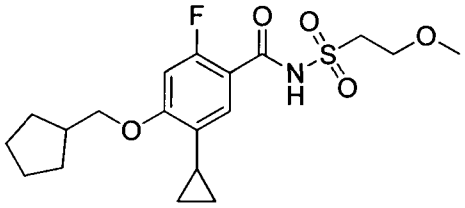
[01678] Synthesis of 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((3-methoxyazetidin-1-yl)sulfonyl)benzamide



[01679] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and azetidine-1-sulfonamide with 3-methoxyazetidine- 1-sulfonamide, the title compound was obtained as a colorless solid (0.04 g, 11%) after trituration in methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.70 (br s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 13.0 Hz, 1H), 4.24-4.11 (m, 3H), 3.99-3.91 (m, 4H), 3.17 (s, 3H), 2.43-2.26 (m, 1H), 2.08-1.95 (m, 1H), 1.86-1.73 (m, 2H), 1.69-1.50 (m, 4H), 1.45-1.31 (m, 2H), 0.93-0.85 (m, 2H), 0.71-0.64 (m, 2H); MS (ES-) *m/z* 425.2 (M-1).

[01680] EXAMPLE 314

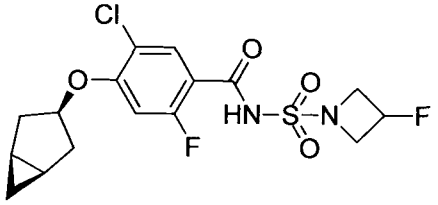
[01681] Synthesis of 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide



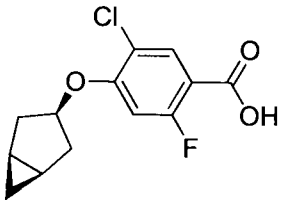
[01682] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with 2-methoxyethanesulfonamide, the title compound was obtained as a colorless solid (0.039 g, 12%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (br s, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.0 Hz, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.71 (s, 4H), 3.21 (s, 3H), 2.42-2.26 (m, 1H), 2.07-1.96 (m, 1H), 1.86-1.73 (m, 2H), 1.68-1.47 (m, 4H), 1.44-1.30 (m, 2H), 0.92-0.84 (m, 2H), 0.70-0.62 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -113.0 (s, 1F); MS (ES-) *m/z* 398.2 (M-1).

[01683] EXAMPLE 315

[01684] Synthesis of 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide

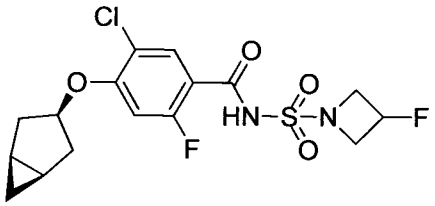


[01685] Step 1. Preparation of 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5- chloro-2-fluorobenzoic acid



[01686] To a mixture of *tert*-butyl 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro- 2-fluorobenzoate (3.50 g, 10.70 mmol) in dichloromethane (50 mL) was added trifluoroacetic acid (10 mL) and the reaction mixture was stirred for 2 hours at ambient temperature. After removal of all volatiles under reduced pressure, the residue was purified by silica gel column chromatography using 0-50% ethyl acetate in hexanes as eluent to afford the title compound as an off-white solid (2.40 g, 83%): MS (ES-) *m/z* 269.2, 271.3 (M-1).

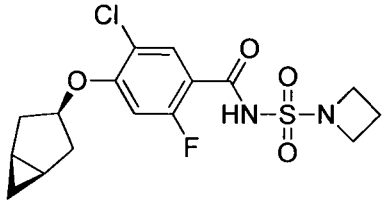
[01687] Step 2. Preparation of 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluoro-*N*-((3-fluoroazetidin-1-yl)sulfonyl)benzamide



[01688] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with 3-fluoroazetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.105 g, 26%) after purification by reverse-phase preparative HPLC followed by trituration in methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 12.6 Hz, 1H), 5.50-5.22 (m, 1H), 5.10 (t, J = 6.4 Hz, 1H), 4.42 (dd, J = 10.9, 5.9 Hz, 1H), 4.34 (dd, J = 10.8, 5.9 Hz, 1H), 4.23 (dd, J = 10.9, 3.3 Hz, 1H), 4.15 (dd, J = 10.7, 3.2 Hz, 1H), 2.32–2.22 (m, 2H), 1.91-1.84 (m, 2H), 1.42-1.33 (m, 2H), 0.59-0.44 (m, 2H); MS (ES-) *m/z* 405.2, 407.2 (M-1).

[01689] EXAMPLE 316

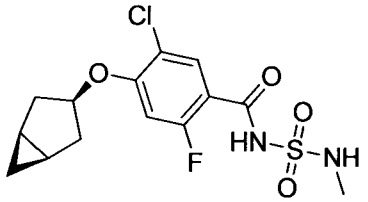
[01690] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]-hexan-3-yloxy)-5-chloro-2-fluorobenzamide



[01691] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.09 mg, 23%) after purification by reverse-phase preparative HPLC followed by trituration in methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 12.5 Hz, 1H), 5.09 (t, J = 6.3 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 2.33-2.08 (m, 4H), 1.88 (d, J = 14.8 Hz, 2H), 1.41-1.32 (m, 2H), 0.60-0.44 (m, 2H); MS (ES-) *m/z* 387.2, 389.2 (M-1).

[01692] EXAMPLE 317

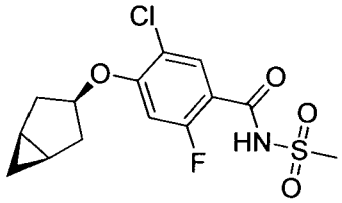
[01693] Synthesis of 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[01694] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluorobenzoic acid and to replace azetidine- 1-sulfonamide with *N*-methylsulfamide, the title compound was obtained as a colorless solid (0.034 g, 9%) after purification by reverse-phase preparative HPLC followed by recrystallization from methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.67 (br s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.69-7.60 (m, 1H), 7.15 (d, J = 12.5 Hz, 1H), 5.08 (t, J = 6.3 Hz, 1H), 2.55 (d, J = 4.7 Hz, 3H), 2.32-2.18 (m, 2H), 1.87 (d, J = 14.8 Hz, 2H), 1.41-1.33 (m, 2H), 0.59-0.43 (m, 2H); MS (ES-) *m/z* 361.2, 363.2 (M-1).

[01695] EXAMPLE 318

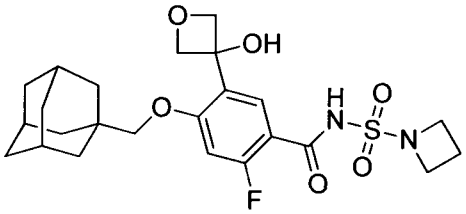
[01696] Synthesis of 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluoro-*N*-(methylsulfonyl)benzamide



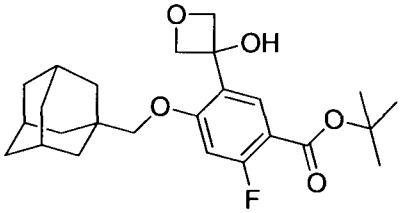
[01697] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-((1*R*,3*r*,5*S*)-bicyclo[3.1.0]hexan-3-yloxy)-5-chloro-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (0.093 g, 27%) after purification by reverse-phase preparative HPLC followed by recrystallization from methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 12.7 Hz, 1H), 5.09 (t, J = 6.4 Hz, 1H), 3.34 (s, 3H), 2.32-2.20 (m, 2H), 1.87 (d, J = 14.8 Hz, 2H), 1.41-1.33 (m, 2H), 0.58-0.44 (m, 2H); MS (ES-) *m/z* 346.2, 348.2 (M-1).

[01698] EXAMPLE 319

[01699] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzamide

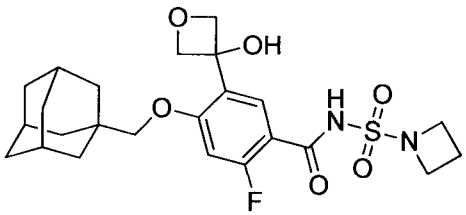


[01700] Step 1. Preparation of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzoate



[01701] To a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoate (0.973 g, 2.00 mmol) in anhydrous tetrahydrofuran (10 mL) was added isopropylmagnesium chloride lithium chloride complex (1.30 M solution in tetrahydrofuran, 1.76 mL, 2.20 mmol) at -40 °C. The reaction mixture was stirred for 1 hour at -40 °C, after which oxetan-3-one (0.432 g, 6.00 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. After quenched with saturated ammonium chloride solution (10 mL), the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with brine (5 mL); dried over sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-50% ethyl acetate in hexanes as eluent to afford the title compound as an amorphous solid (0.336 g, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 12.3 Hz, 1H), 5.01 (d, J = 6.9 Hz, 2H), 4.84 (d, J = 7.0 Hz, 2H), 3.86 (s, 1H), 3.52 (s, 2H), 2.05-1.94 (m, 3H), 1.78-1.55 (m, 12H), 1.54 (s, 9H).

[01702] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzamide



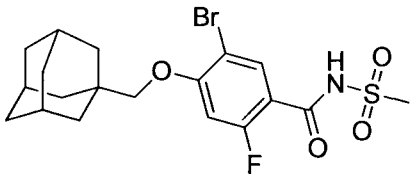
[01703] To a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzoate ((330 mg, 0.76 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred for 2 hour at ambient temperature. Removal of all volatiles

in vacuo gave 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzoic acid as an oily residue (0.29 g, quant.).

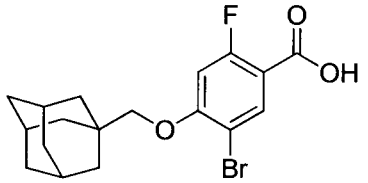
[01704] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(3-hydroxyoxetan-3-yl)benzoic acid and purification by reverse-phase preparative HPLC, the title compound was obtained as a colorless solid (0.036 g, 10%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (br s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 13.0 Hz, 1H), 6.14 (s, 1H), 5.02 (d, J = 6.6 Hz, 2H), 4.65 (d, J = 6.6 Hz, 2H), 4.03 (t, J = 7.6 Hz, 4H), 3.63 (s, 2H), 2.23-2.09 (m, 2H), 2.02-1.94 (m, 3H), 1.79-1.59 (m, 12H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -108.9 (s, 1F); MS (ES-) *m/z* 493.3 (M-1).

[01705] EXAMPLE 320

[01706] Synthesis of 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluoro-*N*- (methylsulfonyl)benzamide

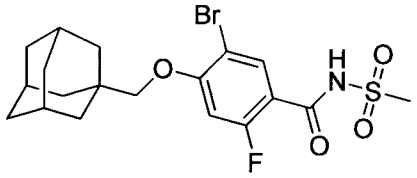


[01707] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluorobenzoic acid



[01708] A mixture of adamantan-1-ylmethanol (3.51 g, 21.10 mmol) and potassium *tert*-butoxide (5.45 g, 48.5 mmol) in anhydrous dimethylsulfoxide (125 mL) was stirred for 20 minutes. To the reaction mixture was then added 5-bromo-2,4-difluorobenzoic acid (5.00 g, 21.10 mmol) followed by anhydrous dimethylsulfoxide (25 mL). The resulting mixture was stirred for 18 hours at ambient temperature. The reaction mixture was diluted with water (300 mL), and adjusted to pH 3 with 3 M hydrochloric acid. The obtained solid was filtered off and rinsed with water (200 mL) to provide a 2:1 mixture of the title compound and 2-adamantan-1-ylmethoxy)-5-bromo-4-fluorobenzoic acid (6.97 g, 86%). Major isomer: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 12.9 Hz, 1H), 3.65 (s, 2H), 1.98-1.83 (m, 3H), 1.72-1.48 (m, 12H); MS (ES-) *m/z* 381.13, 383.12 (M - 1).

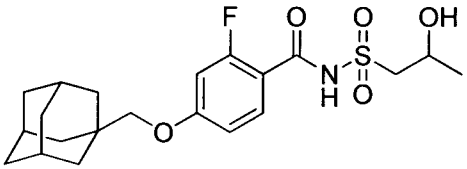
[01709] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluoro-*N*-(methylsulfonyl)benzamide



[01710] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluorobenzoic acid and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (1.00 g, 49%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 12.4 Hz, 1H), 3.71 (s, 2H), 3.35 (s, 3H), 1.98 (br s, 3H), 1.78-1.56 (m, 12H); MS (ES-) *m/z* 458.2, 460.1 (M-1).

[01711] EXAMPLE 321

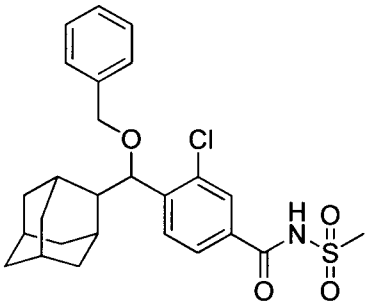
[01712] Synthesis of 4-(adamantan-1-ylmethoxy)-2-fluoro-*N*-((2-hydroxypropyl)sulfonyl)-benzamide



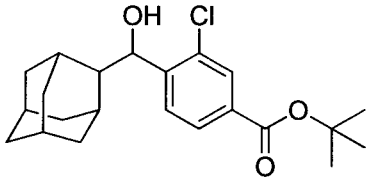
[01713] To a solution of 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluoro-*N*- (methylsulfonyl)benzamide (0.340 g, 0.74 mmol) in anhydrous tetrahydrofuran (5 mL) was added *tert*-butyllithium (1.7 M solution in pentane, 1.31 mL, 2.22 mmol) at -78 °C. The reaction mixture was stirred for 30 minutes at -78 °C followed by addition of acetaldehyde (0.21 mL, 3.70 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. After quenched with 1 N hydrochloric acid (5 mL), the mixture was diluted with ethyl acetate (100 mL). The organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate gave a residue which was purified by reverse-phase preparative HPLC to afford the title compound as an off-white solid (0.075 g, 24%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.60 (t, J = 8.7 Hz, 1H), 6.93 (dd, J = 13.0, 2.2 Hz, 1H), 6.86 (dd, J = 8.7, 2.3 Hz, 1H), 5.04 (br s, 1H), 4.17–4.07 (m, 1H), 3.65–3.56 (m, 1H), 3.63 (s, 2H), 3.45 (dd, J = 14.3, 5.1 Hz, 1H), 2.02–1.94 (m, 3H), 1.76–1.57 (m, 12H), 1.20 (d, J = 6.3 Hz, 3H); MS (ES-) *m/z* 424.2 (M-1).

[01714] EXAMPLE 322

[01715] Synthesis of 4-(adamantan-2-yl(benzyloxy)methyl)-3- chloro-*N*-(methylsulfonyl)-benzamide

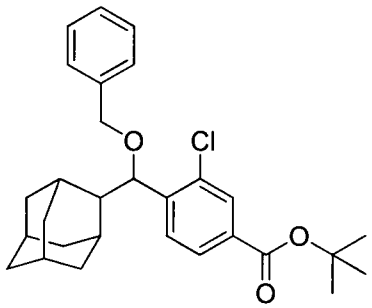
[01716] 

[01717] Step1. Preparation of *tert*-butyl 4-(adamantan-2-yl(hydroxy)methyl)-3-chlorobenzoate



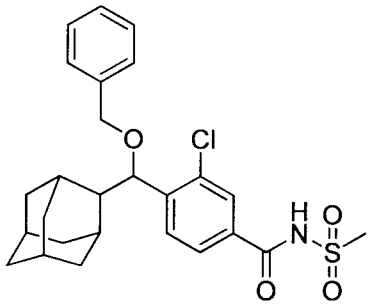
[01718] To a solution of *tert*-butyl 4-bromo-3-chlorobenzoate (0.875 g, 3.00 mmol) in tetrahydrofuran (5 mL) was added isopropylmagnesium chloride lithium chloride complex (1.3 M solution in anhydrous tetrahydrofuran, 2.78 mL, 3.61 mmol) at -40 °C. The reaction was allowed to warm to ambient temperature and stirred for 1 hour (solution A). In a separate flask, a solution of spiro(adamantane-2,2'-oxirane) (0.492 g, 3.00 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with boron trifluoride diethyl etherate (0.38 mL, 3.0 mmol) at 0 °C for 30 minutes (solution B). Solution A was then transferred via cannula to solution B at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. After quenched with saturated ammonium chloride solution (5 mL), the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-100% ethyl acetate in hexanes as eluent to afford the title compound as a colorless solid (0.32 g, 33%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.84 (dd, J = 8.1, 1.4 Hz, 1H), 7.80 (d, J = 1.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 5.44 (br s, 1H), 5.18 (d, J = 10.3 Hz, 1H), 2.36-2.29 (m, 1H), 2.06-1.34 (m, 22H), 1.08-1.01 (m, 1H); MS (ES+) *m/z* 359.2, 361.2 (M-17).

[01719] Step 2. Preparation of *tert*-butyl 4-(adamantan-2-yl(benzyloxy)methyl)- 3-chlorobenzoate



[01720] To a solution of *tert*-butyl 4-(adamantan-2-yl(hydroxy)methyl)-3-chlorobenzoate (0.32 mg, 1.00 mmol) in anhydrous dimethylformamide (5 mL) was added sodium hydride (60% dispersion in mineral oil, 0.048 g, 1.2 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. Benzyl bromide (0.24 mL, 2.00 mmol) and tetrabutylammonium iodide (0.037 g, 0.10 mmol) was added and the reaction mixture was stirred for 16 hours at ambient temperature. After quenched with saturated ammonium chloride solution (10 mL), the mixture was diluted with ethyl acetate (150 mL). The organic phase was washed with water (3 × 10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-20% ethyl acetate in hexanes as eluent to afford the title compound as a colorless oil (0.437 g, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.95 (m, 1H), 7.90 (d, J = 8.18 Hz, 1H), 7.60 (d, J = 7.39 Hz, 1H), 7.46–7.18 (m, 5H), 5.18–5.11 (m, 1H), 4.30 (d, J = 11.54 Hz, 1H), 4.18 (d, J = 11.60 Hz, 1H), 2.41 (s, 1H), 2.12–1.30 (m, 22H), 1.13 (s, 1H).

[01721] Step 3. Preparation of 4-(adamantan-2-yl(benzyloxy)methyl)-3-chloro-*N*-(methylsulfonyl)-benzamide



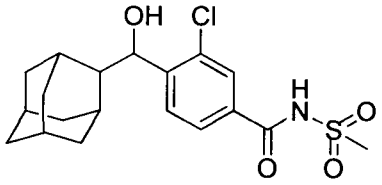
[01722] To a mixture of *tert*-butyl 4-(adamantan-2-yl(benzyloxy)methyl)- 3-chlorobenzoate (0.43 g, 1.05 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred for 2 hour at ambient temperature. Removal of all volatiles under reduced pressure gave 4-(adamantan-2-yl(benzyloxy)methyl)-3-chlorobenzoic acid as an oily residue (0.43 g, quant.), which was used without further purification.

[01723] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-2-yl(benzyloxy)methyl)-3-chlorobenzoic acid and to replace azetidine-1-sulfonamide with

methanesulfonamide, the title compound was obtained as a colorless solid (0.312 g, 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.24 (br s, 1H), 8.04 (d, J = 1.7 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.37-7.22 (m, 5H), 5.08 (d, J = 9.9 Hz, 1H), 4.27 (d, J = 11.8 Hz, 1H), 4.16 (d, J = 11.8 Hz, 1H), 3.37 (s, 3H), 2.38-2.31 (m, 1H), 2.09-1.34 (m, 13H), 1.08-1.02 (m, 1H); MS (ES-) *m/z* 486.2, 488.2 (M-1).

[01724] EXAMPLE 323

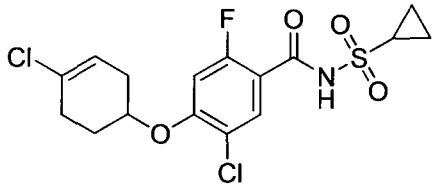
[01725] Synthesis of 4-(adamantan-2-yl(hydroxy)methyl)-3- chloro-*N*-(methylsulfonyl)benzamide



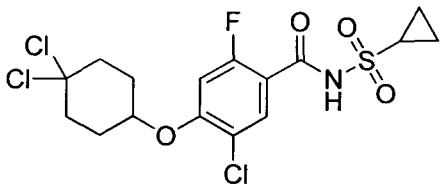
[01726] To a mixture of 4-(adamantan-2-yl(benzyloxy)methyl)-3- chloro-*N*-(methylsulfonyl)benzamide (0.290 g, 0.59 mmol) in methanol (10 mL) and ethyl acetate (10 mL) was added palladium on carbon (10%, 50 mg) and the reaction mixture was stirred for 2 hours under an atmosphere of hydrogen. The reaction mixture was filtered over diatomaceous earth, and the filtrate was concentrated *in vacuo*. The obtained residue was purified by reverse-phase preparative HPLC to afford the title compound as a colorless solid (0.065 g, 28%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 7.94 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.1 Hz, 1H), 5.45 (br s, 1H), 5.23-5.14 (m, 1H), 3.31 (s, 3H), 2.37-2.27 (m, 1H), 2.11-1.35 (m, 13H), 1.11-1.01 (m, 1H); MS (ES-) *m/z* 396.2, 398.2 (M-1).

[01727] EXAMPLE 324

[01728] Synthesis of 5-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide



[01729] And 5-chloro-*N*-(cyclopropylsulfonyl)-4- ((4,4-dichlorocyclohexyl)oxy)-2-fluorobenzamide



[01730] To a mixture of 4,4-dichlorocyclohexanone (WO2011/006794A1) (5.20 g, 31.10 mmol) in anhydrous methanol (100 mL) was added sodium borohydride (2.35 g, 62.20 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. Concentration *in vacuo* yielded a residue which was re-dissolved in methanol (50 mL) and concentrated again *in vacuo*. The

residue was then purified by silica gel column chromatography using 10-100% ethyl acetate in hexanes as eluent to afford 4,4-dichlorocyclohexanol as an orange solid (1.90 g, 36%).

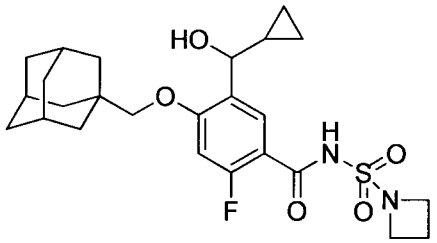
[01731] To a mixture of 4,4-dichlorocyclohexanol (1.60 g, 9.50 mmol) in anhydrous dimethyl sulfoxide (15 mL) was added cesium carbonate (6.20 g, 19.00 mmol) and the reaction mixture was heated at 70 °C for 16 hours. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate (200 mL); washed with water (2 × 20 mL) and brine (10 mL); dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-100% ethyl acetate in hexanes as eluent to afford a mixture of *tert*-butyl 2-chloro-4-((4,4-dichlorocyclohexyl)oxy)- 5-fluorobenzoate and *tert*-butyl 2-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-fluorobenzoate as a colorless oil.

[01732] To a mixture of *tert*-butyl 2-chloro-4-((4,4-dichlorocyclohexyl)oxy)- 5-fluorobenzoate and *tert*-butyl 2-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-fluorobenzoate (0.58 g) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred at ambient temperature for 2 hours. Concentration *in vacuo* gave a mixture of 2-chloro-4-((4,4-dichlorocyclohexyl)oxy)-5-fluorobenzoic acid and 2-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-fluorobenzoic acid as a solid residue which was used without further purification.

[01733] Following the procedure as described in Example 299 Step 2 and making variations as required to replace azetidine-1-sulfonamide with cyclopropanesulfonamide and to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with a mixture of 2-chloro-4-((4,4-dichlorocyclohexyl)oxy)-5-fluorobenzoic acid and 2-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-fluorobenzoic acid, the title compounds were obtained as pure and separated materials after purification by reverse-phase preparative HPLC. Data for the first fraction, 5-chloro-4-((4-chlorocyclohex-3-en-1-yl)oxy)-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide, colorless solid (0.01 g, 2%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 12.7Hz, 1H), 5.79-5.74 (m, 1H), 4.97-4.89 (m, 1H), 3.12-3.01 (m, 1H), 2.50-2.23 (m, 4H), 2.04-1.94 (m, 2H), 1.17-1.08 (m, 4H); MS (ES-) *m/z* 406.1, 408.1 (M-1). Data for second fraction, 5-chloro-*N*-(cyclopropylsulfonyl)-4-((4,4-dichlorocyclohexyl)oxy)-2-fluorobenzamide, colorless solid (0.062 g, 10%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 12.6 Hz, 1H), 4.91-4.82 (m, 1H), 3.12-3.02 (m, 1H), 2.53-2.39 (m, 4H), 2.07-1.85 (m, 4H), 1.16-1.09 (m, 4H); MS (ES+) *m/z* 444.0, 446.0, 448.0 (M+1).

[01734] EXAMPLE 325

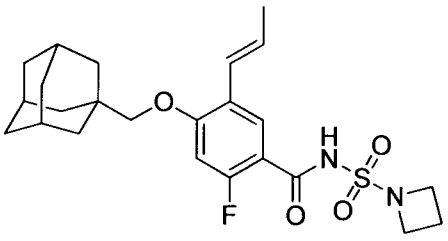
[01735] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-(cyclopropyl(hydroxy)-methyl)-2-fluorobenzamide



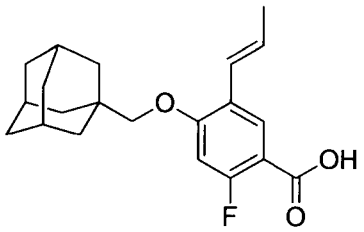
[01736] To a mixture of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1- ylsulfonyl)-2-fluoro-5-iodobenzamide (0.20 g, 0.36 mmol) in anhydrous tetrahydrofuran (5 mL) was added isopropylmagnesium chloride lithium chloride complex (1.3 M solution in tetrahydrofuran, 0.69 mL, 0.90 mmol) at -40 °C. After 1 hour at -40 °C, additional isopropylmagnesium chloride lithium chloride complex (1.3 M solution in tetrahydrofuran, 0.28 mL, 0.36 mmol) was added, the reaction mixture warmed to 0 °C, and stirred for 1 hour. Cyclopropanecarboxaldehyde (excess) was then added, the reaction mixture was allowed to warm to ambient temperature, and stirred for 16 hours. After quenched with 1 N hydrochloric acid (3 mL), the mixture was diluted with ethyl acetate (50 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, and filtered. Concentration of the filtrate *in vacuo* gave a residue which was purified by reverse-phase preparative HPLC to afford the title compound as a colorless solid (0.015 g, 8%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (br s, 1H), 7.73 (d, J = 8.7 Hz, 1H), 6.91 (d, J = 12.7 Hz, 1H), 5.14 (d, J = 4.5 Hz, 1H), 4.61 (dd, J = 5.7, 4.9 Hz, 1H), 4.02-3.90 (m, 4H), 3.66 (d, J = 9.3 Hz, 1H), 3.56 (d, J = 9.3 Hz, 1H), 2.19-2.06 (m, 2H), 2.03-1.95 (m, 3H), 1.76-1.57 (m, 12H), 1.18-1.05 (m, 1H), 0.40-0.25 (m, 4H); MS (ES-) *m/z* 491.2 (M-1).

[01737] EXAMPLE 326

[01738] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzamide

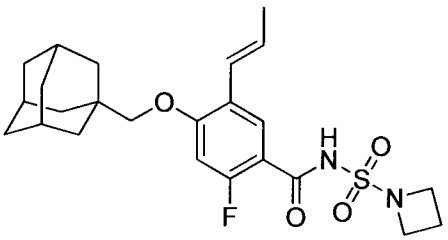


[01739] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)- prop-1-en-1-yl)benzoic acid



[01740] Following the procedure as described in Example 305/306 Step 2 and making variations as required to replace *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-5-chloro- 2-fluorobenzoate with *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-chloro-2-fluorobenzoate and to replace cyclopropylboronic acid with *trans*-propenylboronic acid pinacol ester, *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzoate was obtained as a yellowish oil (1.20 g, quant.). To a mixture of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzoate (0.30 g, 0.75 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred at ambient temperature for 2 hours. Concentration *in vacuo* gave the title compound as a yellowish residue (0.260 g, quant.) which was used without further purification: MS (ES+) *m/z* 345.2 (M+1).

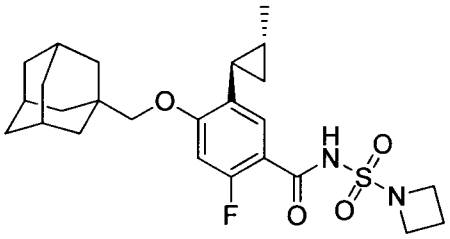
[01741] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzamide



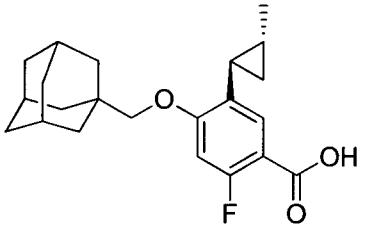
[01742] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzoic acid and purification by reverse-phase preparative HPLC, the title compound was obtained as a colorless solid (0.078 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (br s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 12.9 Hz, 1H), 6.57 (dd, J = 16.0, 1.5 Hz, 1H), 6.38 (qd, J = 15.8, 6.4 Hz, 1H), 4.05 (t, J = 7.7 Hz, 4H), 3.65 (s, 2H), 2.23–2.11 (m, 2H), 2.05–1.95 (m, 3H), 1.87 (dd, J = 6.4, 1.2 Hz, 3H), 1.78–1.60 (m, 12H); MS (ES-) *m/z* 461.2 (M-1).

[01743] EXAMPLE 327

[01744] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(*trans*-2-methylcyclopropyl)benzamide

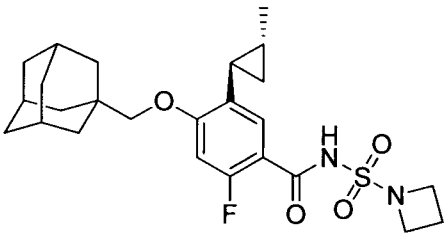


[01745] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(*trans*-2-methylcyclopropyl)benzoic acid



[01746] To a mixture of diethylzinc (1.0 M solution in heptane, 6.75 mL, 6.75 mmol) in anhydrous dichloromethane (2 mL) was added a solution of trifluoroacetic acid (0.52 mL, 6.80 mmol) in anhydrous dichloromethane (3 mL) at 0 °C and the reaction mixture was stirred for 10 minutes at 0 °C. A solution of diiodomethane (0.54 mL, 6.75 mmol) in dichloromethane (2 mL) was added to the reaction mixture at 0 °C and stirring was continued for 10 minutes at 0 °C. To the reaction mixture was then added a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)-prop-1-en-1-yl)benzoate (0.90 g, 2.25 mmol) in anhydrous dichloromethane (3 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. After addition of 1 N hydrochloric acid (10 mL), the mixture was diluted with dichloromethane (100 mL). The organic phase was dried over anhydrous sodium sulfate and filtered. Concentration of the filtrate gave a residue which was purified by reverse-phase preparative HPLC to afford the title compound as an off-white solid (0.086 g, 11%): MS (ES-) *m/z* 357.3 (M-1).

[01747] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-2-fluoro-5-(*trans*-2-methylcyclopropyl)benzamide

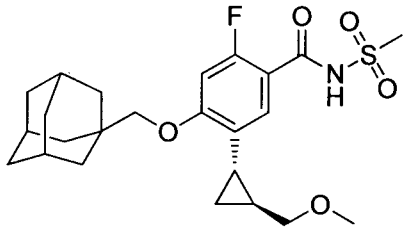


[01748] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-

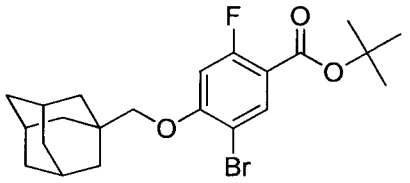
1-ylmethoxy)-2-fluoro-5-(*trans*-2-methylcyclopropyl)benzoic acid, the title compound was obtained as a colorless solid (0.055 g, 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (br s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 13.0 Hz, 1H), 4.04 (t, J = 7.7 Hz, 4H), 3.67 (d, J = 9.4 Hz, 1H), 3.61 (d, J = 9.4 Hz, 1H), 2.22-2.09 (m, 2H), 2.04-1.95 (m, 3H), 1.78-1.59 (m, 12H), 1.22 (d, J = 7.8 Hz, 3H), 1.16-1.14 (m, 1H), 1.05-0.96 (m, 1H), 0.97-0.82 (m, 1H), 0.70-0.62 (m, 1H); MS (ES-) *m/z* 475.3 (M-1).

[01749] EXAMPLE 328

[01750] Synthesis of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(*trans*-2-(methoxymethyl)-cyclopropyl)-*N*-(methylsulfonyl)benzamide

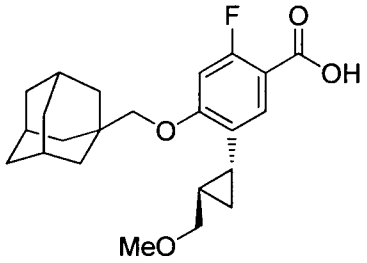


[01751] Step 1. Preparation of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5- bromo-2-fluorobenzoate



[01752] A mixture of 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluorobenzoic acid (6.97 g, 18.19 mmol), di-*tert*-butyl dicarbonate (7.94 g, 36.38 mmol), and 4-dimethylaminopyridine (0.44 g, 3.64 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with 1 M hydrochloric acid (2 x 100 mL), brine (2 x 100 mL), and dried over anhydrous sodium sulfate. Filtration and concentration under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-50% ethyl acetate in hexanes as eluent followed by trituration in methanol to provide the title compound as a colorless solid (1.50 g, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 12.3 Hz, 1H), 3.53 (s, 2H), 2.05-1.97 (m, 3H), 1.79–1.63 (m, 12H, 1.55 (s, 9H); MS (ES+) *m/z* 439.02, 441.04 (M+1).

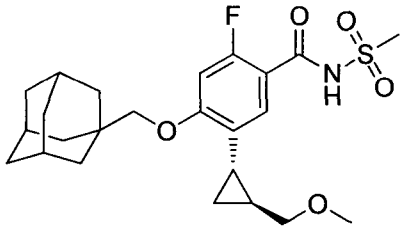
[01753] Step 2. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(*trans*-2- (methoxymethyl)-cyclopropyl)benzoic acid



[01754] To a mixture of *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-bromo-2-fluorobenzoate (1.00 g, 2.28 mmol) in dioxane (15 mL) was added tetrakis(triphenylphosphine)palladium (0.263 g, 0.23 mmol), (*E*)-3-methoxy-1-propen-1-ylboronic acid, pinacol ester (1.36 g, 6.80 mmol), and 2 M sodium bicarbonate solution (4.5 mL, 9.00 mmol). The reaction mixture was thoroughly degassed by passing argon through it and then heated in a microwave at 150 °C for 30 minutes. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (100 mL) and filtered over anhydrous sodium sulfate. Removal of all volatiles under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-50% ethyl acetate in hexanes as eluent to afford *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)- 3-methoxyprop- 1-en-1-yl)benzoate (1.17 g, quant.) as a colorless oil.

[01755] To a mixture of diethylzinc (1.0 M solution in heptane, 6.8 mL, 6.8 mmol) in anhydrous dichloromethane (3 mL) was added a solution of trifluoroacetic acid (0.52 mL, 6.80 mmol) in anhydrous dichloromethane (2 mL) at 0 °C and the reaction mixture was stirred for 15 minutes at 0 °C. A solution of diiodomethane (0.55 mL, 6.82 mmol) in anhydrous dichloromethane (2 mL) was added to the reaction mixture at 0 °C and stirring was continued for 15 minutes at 0 °C. To the reaction mixture was then added a solution of *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluoro-5-((*E*)- 3-methoxyprop-1-en-1-yl)benzoate (1.17 g) in dichloromethane (3 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. After addition of saturated sodium bicarbonate solution (10 mL), the mixture was diluted with dichloromethane (100 mL). The organic phase was washed with brine (10 mL) dried over sodium sulfate and filtered. Concentration of the filtrate *in vacuo* gave a residue which was treated with trifluoroacetic acid (2 mL) in dichloromethane (20 mL) for 1 hour. After evaporation of all volatiles under reduced pressure, the residue was triturated with diethyl ether (5 mL) to afford the title compound as a colorless solid (0.554 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 12.9 Hz, 1H), 3.57 (dd, J = 10.3, 6.3 Hz, 1H), 3.55–3.48 (m, 2H), 3.37 (s, 3H), 3.36–3.29 (dd, J = 10.3, 7.2 Hz, 1H), 2.07–1.99 (m, 3H), 1.93 (td, J = 8.9, 5.1, 5.1 Hz, 1H), 1.82–1.62 (m, 12H), 1.38–1.25 (m, 1H), 1.00 (td, J = 8.4, 5.3, 5.3 Hz, 1H), 0.89 (td, J = 8.8, 5.2, 5.2 Hz, 1H).

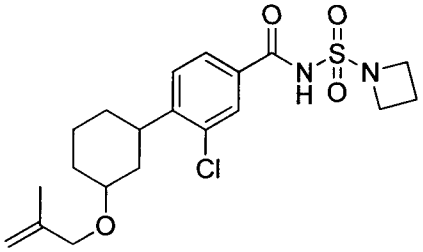
[01756] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(*trans*-2- (methoxymethyl)-cyclopropyl)-*N*-(methylsulfonyl)benzamide



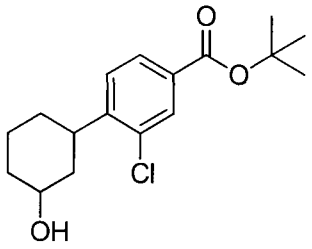
[01757] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 4-(adamantan-1-ylmethoxy)-2-fluoro-5-(*trans*-2-(methoxymethyl)cyclopropyl)benzoic acid and to replace azetidine-1-sulfonamide with methanesulfonamide, the title compound was obtained as a colorless solid (0.0678 g, quant.): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (br s, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 13.1 Hz, 1H), 3.66 (d, J = 9.4 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.46-3.35 (m, 2H), 3.34 (s, 3H), 3.25 (s, 3H), 2.04-1.89 (m, 4H), 1.78-1.61 (m, 12H), 1.34-1.22 (m, 1H), 1.06-0.97 (m, 1H), 0.90-0.81 (m, 1H); MS (ES-) *m/z* 464.2 (M-1).

[01758] EXAMPLE 329

[01759] Synthesis of *N*-(azetidin-1-ylsulfonyl)-3-chloro-4-(3-((2-methylallyl)oxy)-cyclohexyl)-benzamide



[01760] Step 1. Preparation of *tert*-butyl 3-chloro-4-(3-hydroxycyclohexyl)benzoate

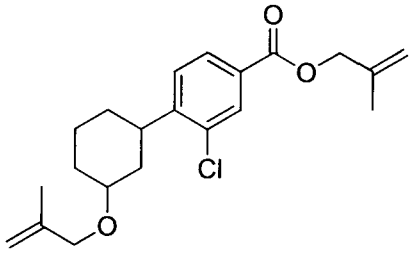


[01761] To a mixture of *tert*-butyl 4-bromo-3-chlorobenzoate (4.00 g, 13.70 mmol) in anhydrous tetrahydrofuran (40 mL) was added isopropylmagnesium chloride (1.3 M solution in tetrahydrofuran, 13.8 mL, 17.9 mmol) at -40 °C. The reaction mixture was warmed to ambient temperature and stirred for 1 hour. To this mixture was then added a solution of copper(I) cyanide (1.35 g, 15.10 mmol) and lithium chloride (1.28 g, 30.20 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred for 10 minutes at 0 °C, then 2-cyclohexen-1one (1.32 mL, 13.70 mmol) and trimethylsilyl chloride (1.74 mL,

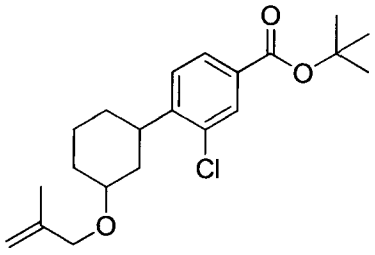
13.80 mmol) were added to the reaction mixture. The reaction mixture was stirred for 16 hours at ambient temperature. After addition of 1 N hydrochloric acid (10 mL), the reaction mixture was stirred for 1 hour and then diluted with ethyl acetate (150 mL). The organic phase was washed with 1 N hydrochloric acid (10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate gave *tert*-butyl 3-chloro-4-(3-oxocyclohexyl)benzoate as an oil (4.20 g, quant.), which was used without further purification.

[01762] To a mixture of *tert*-butyl 3-chloro-4-(3-oxocyclohexyl)benzoate in anhydrous methanol (50 mL) was added sodium borobydride (1.04 g, 27.40 mmol) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C, after which saturated ammonium chloride solution (10 mL) was added. All volatiles were evaporated under reduced pressure, and the residue was partitioned between ethyl acetate (200 mL) and water (20 mL). The organic phase was washed with brine (10 mL), dried over sodium sulfate, and filtered. Concentration under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-40% ethyl acetate in hexanes as eluent to afford the title compound as colorless oil (2.24 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 1H), 7.84-7.79 (m, 1H), 7.32-7.27 (m, 1H), 3.85-3.69 (m, 1H), 3.16-3.03 (m, 1H), 2.19-2.04 (m, 2H), 1.96-1.77 (m, 2H), 1.63-1.18 (m, 14H); MS (ES+) *m/z* 255.2, 257.1 (M-55).

[01763] Step 2. Preparation of 2-methylallyl 3-chloro-4-(3-((2-methylallyl)- oxy)cyclohexyl)benzoate



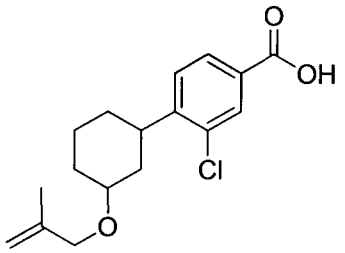
[01764] and *tert*-butyl 3-chloro-4-(3-hydroxycyclohexyl)benzoate



[01765] To a mixture of *tert*-butyl 3-chloro-4-(3-hydroxycyclohexyl)benzoate (1.10 g, 3.54 mmol) in anhydrous dimethylformamide (15 mL) was added sodium hydride (60% dispersion in mineral oil, 0.17 g, 4.25 mmol) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C before 3-bromo- 2-methylpropene (0.71 mL, 7.08 mmol) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. After addition of saturated ammonium chloride solution (10 mL) and ethyl acetate (150 mL), the organic phase was washed with water (3 × 10 mL), brine (10 mL), and dried over sodium

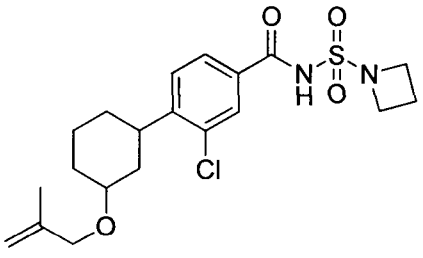
sulfate. Filtration and concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-15% ethyl acetate in hexanes as eluent to afford the title compounds as pure and separated materials. Data for the first fraction, *tert*-butyl 3-chloro-4-(3-hydroxycyclohexyl)benzoate, colorless oil (0.278 g, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.88 (m, 1H), 7.83-7.77 (m, 1H), 7.31-7.25 (m, 1H), 4.94 (s, 1H), 4.83 (s, 1H), 3.91 (s, 2H), 3.46-3.33 (m, 1H), 3.11-2.95 (m, 1H), 2.24-2.05 (m, 2H), 1.93-1.74 (m, 2H), 1.70 (s, 3H), 1.54 (s, 9H), 1.47-1.14 (m, 4H). Data for the second fraction, 2-methylallyl 3-chloro-4-(3-((2-methylallyl)oxy)cyclohexyl)benzoate, colorless oil (0.153 g, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–8.00 (m, 1H), 7.91–7.85 (m, 1H), 7.36–7.30 (m, 1H), 5.03 (s, 1H), 4.95 (s, 2H), 4.84 (s, 2H), 4.70 (s, 1H), 3.92 (s, 2H), 3.47-3.34 (m, 1H), 3.12-2.99 (m, 1H), 2.26-2.08 (m, 2H), 1.95-1.82 (m, 2H), 1.82 (s, 3H), 1.71 (s, 3H), 1.48-1.17 (m, 4H).

[01766] Step 3. Preparation of 3-chloro-4-(3-((2-methylallyl)oxy)cyclohexyl)benzoic acid



[01767] To a mixture of 2-methylallyl 3-chloro-4-(3-((2-methylallyl)oxy)cyclohexyl)- benzoate (0.153 g, 0.42 mmol) in tetrahydrofuran (2 mL) and methanol (1 mL) was added a solution of lithium hydroxide monohydrate (0.088 g, 2.10 mmol) in water (2 mL). The reaction mixture was stirred for 16 hours at ambient temperature. After dilution with dichloromethane (50 mL), 1N hydrochloric acid (5 mL) was added. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The title compound was obtained as a colorless solid (0.130 g, quant.) and used without further purification: MS (ES-) *m/z* 307.2, 309.2 (M-1).

[01768] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-3-chloro-4-(3-((2-methylallyl)oxy)cyclohexyl)benzamide



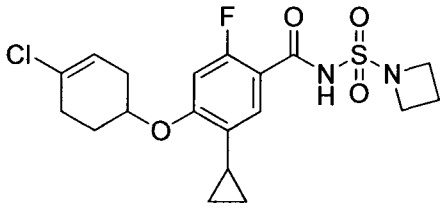
[01769]

[01770] Following the procedure as described in Example 299 Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with 3-chloro-4-(3-((2-methylallyl)oxy)cyclohexyl)benzoic acid, the title compound was obtained as a colorless solid (0.114 g, 64%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (br s, 1H), 8.02 (d, J = 1.1 Hz, 1H), 7.90 (dd,

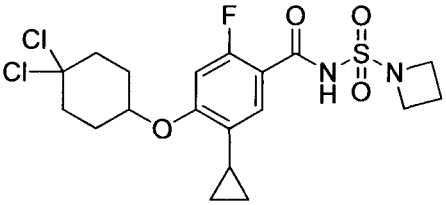
J = 8.2, 1.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 4.93 (s, 1H), 4.82 (s, 1H), 4.06 (t, J = 7.7 Hz, 4H), 3.89 (s, 2H), 3.46–3.29 (m, 1H), 3.09–2.95 (m, 1H), 2.24–2.02 (m, 4H), 1.92–1.81 (m, 1H), 1.77-1.68 (m, 1H), 1.67 (s, 3H), 1.49–1.12 (m, 4H); MS (ES+) *m/z* 427.1 (M+1).

[01771] EXAMPLE 330/331

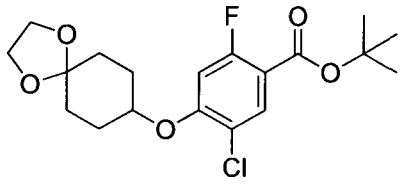
[01772] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-cyclopropyl-2-fluorobenzamide



[01773] and *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)-oxy)-2-fluorobenzamide

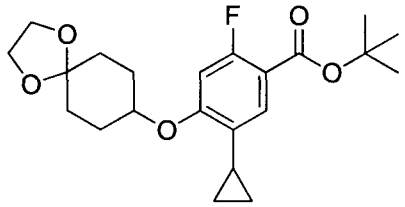


[01774] Step 1. Preparation of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)- 5-chloro-2-fluorobenzoate



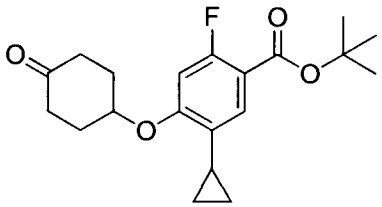
[01775] To a mixture of 1,4-dioxaspiro[4.5]decan-8-ol (2.40 g, 15.20 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (3.78 g, 15.20 mmol) in anhydrous dimethyl sulfoxide was added potassium *tert*-butoxide (2.56 g, 22.80 mmol) and the reaction mixture was stirred for 16 hours at ambient temperature. After dilution with ethyl acetate (200 mL), the organic phase was washed with water (3 × 10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate under reduced pressure gave a residue which was purified by silica gel column chromatography using 0-30% ethyl acetate in hexanes as eluent to afford the title compound as a colorless oil (0.709 g, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 12.3 Hz, 1H), 4.53–4.46 (m, 1H), 3.97–3.92 (m, 4H), 2.04–1.58 (m, 8H), 1.55 (d, J = 1.0 Hz, 9H).

[01776] Step 2. Preparation of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)-5-cyclopropyl-2-fluorobenzoate



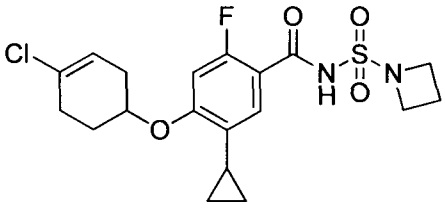
[01777] Following the procedure as described in Example 305/306, Step 2 and making variations as required to replace *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy) -5-chloro-2-fluorobenzoate with *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)- 5-chloro-2-fluorobenzoate, the title compound was obtained as a yellowish oil (0.557 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 13.2 Hz, 1H), 4.54-4.39 (m, 1H), 3.97-3.93 (m, 4H), 2.07-1.58 (m, 9H), 1.55 (s, 9H), 0.92–0.82 (m, 2H), 0.63-0.57 (m, 2H).

[01778] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4- oxocyclohexyl)oxy)benzoate

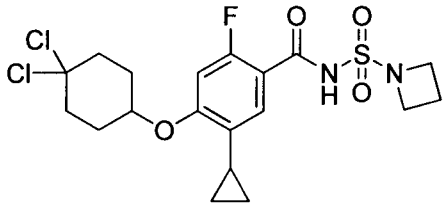


[01779] To a mixture of *tert*-butyl 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)-5-cyclopropyl- 2-fluorobenzoate (0.557 g, 1.44 mmol) in tetrahydrofuran (1.5 mL) and water (1.5 mL) was added trifluoroacetic acid (0.5 mL) and the reaction mixture was stirred for 16 hours at ambient temperature. After addition of dichloromethane (100 mL), the mixture was washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. Filtration and concentration of the filtrate *in vacuo* gave a residue which was purified by silica gel column chromatography using 0-30% ethyl acetate in hexanes as eluent to afford the title compound as a colorless oil (0.300 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 12.6 Hz, 1H), 4.80-4.71 (m, 1H), 2.77-2.62 (m, 2H), 2.42-2.27 (m, 4H), 2.14-1.93 (m, 3H), 1.56 (s, 9H), 0.94-0.84 (m, 2H), 0.65–0.60 (m, 2H).

[01780] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex- 3-en-1-yl)oxy)-5-cyclopropyl-2-fluorobenzamide



[01781] and *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)oxy)-2-fluorobenzamide

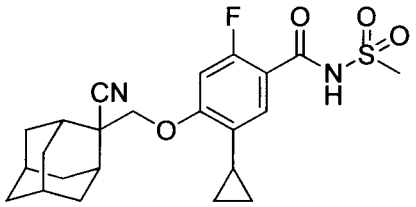


[01782] To a mixture of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-oxocyclohexyl)oxy)- benzoate (0.30 g, 0.86 mmol) in anhydrous toluene (10 mL) was added phosphorus pentachloride (0.537 g, 2.58 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. After cooling to 0 °C, water (10 mL) was added to the reaction mixture followed by anhydrous dichloromethane (100 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a mixture of 4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-cyclopropyl-4-((4,4-dichlorocyclohexyl)oxy)-2-fluorobenzoic acid as a colorless oil (0.40 g, quant.), which was used without further purification.

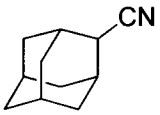
[01783] Following the procedure as described in Example 299, Step 2 and making variations as required to replace 4-(adamantan-1-ylmethoxy)-2-fluoro-5-iodobenzoic acid with a mixture of 4-((4-chlorocyclohex-3-en-1-yl)oxy)-5-cyclopropyl-2-fluorobenzoic acid and 5-cyclopropyl-4-((4,4-dichlorocyclohexyl)oxy)-2-fluorobenzoic acid, the title compounds were obtained as pure and separated materials after purification by reverse-phase preparative HPLC. Data for the first fraction, *N*-(azetidin-1-ylsulfonyl)-4-((4-chlorocyclohex-3-en-1-yl)oxy)- 5-cyclopropyl-2-fluorobenzamide, colorless solid (0.011 g, 3%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 7.15 (d, J = 7.0 Hz, 1H), 7.11 (d, J = 11.8 Hz, 1H), 5.79-5.75 (m, 1H), 4.91-4.83 (m, 1H), 4.03 (t, J = 7.7 Hz, 4H), 2.48-2.39 (m, 4H), 2.36-2.24 (m, 1H), 2.21-2.09 (m, 2H), 2.05-1.92 (m, 2H), 0.91-0.82 (m, 2H), 0.70-0.64 (m, 2H); MS (ES-) *m/z* 427.2, 429.3 (M-1). Data for second fraction, *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((4,4-dichlorocyclohexyl)- oxy)-2-fluorobenzamide), colorless solid (0.058 g, 15%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 12.9 Hz, 1H), 4.78 (br s, 1H), 4.12–3.87 (m, 4H), 2.60–2.38 (m, 4H), 2.22–1.85 (m, 7H), 0.96–0.84 (m, 2H), 0.69–0.62 (m, 2H); MS (ES-) *m/z* 463.2, 465.2 (M-1).

[01784] EXAMPLE 332

[01785] Synthesis of 4-((-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide

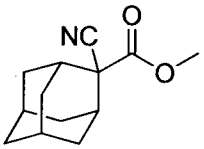


[01786] Step 1. Preparation of adamantane-2-carbonitrile



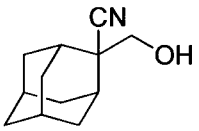
[01787] To a solution of 2-adamantanone (6.24 g, 41.50 mmol) in anhydrous 1,2-dimethoxyethane (150 mL) was added anhydrous ethanol (3.6 mL, 61.00 mmol) and *p*-toluenesulfonylmethyl isocyanide (10.0 g, 51.50 mmol) at 0 °C. Potassium *tert*-butoxide (7.03 g, 62.70 mmol) was added in portions over 35 minutes under nitrogen atmosphere. The reaction mixture was stirred for 3.5 hours at ambient temperature. The mixture was filtered through a pad of diatomaceous earth that was washed with ethyl acetate (200 mL). The filtrate was washed with brine (2 × 200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of 0-10% ethyl acetate in hexanes to afford the title compound (5.16 g, 77% yield) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 1H), 2.15-2.11 (m, 4H), 1.92-1.85 (m, 4H), 1.75-1.70 (m, 6H); MS (ES-) *m/z* 162.2 (M + 1).

[01788] Step 2. Preparation of methyl 2-cyanoadamantane-2-carboxylate



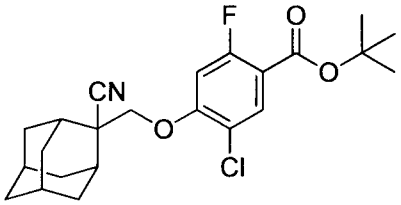
[01789] To a solution of adamantane-2-carbonitrile (1.17 g, 7.23 mmol) in anhydrous tetrahydrofuran (75 mL) was added lithium diisopropylamide (2.0 M solution in tetrahydrofuran, ethylbenzene and heptanes, 5.4 mL, 11.00 mmol) -78 °C. The reaction mixture was stirred under a nitrogen atmosphere for 30 minutes, and then methyl chloroformate (0.83 mL, 11.00 mmol) was added. After 1.5 hour, the reaction was warmed to ambient temperature and quenched by addition of 1 M hydrochloric acid (150 mL). The mixture was diluted with ethyl acetate (200 mL), washed with 1 M hydrochloric acid (150 mL), brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of 0-10% ethyl acetate in hexanes to afford the title compound as a colorless oil (0.95 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 2.51 (br s, 2H), 2.23-2.18 (m, 2H), 1.93-1.91 (m, 1H), 1.85-1.71 (m, 9H); MS (ES-) *m/z* 220.2 (M + 1).

[01790] Step 3. Preparation of 2-(hydroxymethyl)adamantane-2-carbonitrile



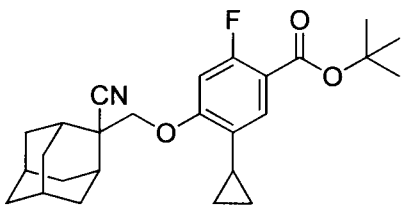
[01791] To a solution of methyl 2-cyanoadamantane-2-carboxylate (1.33 g, 6.07 mmol) in anhydrous tetrahydrofuran (50 mL) was added anhydrous methanol (0.49 mL, 12 mmol) and lithium borohydride (4.0 M solution in tetrahydrofuran, 3.0 mL, 12 mmol). The mixture was heated to reflux under a nitrogen atmosphere for 7 hours, cooled to ambient temperature and quenched with careful addition of saturated aqueous ammonium chloride (10 mL). The mixture was diluted with ethyl acetate (200 mL), washed with a 3:1 mixture of saturated aqueous ammonium chloride and water (2 × 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound (1.06 g, 91%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 2H), 2.24-2.20 (m, 2H), 2.10-1.97 (m, 4H), 1.86-1.84 (m, 5H), 1.73-1.64 (m, 4H); MS (ES-) *m/z* 192.2 (M + 1).

[01792] Step 4. Preparation of *tert*-butyl 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluorobenzoate



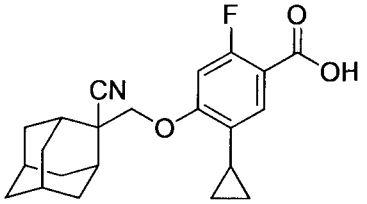
[01793] To a solution of 2-(hydroxymethyl)adamantane-2-carbonitrile (0.369 g, 1.93 mmol) and *tert*-butyl-5-chloro-2,4-difluorobenzoate (0.96 g, 3.86 mmol) in dimethylsulfoxide (30 mL) was added potassium *tert*-butoxide (0.42 g, 3.76 mmol). The mixture was stirred at ambient temperature for 0.5 hour, then diluted with ethyl acetate (200 mL). The organic layer was washed with 1 M hydrochloric acid (200 mL), brine (2 × 150 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of 0-30% ethyl acetate in hexanes to afford the title compound (0.64 g, 79% yield) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 11.7 Hz, 1H), 4.29 (s, 2H), 2.36-2.30 (m, 4H), 2.02 (br s, 1H), 1.91-1.74 (m, 9H), 1.56 (s, 9H); MS (ES-) *m/z* 420.1 (M + 1).

[01794] Step 5. Preparation of *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate



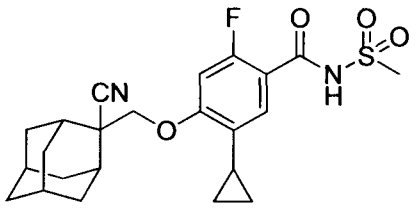
[01795] To a solution of *tert*-butyl 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)- 2-fluorobenzoate (1.12 g, 2.66 mmol) in toluene (40 mL) was added water (5 mL), cyclopropylboronic acid (1.32 g, 15.40 mmol), tribasic potassium phosphate (1.69 g, 7.94 mmol), tricyclohexylphosphine tetrafluoroborate (0.658 g, 2.13 mmol) and palladium(II) acetate trimer (0.25 g, 1.09 mmol) while degassing with argon. The reaction mixture was heated to reflux under an argon atmosphere for 16 hours, cooled to ambient temperature. The mixture was filtered through a pad of diatomaceous earth that was washed with ethyl acetate (100 mL). The filtrate was diluted with ethyl acetate (100 mL), washed with a 3:1 mixture of saturated aqueous ammonium chloride and water (150 mL), brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of 0-10% ethyl acetate in hexanes to afford the title compound as a yellow foamy solid (1.01 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 12.2 Hz, 1H), 4.26 (s, 2H), 2.36-2.27 (m, 4H), 2.08-2.00 (m, 2H), 1.91-1.87 (m, 5H), 1.78-1.73 (m, 4H), 1.56 (s, 9H), 0.94-0.87 (m, 2H), 0.64-0.59 (m, 2H); MS (ES-) *m/z* 426.1 (M + 1).

[01796] Step 6. Preparation of 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid



[01797] To a solution of *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoate (0.38 g, 0.88 mmol) in dichloromethane (30 mL) trifluoroacetic acid (10 mL) was added. The solution was stirred at ambient temperature for 16 houres and concentrated *in vacuo* to give the title compound as a pale yellow solid (0.33 g, quant.): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.86 (br s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 13.0 Hz, 1H), 4.45 (s, 2H), 2.16-1.78 (m, 11H), 1.70-1.60 (m, 4H), 0.90-0.84 (m, 2H), 0.60-0.55 (m, 2H); MS (ES-) *m/z* 468.2 (M - 1).

[01798] Step 7. Preparation of 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide

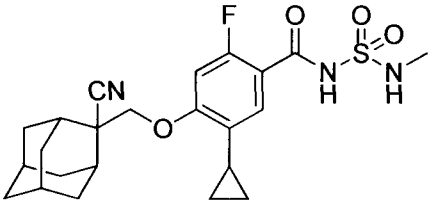


[01799] To a solution of 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl -2-fluorobenzoic acid (0.17 g, 0.45 mmol) in anhydrous tetrahydrofuran (5 mL) was added 1,1'-carbonyldiimidazole (0.15 g, 0.89 mmol). The reaction solution was heated to reflux under a nitrogen atmosphere for 15 minutes and cooled to ambient temperature. To this reaction solution methanesulfonamide (0.10 g, 1.05 mmol) and

1,8-diazabicyclo[5.4.0]undec-7-ene (0.22 mL, 1.40 mmol) was added. The mixture was stirred at ambient temperature for 2.5 hours, then diluted with ethyl acetate (10 mL), washed with 1 M hydrochloric acid (2 × 10 mL) and brine (2 × 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound as a colorless powder (0.019 g, 10%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (br s, 1H), 7.16-7.12 (m, 2H), 4.46 (s, 2H), 3.31 (s, 3H), 2.16-1.79 (m, 11H), 1.70-1.61 (m, 4H), 0.90-0.84 (m, 2H), 0.69-0.64 (m, 2H); MS (ES-) *m/z* 445.2 (M - 1).

[01800] EXAMPLE 333

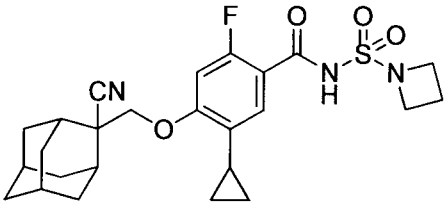
[01801] Synthesis of 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(N-methylsulfamoyl)benzamide



[01802] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with methyl sulfamide, the title compound was obtained following trituration with diethyl ether (10 mL) as a colorless powder (0.11 g, 51%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.57-7.55 (m, 1H), 7.14-7.07 (m, 2H), 4.45 (s, 2H), 2.51 (d, J = 4.7 Hz, 3H), 2.16-1.79 (m, 11H), 1.70-1.61 (m, 4H), 0.89-0.83 (m, 2H), 0.68-0.63 (m, 2H); MS (ES-) *m/z* 460.2 (M - 1).

[01803] EXAMPLE 334

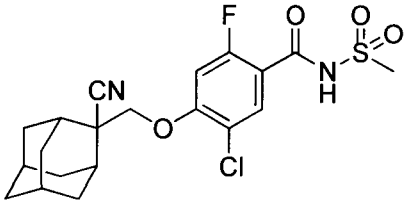
[01804] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzamide



[01805] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained following trituration with diethyl ether (10 mL) as a colorless powder (0.052 g, 22%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (br, s, 1H), 7.17-7.12 (m, 2H), 4.46 (s, 2H), 4.02 (t, J = 7.7 Hz, 4H), 2.16-1.93 (m, 10H), 1.87-1.79 (m, 3H), 1.70-1.61 (m, 4H), 0.90-0.84 (m, 2H), 0.70-0.64 (m, 2H); MS (ES-) *m/z* 486.2 (M - 1).

[01806] EXAMPLE 335

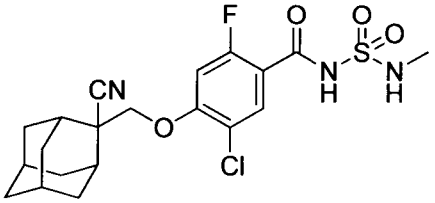
[01807] Synthesis of 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[01808] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)- 2-fluorobenzoic acid, the title compound was obtained following trituration with diethyl ether (10 mL) as a colorless powder (0.19 g, 77%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 12.3 Hz, 1H), 4.54 (s, 2H), 3.32 (s, 3H), 2.15-2.07 (m, 4H), 1.97-1.78 (m, 6H), 1.70-1.60 (m, 4H); MS (ES-) *m/z* 439.1, 441.1 (M - 1).

[01809] EXAMPLE 336

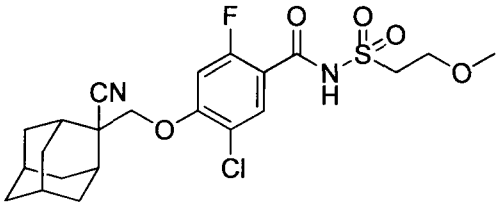
[01810] Synthesis of 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluoro-*N*-(*N*-methylsulfamoyl)benzamide



[01811] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with methyl sulfamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following trituration with diethyl ether (10 mL) as a colorless powder (0.073 g, 52%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.73-7.66 (m, 2H), 7.34 (d, J = 12.2 Hz, 1H), 4.54 (s, 2H), 2.53 (d, J = 4.6 Hz, 3H), 2.15-2.07 (m, 4H), 1.97-1.78 (m, 6H), 1.70-1.60 (m, 4H); MS (ES-) *m/z* 454.1, 456.1 (M - 1).

[01812] EXAMPLE 337

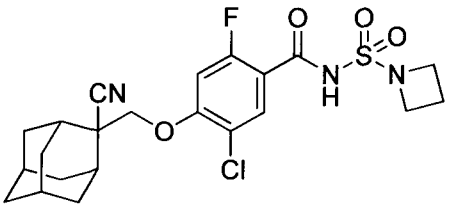
[01813] Synthesis of 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluoro-*N*-((2-methoxyethyl)sulfonyl)benzamide



[01814] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with 2-methoxyethanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following trituration with a 5:1 mixture of hexanes in diethyl ether (10 mL) as a colorless powder (0.094 g, 63%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 12.2 Hz, 1H), 4.54 (s, 2H), 3.70 (s, 4H), 3.18 (s, 3H), 2.15-2.07 (m, 4H), 1.97-1.78 (m, 6H), 1.70-1.60 (m, 4H); MS (ES-) *m/z* 483.2, 485.2 (M - 1).

[01815] EXAMPLE 338

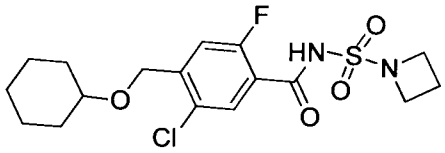
[01816] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-((2-cyanoadamantan-2-yl)-methoxy)-2-fluorobenzamide



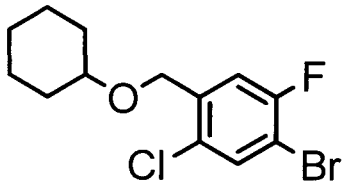
[01817] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyano-adamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((2-cyanoadamantan-2-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 18%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.41 (d, J = 12.2 Hz, 1H), 4.54 (s, 2H), 4.02 (t, J = 7.7, 7.7 Hz, 4H), 2.17-2.07 (m, 6H), 1.98-1.78 (m, 6H), 1.70-1.61 (m, 4H); MS (ES-) *m/z* 480.1, 482.1 (M - 1).

[01818] EXAMPLE 339

[01819] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4- ((cyclohexyloxy)methyl)-2-fluorobenzamide

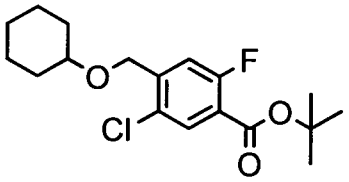


[01820] Step 1. Preparation of 1-bromo-5-chloro-4-(cyclohexyloxymethyl)- 2-fluorobenzene



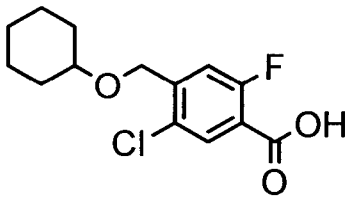
[01821] To a solution of (4-bromo-2-chloro-5-fluorophenyl)methanol (5.00 g, 21.00 mmol) in dichloromethane (150 mL) was added phosphorous tribromide (8.53 g, 31.50 mmol) at 0 °C. The clear reaction solution was stirred at the same temperature for 1 hour, then at an ambient temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to dryness to obtain viscous yellow liquid which was added to a stirred mixture of cyclohexanol (1.68 g, 16.80 mmol) and sodium hydride (60% dispersion in mineral oil, 1.93 g, 21.00 mmol,) in *N*, *N*-dimethylformamide (15 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 16 hours and quenched with addition of saturated ammonium chloride (100 mL). The organic layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered the solid. The filtrate was concentrated *in vacuo* to dryness. The residue was purified by flash column chromatography with ethyl acetate in hexanes (10%) to afford the title compound (2.60 g, 38%) as a viscous liquid: MS (ES+) *m/z* 320.9, 318.9 (M + 1).

[01822] Step 2. Preparation of *tert*-butyl 5-chloro-4-(cyclohexyloxymethyl)- 2-fluorobenzoate



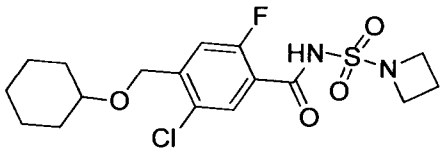
[01823] To a solution of 1-bromo-5-chloro-4-(cyclohexyloxymethyl)-2-fluorobenzene (2.60 g, 8.13 mmol) in tetrahydrofuran (100 mL) was added a solution of *iso*propylmagnesium chloride (8.1 mL, 16.3 mmol, 2.0 M solution in tetrahydrofuran) at 0 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then added a solution of di-*tert*-butyl dicarbonate (3.54 g, 16.3 mmol) in tetrahydrofuran (10 mL). The mixture was stirred at an ambient temperature for 16 h, then diluted with ethyl acetate (100 mL) and washed with saturated ammonium chloride (3 x 50 mL), brine (3 x 50 mL), dried over anhydrous sodium sulfate and filtered the solid. The filtrate was concentrated *in vacuo* to dryness to afford the title compound (1.86 g, 65%) as a pale yellow gum which was directly subjected to next step without any further purification: MS (ES+) *m/z* 342.1, 344.1 (M + 23).

[01824] Step 3. 5-chloro-4-(cyclohexyloxymethyl)-2-fluorobenzoic acid



[01825] To a solution of *tert*-butyl 5-chloro-4-(cyclohexyloxymethyl)-2-fluorobenzoate (1.86 g, 5.43 mmol) in dichloromethane (50 mL) was added trifluoroacetic acid (20 mL). The reaction solution was stirred at ambient temperature for 3 hours, then concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with brine (3 x 25 mL), dried over anhydrous sodium sulfate, filtered the solid. The filtrate was concentrated *in vacuo* to dryness to afford the title compound (0.50 g, 32% crude yield) which was subjected to next step without any further purification: MS (ES+) *m/z* 287.0, 285.0 (M + 1).

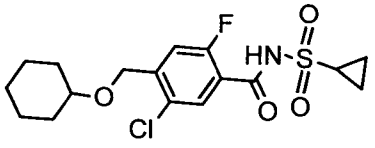
[01826] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-((cyclohexyloxy)-methyl)-2-fluorobenzamide



[01827] To a solution of 5-chloro-4-(cyclohexyloxymethyl)-2-fluorobenzoic acid (0.12 g, 0.42mmol) in anhydrous tetrahydrofuran (5 mL) was added 1,1'-carbonyldiimidazole (0.088 g, 0.55 mmol). The reaction solution was heated to reflux under a nitrogen atmosphere for 15 minutes and cooled to ambient temperature. To this solution was added azetidine-1-sulfonamide (0.086 g, 63 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.16 g, 1.05 mmol). The mixture was stirred at ambient temperature for 16 hours, then diluted with ethyl acetate (15 mL) and washed with 1 M hydrochloric acid (2 × 10 mL) and brine (2 × 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by reverse-phase preparative HPLC to afford the title compound (0.005 g, 3%) as a colorless powder: MS (ES+) *m/z* 405.1, 407.1 (M + H)

[01828] Example 340

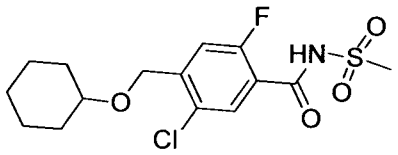
[01829] Synthesis of 5-chloro-4-((cyclohexyloxy)methyl)-N- (cyclopropylsulfonyl)-2-fluorobenzamide



[01830] Following the procedure as described in Example 339 Step 4 and making non-critical variations to replace azetidine-1-sulfonamide with cyclopropanesulfonamide, the title compound was obtained (0.005 g, 3%) as a colourless solid: MS (ES+) *m/z* 390.1, 392.1 (M + H).

[01831] Example 341

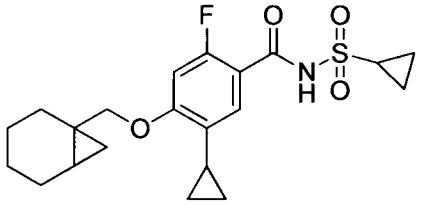
[01832] Synthesis of 5-chloro-4-((cyclohexyloxy)methyl)-2-fluoro- N-(methylsulfonyl)benzamide



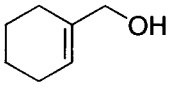
[01833] Following the procedure as described in Example 339 Step 4 and making non-critical variations to replace azetidine-1-sulfonamide with methane sulfonamide, the title compound was obtained (0.005 g, 3% yield) as a colorless solid: MS (ES+) *m/z* 364.1, 366.1 (M + H).

[01834] EXAMPLE 342

[01835] Synthesis of 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide

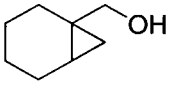


[01836] Step 1. Preparation of cyclohexenylmethanol



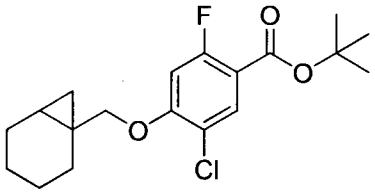
[01837] To a mixture of lithium aluminum hydride (9.19 g, 248 mmol) in anhydrous diethyl ether was added a solution of methyl cyclohex-1-enecarboxylate (11.60 g, 82.80 mmol) at 0 °C over 20 minutes. The reaction mixture was stirred at the same temperature for another 25 minutes then poured onto ice in diethyl ether (500 mL). The mixture was stirred at ambient temperature for 16 hours and filtered the solid. The filtrate was concentrated *in vacuo* to dryness and the residue was purified by column chromatography with ethyl acetate in hexanes (30%) to afford the title compound as a colorless liquid (8.76 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64-5.58 (m, 1H), 3.90 (s, 2H), 3.35 (d, J = 6.4 Hz, 1H), 2.00-1.90 (m, 4H), 1.72-1.50 (m, 4H).

[01838] Step 2. Preparation of bicyclo[4.1.0]heptan-1-ylmethanol



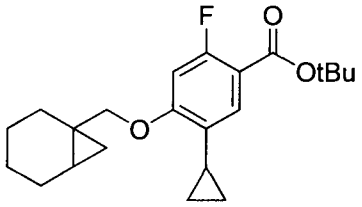
[01839] To a solution of diethyl zinc (1.0 M in hexanes, 15.70 mL, 15.70 mmol) in anhydrous dichloromethane (15.7 mL) was added dropwise trifluoroacetic acid (1.79 g in 15.7 mL anhydrous dichloromethane, 15.7 mmol) at 0 °C over 20 minutes. The reaction mixture was stirred at the same temperature for 20 minutes, and then added dropwise a solution of diidomethane (4.20 g, 15.70 mmol) in anhydrous dichloromethane (15.7 mL) at 0 °C over 10 minutes. The reaction mixture was further stirred at the same temperature for another 20 minutes. To this reaction mixture was added a solution of cyclohexenylmethanol (1.07 g, 6.30 mmol) in anhydrous dichloromethane (17 mL) at 0 °C. The resulting mixture was warmed to ambient temperature and further stirred for 1 hour. The mixture was quenched with a saturated solution of ammonium chloride (50 mL) and separated the organic layer. The aqueous layer was extracted with dichloromethane (15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with diethyl ether in hexanes (30%) to afford the title compound as colorless oil (1.00 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32 (dd, J = 10.9, 10.9 Hz, 2H), 1.90-1.80 (m, 2H), 1.75-1.55 (m, 2H), 1.34 (br, s, 1H), 1.26-1.14 (m, 2H), 0.45 (dd, J = 9.3, 4.5 Hz, 1H), 0.24 (t, J = 4.9 Hz, 1H).

[01840] Step 3. Preparation of *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-chloro-2-fluorobenzoate



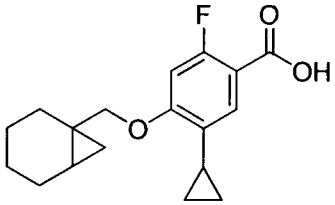
[01841] A mixture of bicyclo[4.1.0]heptan-1-ylmethanol (0.86 g, 6.80 mmol), *tert*-butyl 5-chloro-2,4-difluorobenzoate (1.69 g, 6.80 mmol) and cesium carbonate (4.40 g, 13.7 mmol) in anhydrous dimethylsulfoxide (15 mL) was heated at 100 °C under nitrogen for 16 hours. The reaction mixture was filtered through a pad of diatomaceous earth and rinsed with ethyl acetate (100 mL). The organic layer was washed with 1.0 M hydrochloric acid (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a mixture of hexanes in ethyl acetate (9:1) to afford the title compound as a white solid (1.30 g, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 18.4 Hz, 1H), 6.54 (d, J = 12.20 Hz, 1H), 3.81 (d, J = 9.1 Hz, 1H), 3.68 (d, J = 9.1 Hz, 1H), 1.98-1.79 (m, 4H), 1.39-1.29 (m, 3H), 1.56 (s, 9H), 1.02-0.94 (m , 1H), 0.89-0.83 (m, 1H), 0.67-0.62 (m, 1H), 0.40-0.37 (m, 1H); MS (ES+) *m/z* 377.2, 379.2 (M + 23).

[01842] Step 4. Preparation of *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5- cyclopropyl-2-fluorobenzoate



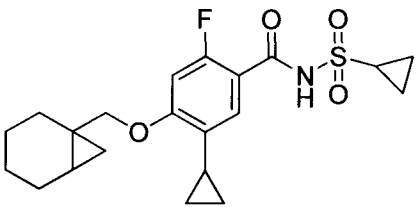
[01843] In a sealed tube containing *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-chloro-2-fluorobenzoate (1.30 g, 3.70 mmol), cyclopropylboronic acid (0.47 g, 5.50 mmol), tricyclohexylphosphine tetrafluoroborate (0.27 g, 0.74 mmol) and palladium acetate (0.08 g, 0.37 mmol) and potassium phosphate (3.13 g, 14.8 mmol) in toluene (20 mL) and water (2.0 mL) was bubbled with a nitrogen atmosphere for 10 minutes. The reaction mixture was heated to 140 °C for 6 hours and cooled to ambient temperature. The solvent was concentrated *in vacuo* to dryness. The crude residue was purified column chromatography (10% gradient ethyl acetate in hexanes) afforded the title compound as a colorless solid (1.00 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.5 Hz, 1H), 6.42 (d, J = 12.8 Hz, 1H), 3.61 (d, J = 9.1 Hz, 1H), 3.78 (d, J = 9.1 Hz, 1H), 1.96-1.52 (m, 7H), 1.55 (s, 9H), 0.92-0.82 (m, 4H), 0.67-0.61 (m, 4H), 0.38-0.33 (m, 1H).

[01844] Step 5. Preparation of 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)- 5-cyclopropyl-2-fluorobenzoic acid



[01845] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate, the title compound was obtained as a colorless solid (0.30 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.5 Hz, 1H), 6.42 (d, J = 12.8 Hz, 1H), 3.61 (d, J = 9.1 Hz, 1H), 3.78 (d, J = 9.1 Hz, 1H), 1.96-1.52 (m, 7H), 0.92-0.82 (m, 4H), 0.67-0.61 (m, 4H), 0.38-0.33 (m, 1H).

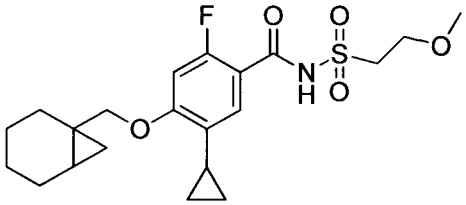
[01846] Step 6. Preparation of 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide (XPC127406)



[01847] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with cyclopropanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (br s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 13.1 Hz, 1H), 3.92-3.73 (m, 2H), 3.13-3.01 (m, 1H), 2.10-1.96 (m, 1H), 1.95-1.49 (m, 4H), 1.40-1.03 (m, 8H), 1.03-0.93 (m, 1H), 0.94-0.82 (m, 2H), 0.77-0.59 (m, 3H), 0.41-0.32 (m, 1H); MS (ES+) *m/z* 408.1 (M + 1)

[01848] Example 343

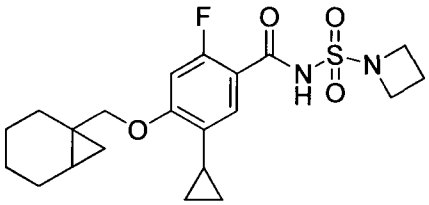
[01849] Synthesis of 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-2-fluoro-N-((2-methoxyethyl)sulfonyl)benzamide



[01850] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with 2-methoxyethanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[4.1.0]-heptan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.035 g, 39%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 13.1 Hz, 1H), 3.72 (s, 3H), 3.36-3.31 (m, 4H), 3.22-3.19 (m, 2H), 2.12-1.96 (m, 1H), 1.95-1.67 (m, 3H), 1.66-1.50 (m, 1H), 1.44-1.04 (m, 4H), 1.02-0.82 (m, 3H), 0.76-0.55 (m, 3H), 0.43-0.30 (m, 1H); MS (ES+) *m/z* 426.1 (M + 1)

[01851] Example 344

[01852] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide

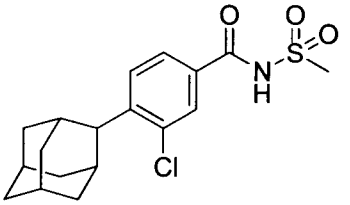


[01853] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was

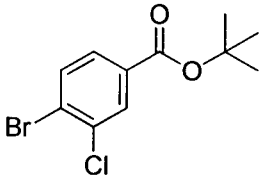
obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br, s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 13.0 Hz, 1H), 4.09-3.98 (m, 4H), 3.92-3.84 (m, 1H), 3.80-3.74 (m, 1H), 2.23-1.98 (m, 3H), 1.96-1.68 (m, 3H), 1.66-1.52 (m, 1H), 1.34-1.13 (m, 4H), 1.04-0.83 (m, 3H), 0.75-0.60 (m, 3H), 0.41-0.33 (m, 1H); MS (ES+) *m/z* 423.1 (M + 1)

[01854] EXAMPLE 345

[01855] Synthesis of 4-(adamantan-2-yl)-3-chloro-*N*-(methylsulfonyl)benzamide

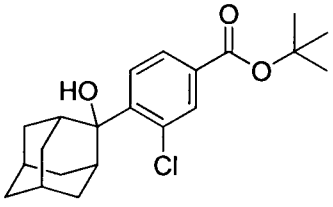


[01856] Step 1. Preparation of *tert*-butyl 4-bromo-3-chlorobenzoate



[01857] To a solution of 4-bromo-3-chlorobenzoic acid (30.0 g, 127.00 mmol) in anhydrous tetrahydrofuran (500 mL) was added di-*tert*-butyl dicarbonate (62.60 g, 277.00 mmol) and *N*,*N*-dimethylaminopyridine (3.11 g, 25.50 mmol). The mixture was stirred at ambient temperature for 18 hours and concentrated *in vacuo* to half its volume. The mixture was diluted with ethyl acetate (500 mL), washed with 1 M hydrochloric acid (2 × 500 mL), saturated aqueous sodium bicarbonate (2 × 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound as a colorless oil that was used without further purification (31.20 g, 84%).

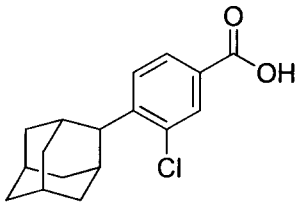
[01858] Step 2. Preparation of *tert*-butyl 3-chloro-4-(2-hydroxyadamantan-2-yl)benzoate



[01859] To a cold (-40 °C) solution of 2-adamantanone (1.50 g, 10.00 mmol) and *tert*-butyl 4-bromo-3-chlorobenzoate (2.45 g, 10.00 mmol) in anhydrous tetrahydrofuran (120 mL) was added *iso*propylmagnesium chloride lithium chloride complex (1.3 M solution in tetrahydrofuran, 10 mL, 13 mmol). The reaction mixture was warm to ambient temperature over 2 hours and heated to reflux for 1 hour. After cooling to ambient temperature, the mixture was quenched with saturated aqueous ammonium chloride (10 mL), diluted with ethyl acetate (200 mL), washed with saturated aqueous ammonium chloride (2 × 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to dryness. The

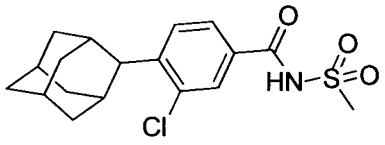
residue was purified by column chromatography with a gradient of 0-30% ethyl acetate in hexanes to afford the title compound as a colorless gum (0.58 g, 16%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 1.4 Hz, 1H), 7.84 (dd, J = 1.3, 8.3 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 2.90 (br s, 3H), 2.51-2.47 (m, 2H), 1.87-1.65 (m, 10H), 1.59 (s, 9H); MS (ES-) *m/z* 363.2, 365.1 (M + 1).

[01860] Step 3. Preparation of 4-(adamantan-2-yl)-3-chlorobenzoic acid



[01861] To a solution of *tert*-butyl 3-chloro-4-(2-hydroxyadamantan-2-yl)benzoate (0.581 g, 1.60 mmol) in dichloromethane (50 mL) was added triethylsilane (5 mL) and trifluoroacetic acid (5 mL). The reaction mixture was stirred at ambient temperature for 20 hours and the reaction solution was concentrated *in vacuo* to dryness. The residue was triturated with hexanes (15 mL) to afford the title compound (0.27 g, 57%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 1.6, 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 3.33 (s, 1H), 2.33 (br s, 2H), 1.98-1.92 (m, 8H), 1.78 (s, 2H), 1.70-1.66 (m, 2H) (OH not observed); MS (ES-) *m/z* 289.3, 291.3 (M - 1).

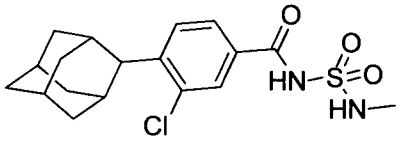
[01862] Step 4. Preparation of 4-((adamantan-2-yl)-3-chloro-*N*- (methylsulfonyl)benzamide



[01863] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-2-yl)-3-chlorobenzoic acid, the title compound was obtained following trituration with hexanes (10 mL) as a colorless solid (0.11 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.86-7.85 (m, 1H), 7.73-7.66 (m, 2H), 3.43 (s, 3H), 3.31 (s, 1H), 2.31 (s, 2H), 2.03-1.90 (m, 8H), 1.78 (s, 2H), 1.70-1.65 (m, 2H); MS (ES-) *m/z* 368.2, 366.2 (M - 1).

[01864] EXAMPLE 346

[01865] Synthesis of 4-(adamantan-2-yl)-3-chloro-*N*-(*N*-methylsulfamoyl)benzamide

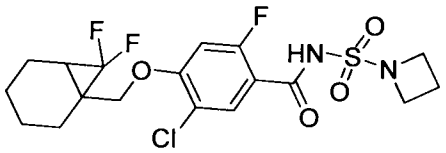


[01866] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with methyl sulfamide and to replace

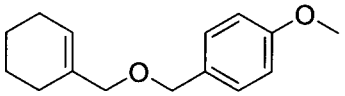
4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-2-yl)-3-chlorobenzoic acid, the title compound was obtained following trituration with hexanes as a colorless solid (0.11 g, 66%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H) 7.98-7.97 (m, 1H), 7.88-7.85 (m, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.64-7.60 (m, 1H), 3.22 (s, 1H), 2.50 (d, J = 4.4 Hz, 3H), 2.23 (s, 2H), 1.95-1.85 (m, 8H), 1.72 (s, 2H), 1.63-1.59 (m, 2H); MS (ES-) *m/z* 381.2, 383.2 (M - 1).

[01867] EXAMPLE 347

[01868] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4- ((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide

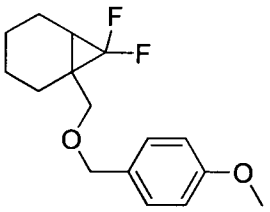


[01869] Step 1. Preparation of 1-((cyclohexenylmethoxy)methyl)-4-methoxybenzene



[01870] To a mixture of cyclohexenylmethanol (2.50 g, 22.3 mmol) in *N*, *N*-dimethylformamide (40 mL) and sodium hydride (60% dispersion in mineral oil, 0.89 g, 22.3 mmol) was added in portions at 0 °C. The reaction mixture was stirred for 0.5 hour, then added 1-(chloromethyl)-4-methoxybenzene (3.49 g, 22.3 mmol). The reaction mixture was stirred for another 0.5 hour and quenched with slow addition of water (50 mL). The organic layer was extracted with ethyl acetate (80 mL) and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate in hexanes (10%) to afford the title compound as a colorless liquid (3.50 g, 68%).

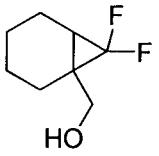
[01871] Step 2. Preparation of 7,7-difluoro-1-((4-methoxybenzyloxy)- methyl)bicyclo[4.1.0]heptane



[01872] To a microwave 5 mL vial was added 1-((cyclohexenylmethoxy)- methyl)-4-methoxybenzene (0.46 g, 2.00 mmol), trimethyl(2,2,2-trifluoroethyl)silane (0.57 g, 4.00 mmol) and sodium iodide (0.66 g, 4.40 mmol) in anhydrous tetrahydrofuran (1.0 mL). The vial was degassed with nitrogen and sealed. The reaction mixture was heated in the microwave reactor at 115 °C for 1 hour. The reaction vial was cooled and the TLC showed presence of starting material. To the reaction vial was added trimethyl(2,2,2-trifluoroethyl)silane (0.5 mL) and continued heating in the microwave at the same temperature for another 1 hour. The reaction was filtered, washed with ethyl acetate (10 ml). The filtrate

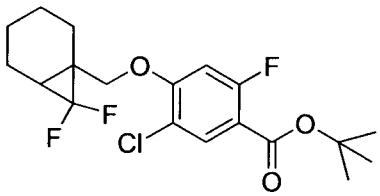
was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate in hexanes (20%) to afford the title compound as colourless liquid (0.45 g, 80%).

[01873] Step 3. Preparation of (7,7-difluorobicyclo[4.1.0]heptan-1-yl)methanol



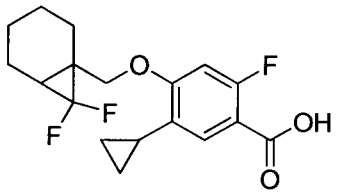
[01874] To a solution of 7,7-difluoro-1-((4-methoxybenzyloxy)methyl)- bicyclo[4.1.0]heptane (2.50 g, 8.90 mmol) in dichloromethane (20 mL) and water (3.0 mL) was added DDQ (3.00 g, 13.3 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 3 hour. Water (1.5 mL) was added followed by sodium sulfate (10 g). The resulting suspension was filtered through a short pad of silica gel column with ethyl acetate in hexanes (30%) to afford the title compound as a colorless liquid (0.90 g, 62%).

[01875] Step 4. Preparation of *tert*-butyl 5-chloro-4-((7,7- difluorobicyclo[4.1.0]heptan-1-yl)-methoxy)-2-fluorobenzoate



[01876] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with (7,7-difluorobicyclo[4.1.0]heptan- 1-yl)methanol, the title compound was obtained as a colorless gum (1.90 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 1H), 6.59 (d, J = 11.9 Hz, 1H), 4.05-3.88 (m, 2H), 2.00-1.67 (m, 4H), 1.58 (s, 9H), 1.44-1.29 (m, 5H); MS (ES+) *m/z* 341.1, 343.1 (M + 1).

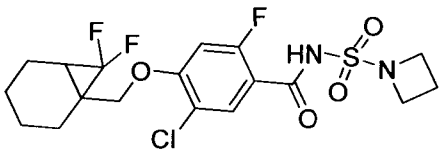
[01877] Step 5. Preparation of 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid



[01878] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]- heptan-1-yl)methoxy)-2-fluorobenzoate, the title compound was obtained (0.48 g, 80%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 1H),

6.51 (d, J = 12.6 Hz, 1H), 4.00-3.90 (m, 2H), 1.97-1.71 (m, 5H), 1.47-1.22 (m, 5H), 0.95-0.86 (m, 2H), 0.69-0.61 (m, 2H).

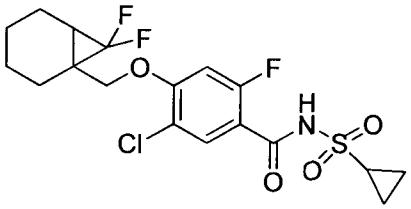
[01879] Step 6. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-((7,7- difluorobicyclo[4.1.0]-heptan-1-yl)methoxy)-2-fluorobenzamide



[01880] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.2 Hz, 1H), 4.28-4.20 (m, 1H), 4.14-3.97 (m, 4H), 2.25-2.08 (m, 2H), 1.98-1.52 (m, 6H), 1.39-1.16 (m, 4H); MS (ES+) *m/z* 459.1 (M + 1).

[01881] EXAMPLE 348

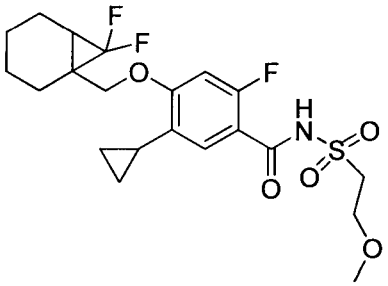
[01882] Synthesis of 5-chloro-*N*-(cyclopropylsulfonyl)-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide



[01883] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with cyclopropanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.045 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.08 (br, s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 4.31-4.03 (m, 2H), 3.14-2.97 (m, 1H), 1.99-1.57 (m, 5H), 1.38-1.18 (m, 4H), 1.18-1.06 (m, 4H); MS (ES+) *m/z* 444.1 (M + 1).

[01884] EXAMPLE 349

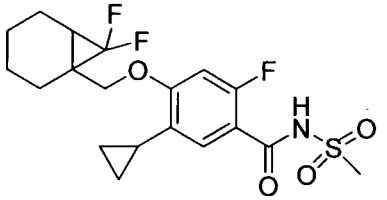
[01885] Synthesis of 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluoro-N-((2-methoxyethyl)sulfonyl)benzamide



[01886] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with 2-methoxyethanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.045 g, 74%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (br s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.8 Hz, 1H), 4.23-3.92 (m, 2H), 3.72 (s, 3H), 3.39-3.28 (m, 2H), 3.23-3.18 (m, 2H), 2.08-1.58 (m, 6H), 1.38-1.16 (m, 4H), 0.96-0.84 (m, 2H), 0.74-0.64 (m, 2H); MS (ES+) *m/z* 463.0 (M + 1)

[01887] EXAMPLE 350

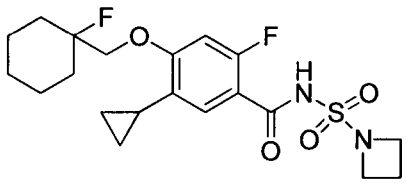
[01888] Synthesis of 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



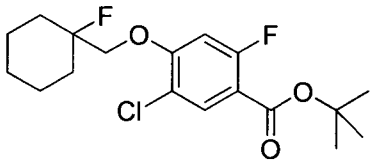
[01889] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.045 g, 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.9 Hz, 1H), 4.21-3.96 (m, 2H), 3.34 (s, 3H), 2.09-1.57 (m, 6H), 1.37-1.18 (m, 4H), 0.95-0.85 (m, 2H), 0.74-0.67 (m, 2H); MS (ES+) *m/z* 418.1 (M + 1).

[01890] EXAMPLE 351

[01891] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)methoxy)benzamide

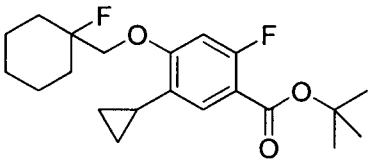


[01892] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((1-fluorocyclohexyl)- methoxy)-benzoate



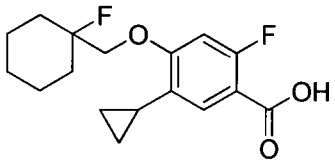
[01893] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with (1-fluorocyclohexyl)methanol, the title compound was obtained as a colorless gum (1.7 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 12.0 Hz, 1H), 3.98 (d, J = 17.6 Hz, 2H), 2.06-1.88 (m, 2H), 1.74-1.58 (m, 6H), 1.55 (s, 9H), 1.37-1.21 (m, 2H).

[01894] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)-methoxy)-benzoate



[01895] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-2-fluoro-4-((1-fluorocyclohexyl)methoxy)benzoate, the title compound was obtained as a colorless gum (1.60 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 12.5 Hz, 1H), 3.93 (d, J = 17.8 Hz, 2H), 2.04-1.87 (m, 4H), 1.73-1.55 (m, 6H), 1.54 (s, 9H), 1.36-1.20 (m, 3H), 0.91-0.80 (m, 2H), 0.65-0.57 (m, 2H).

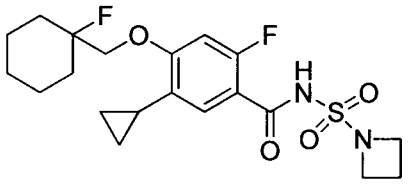
[01896] Step 3. Preparation of 5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)- methoxy)benzoic acid



[01897] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoate with *tert*-butyl

5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)- methoxy)benzoate, the title compound was obtained as a colorless solid (0.48 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 12.5 Hz, 1H), 3.98 (d, J = 17.9 Hz, 2H), 2.10-1.89 (m, 2H), 1.76-1.51 (m, 6H), 1.39-1.21 (m, 1H), 0.95-0.86 (m, 2H), 0.69-0.59 (m, 2H).

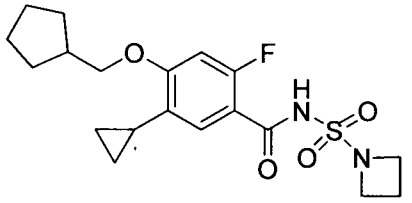
[01898] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)methoxy)benzamide



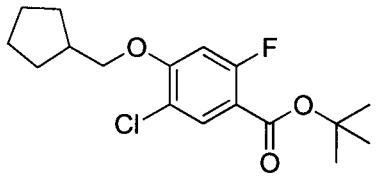
[01899] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methane sulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyano-adamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((1-fluorocyclohexyl)methoxy)benzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (br s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 4.16 (d, J = 8.3 Hz, 2H), 4.05 (dd, J = 8.3, 4H), 2.25-1.82 (m, 5H), 1.78-1.45 (m, 7H), 1.41-1.21 (m, 1H), 0.96-0.86 (m, 2H), 0.75-0.63 (m, 2H); MS (ES+) *m/z* 429.1 (M + 1)

[01900] EXAMPLE 352

[01901] Synthesis of *N*-(Azetidin-1-ylsulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide

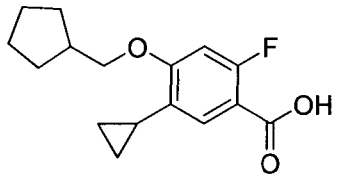


[01902] Step 1. Preparation of *tert*-butyl 5-chloro-4-(cyclopentylmethoxy)- 2-fluorobenzoate



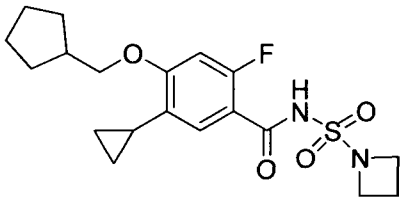
[01903] Following the procedure as described in Example 342 step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with cyclopentylmethanol, the title compound was obtained as a colorless gum (3.0 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 3.91-3.87 (m, 2H), 1.93-1.76 (m, 2H), 1.71-1.58 (m, 5H), 1.56 (s, 9H), 1.43-1.25 (m, 2H).

[01904] Step 2. Preparation of 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid



[01905] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoate *with tert*-butyl 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoate, the title compound was obtained as a colorless solid (3.0 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 7.72 Hz, 1H), 6.85 (d, J = 7.72 Hz, 1H), 3.92 (d, J = 6.78 Hz, 2H), 2.38-2.22 (m, 1H), 2.05-1.89 (m, 1H), 1.83-1.67 (m, 2H), 1.64-1.44 (m, 4H), 1.41-1.26 (m, 2H), 0.89-0.79 (m, 2H), 0.60-0.52 (m, 2H).

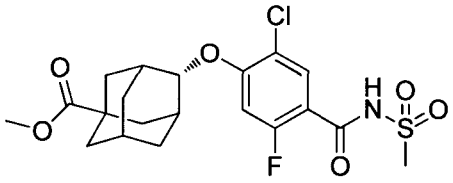
[01906] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide



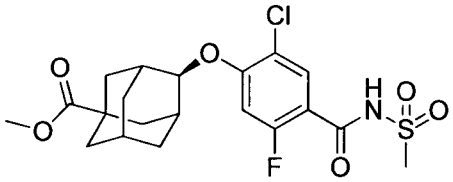
[01907] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.037 g, 37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 13.0 Hz, 1H), 4.15-3.89 (m, 6H), 2.42-2.28 (m, 1H), 2.23-2.10 (m, 2H), 2.08-1.96 (m, 1H), 1.87-1.71 (m, 2H), 1.70-1.46 (m, 4H), 1.45-1.28 (m, 2H), 0.95-0.82 (m, 2H), 0.73-0.64 (m, 2H); MS (ES+) *m/z* 397.2 (M + 1)

[01908] EXAMPLE 353/354

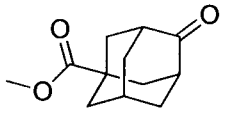
[01909] Synthesis of (1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)carbamoyl)-phenoxy)adamantane-1-carboxylate



[01910] And (1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)-carbamoyl)-phenoxy)adamantane-1-carboxylate

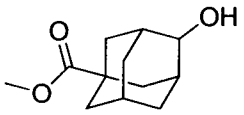


[01911] Step 1. Preparation of (1*s*,3*R*,5*S*,7*s*)-methyl 4-oxoadamantane-1-carboxylate



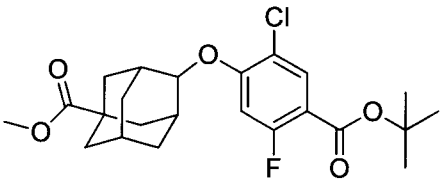
[01912] To a solution of (1*s*,3*R*,5*S*,7*s*)-4-oxoadamantane-1-carboxylic acid (10.00 g, 51.50 mmol) in methanol (100 mL) was added thionyl chloride (5.0 mL, 69.00 mmol). The mixture was heated to reflux for 4 hours, cooled to ambient temperature and concentrated *in vacuo* to dryness. The residue was dissolved in ethyl acetate (200 mL), washed with saturated aqueous sodium bicarbonate (2 × 150 mL), brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound as a colorless oil (8.60 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.57 (br s, 2H), 2.18-2.17 (m, 5H), 2.10-1.99 (m, 6H).

[01913] Step 2. Preparation of (1*s*,3*R*,5*S*,7*s*)-methyl 4-hydroxyadamantane-1-carboxylate



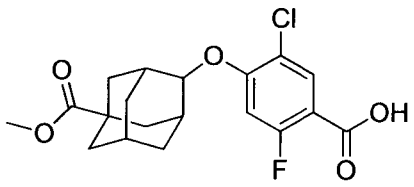
[01914] To a cold (0 °C) solution of (1*s*,3*R*,5*S*,7*s*)-methyl 4-oxoadamantane-1-carboxylate (4.50 g, 22.00 mmol) in methanol (50 mL) was added sodium borohydride (0.99 g, 26.00 mmol). The mixture was stirred for 2 hours and quenched with saturated aqueous ammonium chloride (10 mL). The mixture was diluted with ethyl acetate (200 mL), washed with saturated aqueous ammonium chloride (2 × 150 mL) and brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound as a colorless oil (2.51 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (br s, 0.5H), 3.82 (br s, 0.5H), 3.65 (s, 1.5H), 3.64 (s, 1.5H), 2.25-2.21 (m, 1H), 2.10-1.77 (m, 10.5H), 1.68-1.63 (m, 1.5H), 1.48-1.44 (m, 1H); MS (ES-) *m/z* 211.2 (M + 1).

[01915] Step 3. Preparation of (1*s*,3*R*,5*S*,7*s*)-methyl 4-(4-(*tert*-butoxycarbonyl)-2-chloro-5-fluorophenoxy)adamantane-1-carboxylate



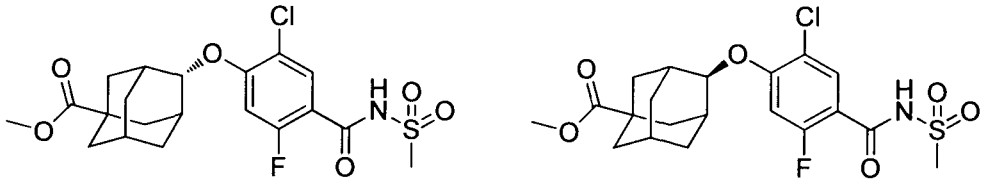
[01916] Following the procedure as described in Example 332 Step 4 and making non-critical variations to replace (1*r*,3*r*,5*r*,7*r*)-2-(hydroxymethyl)adamantane-2-carbonitrile with (1*s*,3*R*,5*S*,7*s*)-methyl 4-hydroxyadamantane-1-carboxylate, the title compound was obtained following purification by column chromatography with a 0-30% gradient of ethyl acetate in hexanes as a colorless oil and a ~1:1 mix of diastereomers (0.55 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 0.5H), 7.86 (d, *J* = 7.8 Hz, 0.5H), 6.61 (d, *J* = 12.3 Hz, 0.5H), 6.60 (d, *J* = 12.3 Hz, 0.5H), 4.47 (br s, 0.5H), 4.41 (br s, 0.5H), 3.66 (s, 1.5H), 3.65 (s, 1.5H), 2.32-2.15 (m, 4H), 2.07-1.86 (m, 7H), 1.76-1.69 (m, 2H), 1.55 (s, 9H); MS (ES-) *m/z* 439.2, 441.2 (M + 1).

[01917] Step 4. Preparation of 5-chloro-2-fluoro-4-(((1*R*,3*S*,5*s*,7*s*)-5-(methoxycarbonyl)-adamantan-2-yl)oxy)benzoic acid



[01918] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl- 2-fluorobenzoate with (1*s*,3*R*,5*S*,7*s*)-methyl 4-(4-(*tert*-butoxycarbonyl)-2-chloro-5-fluorophenoxy)adamantane-1-carboxylate, the title compound was obtained as a colorless solid as a ~1:1 mix of diastereomers (0.52 g, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.01 (m, 1H), 7.52 (br s, 1H), 6.68-6.63 (m, 1H), 4.51 (br s, 0.5H), 4.45 (br s, 0.5H), 3.68 (s, 1.5H), 3.66 (s, 1.5H), 2.32-2.16 (m, 4H), 2.08-1.74 (m, 8H), 1.55-1.51 (m, 1H); MS (ES-) *m/z* 383.0, 384.9 (M + 1).

[01919] Step 5. Preparation of (1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)-carbamoyl)phenoxy)adamantane-1-carboxylate and (1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)- carbamoyl)phenoxy)adamantane-1-carboxylate

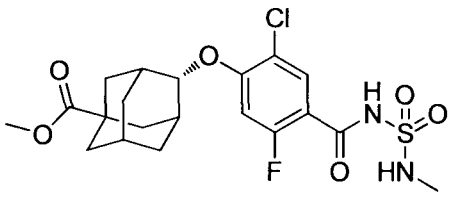


[01920] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2-fluoro-4-(((1*R*,3*S*,5*s*,7*s*)-5- (methoxycarbonyl)adamantan-2-yl)oxy)benzoic acid, the title compounds were obtained following purification by reverse-phase HPLC as pure and separated materials. Data for the first fraction, (1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro- 4-((methylsulfonyl)-carbamoyl)phenoxy)adamantane-1-carboxylate: a colorless solid (not weighed): ^{1}H NMR (300 MHz,

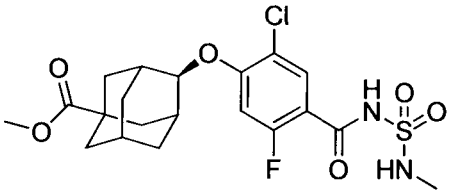
DMSO-d_6) δ 12.04 (br s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 12.7 Hz, 1H), 4.74 (br s, 1H), 3.55 (s, 3H), 3.31 (s, 3H), 2.16-2.08 (m, 4H), 1.93 (br s, 1H), 1.81-1.72 (m, 6H), 1.64 (br s, 1H), 1.60 (br s, 1H); MS (ES-) *m/z* 458.12, 460.10 (M - 1). Data for the second fraction, (1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((methylsulfonyl)- carbamoyl)phenoxy)adamantane-1-carboxylate : a colorless solid (not weighed): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (br s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 12.7 Hz, 1H), 4.81 (br s, 1H), 3.58 (s, 3H), 3.31 (s, 3H), 2.13 (br s, 3H), 2.01-1.74 (m, 8H), 1.45-1.43 (m, 2H); MS (ES-) *m/z* 458.1, 460.1 (M - 1).

[01921] EXAMPLES 355/356

[01922] Synthesis of (1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4- ((*N*-methylsulfamoyl)-carbamoyl)phenoxy)adamantane-1-carboxylate



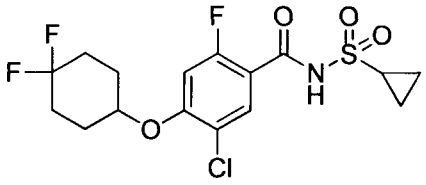
[01923] And (1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((*N*- methylsulfamoyl)carbamoyl)-phenoxy)adamantane-1-carboxylate



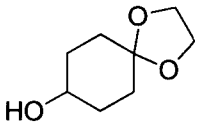
[01924] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with methyl sulfamide and to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2-fluoro-4-(((1*R*,3*S*,5*s*,7*s*)-5-(methoxycarbonyl)adamantan-2-yl)oxy)benzoic acid, the title compounds were obtained following purification by reverse-phase HPLC as pure and separated materials. Data for the first fraction, (1*s*,3*R*,4*r*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((*N*-methylsulfamoyl)carbamoyl)-phenoxy)adamantane-1-carboxylate: a colorless solid (not weighed): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.66-7.61 (m, 1H), 7.32 (d, J = 12.6 Hz, 1H), 4.73 (br s, 1H), 3.55 (s, 3H), 2.52 (d, J = 4.7 Hz, 3H), 2.16-2.08 (m, 4H), 1.93 (br s, 1H), 1.81-1.72 (m, 6H), 1.64 (br s, 1H), 1.60 (br s, 1H); MS (ES-) *m/z* 474.99, 476.98 (M - 1). Data for the second fraction, (1*s*,3*R*,4*s*,5*S*,7*s*)-methyl 4-(2-chloro-5-fluoro-4-((*N*-methylsulfamoyl)- carbamoyl)phenoxy)adamantane-1-carboxylate: a colorless solid (not weighed): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 7.71-7.63 (m, 2H), 7.34 (d, J = 12.5 Hz, 1H), 4.80 (br s, 1H), 3.58 (s, 3H), 2.52 (d, J = 4.7 Hz, 3H), 2.13 (br s, 2H), 2.01-1.74 (m, 9H), 1.47 (br s, 1H), 1.43 (br s, 1H); MS (ES-) *m/z* 474.9, 576.9 (M - 1).

[01925] EXAMPLE 357

[01926] Synthesis of 5-chloro-N-(cyclopropylsulfonyl)-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzamide

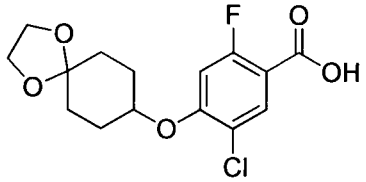


[01927] Step 1. Preparation of 1,4-dioxaspiro[4.5]decan-8-ol



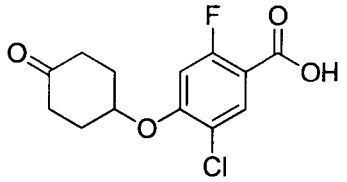
[01928] A solution of 1,4-dioxaspiro[4.5]decan-8-one (20.40 g, 130.60 mmol) in anhydrous methanol (200 mL) at 0°C, under nitrogen, was treated with sodium borohydride (2.50 g, 65.30 mmol), portion wise. The resulting mixture was stirred for 24 hours and concentrated *in vacuo* to dryness. The residue was diluted with ethyl acetate (300 mL), washed with 1 M hydrochloric acid (3 x 100 mL), brine (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a colorless oil (11.2 g, 51%): ^{1}H NMR (300 MHz, CDCl3) δ 3.91-3.87 (m, 4H), 3.79-3.70 (m, 1H), 1.92 (br s, 1H), 1.89-1.71 (m, 4H), 1.67-1.47 (m, 4H); MS (ES+) *m/z* 140.9 (M - OH).

[01929] Step 2. Preparation of 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)- 5-chloro-2-fluorobenzoic acid



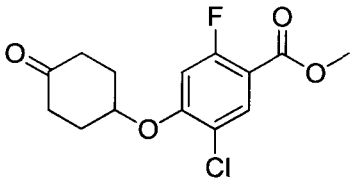
[01930] To a solution of 1,4-dioxaspiro[4.5]decan-8-ol (12.90 g, 81.50 mmol) in dimethylsulfoxide (800 mL) was added potassium *tert*-butoxide (21.00 g, 187.00 mmol). The reaction mixture was stirred at ambient temperature for 15 minutes under nitrogen. To this mixture was added 5-chloro-2,4-difluorobenzoic acid (15.70 g, 81.70 mmol). The mixture was stirred at ambient temperature for 3 days, after which it was split into two equal portions. Each portion was diluted with ethyl acetate (700 mL), washed with 1 M hydrochloric acid (700 mL), a 1:1 mixture of 1 M hydrochloric acid and brine (700 mL), and brine (700 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of a solution of 0.2% acetic acid in ethyl acetate and hexanes from 0-50%, to afford the title compound as a light yellow solid (5.66 g, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 6.69 (d, J = 12.4 Hz, 1H), 4.54-4.51 (m, 1H), 3.97-3.95 (m, 4H), 2.06-1.93 (m, 4H), 1.81-1.74 (m, 1H), 1.70-1.51 (m, 3H); MS (ES-) *m/z* 329.1, 331.1 (M - 1).

[01931] Step 3. Preparation of 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoic acid



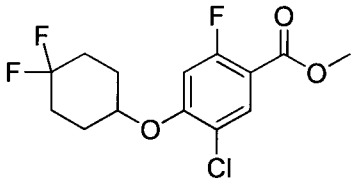
[01932] To a solution of 4-(1,4-dioxaspiro[4.5]decan-8-yloxy)-5-chloro-2-fluorobenzoic acid (2.95 g, 8.92 mmol) in acetone (100 mL) was added 3 M hydrochloric acid (80 mL). The solution was heated to reflux for 17 hours and cooled to ambient temperature. The mixture was diluted with brine (200 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of a solution of 0.2% acetic acid in ethyl acetate and hexanes from 0-50% to afford the title compound as a colorless solid (1.14 g, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 11.9 Hz, 1H), 4.82 (br s, 1H), 2.81-2.70 (m, 2H), 2.41-2.35 (m, 4H), 2.15-2.03 (m, 2H) (OH not observed); MS (ES-) *m/z* 285.1, 287.1 (M - 1).

[01933] Step 4. Preparation of methyl 5-chloro-2-fluoro-4-((4- oxocyclohexyl)oxy)benzoate



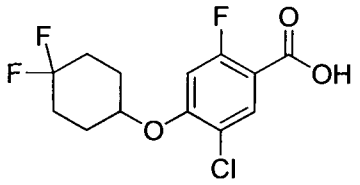
[01934] To a solution of 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoic acid (1.14 g, 3.98 mmol) in anhydrous tetrahydrofuran (50 mL) was added 1,1'-carbonyldiimidazole (1.71 g, 10.50 mmol). The solution was heated to reflux under a nitrogen atmosphere for 1 hours and cooled to ambient temperature. To the solution was added anhydrous methanol (0.49 mL, 12.00 mmol) and 1,8-diazabicycloundec-7-ene (1.8 mL, 12.00 mmol). The solution was stirred at ambient temperature for 4 h, then diluted with ethyl acetate (150 mL) and washed with 1 M hydrochloric acid (2 × 150 mL), brine (150 mL), dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford the title compound as an off-white solid (1.05 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 12.0 Hz, 1H), 4.79 (br s, 1H), 3.89 (s, 3H), 2.79-2.68 (m, 2H), 2.39-2.31 (m, 4H), 2.13-2.02 (m, 2H); MS (ES+) *m/z* 300.9 (M + 1).

[01935] Step 5. Preparation of methyl 5-chloro-4-((4,4- difluorocyclohexyl)oxy)-2-fluorobenzoate



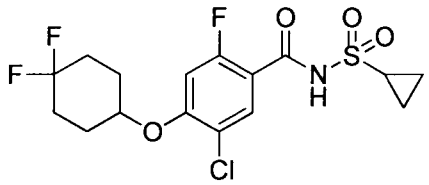
[01936] To a cold (0 °C) solution of diethylaminosulfur trifluoride (1.2 mL, 9.30 mmol) in anhydrous 1,2-dichloroethane (15 mL) was added a solution of methyl 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoate (1.02 g, 3.40 mmol) in 1,2-dichloroethane (5 mL) dropwise over 5 minutes. The mixture was allowed to warm to ambient temperature and stirred under a nitrogen atmosphere for 4 hours. The mixture was quenched with saturated aqueous ammonium chloride (5 mL), diluted with saturated aqueous ammonium chloride (75 mL) and water (25 mL). The mixture was extracted with dichloromethane (2 × 150 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of ethyl acetate in hexanes from 0-35% to afford the title compound as a colorless solid (0.70 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 12.0 Hz, 1H), 4.60 (br s, 1H), 3.88 (s, 3H), 2.50-1.88 (m, 8H); ^{19}F NMR (282 MHz, CDCl3) δ - 92.3 (d, J = 234 Hz, 1F), -102.6 (d, J = 237 Hz, 1F), -107.0 (s, 1F); MS (ES+) *m/z* 322.9, 324.9 (M + 1).

[01937] Step 6. Preparation of 5-chloro-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzoic acid



[01938] To a solution of methyl 5-chloro-4-((4,4-difluorocyclohexyl)oxy)- 2-fluorobenzoate (0.314 g, 0.973 mmol) in tetrahydrofuran (15 mL) and water (10 mL) was added lithium hydroxide (0.148 g, 6.18 mmol). The mixture was heated to reflux for 1.5 hours, cooled to ambient temperature. The reaction was diluted with 1 M hydrochloric acid (150 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography, with a gradient of a solution of 0.2% acetic acid in ethyl acetate and hexanes from 0-50% to afford the title compound as a colorless solid (0.25 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 12.1 Hz, 1H), 4.63 (br s, 1H), 2.52-1.90 (m, 8H); ^{19}F NMR (282 MHz, $CDCl_3$) δ - 92.3 (d, J = 238 Hz, 1F), -102.6 (d, J = 238 Hz, 1F), -105.3 (s, 1F); MS (ES-) *m/z* 307.2, 309.2 (M - 1).

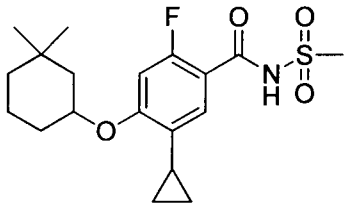
[01939] Step 7. Preparation of 5-chloro-*N*-(cyclopropylsulfonyl)-4-((4,4- difluorocyclohexyl)-oxy)-2-fluorobenzamide



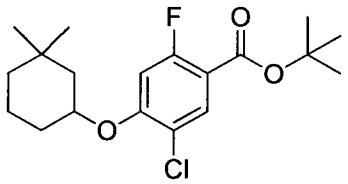
[01940] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with cyclopropanesulfonamide and to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzoic acid and methanol with cyclopropyl sulfonamide, the title compound was obtained as a colorless solid (0.047 g, 31%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 12.6 Hz, 1H), 4.85 (br s, 1H), 3.07-2.98 (m, 1H), 2.07-1.87 (m, 8H), 1.09-1.05 (m, 4H); ^{19}F NMR (282 MHz, DMSO-d_6) δ - 92.3 (d, J = 231 Hz, 1F), -98.5 (d, J = 231 Hz, 1F), -109.9 (s, 1F); MS (ES-) *m/z* 410.0, 412.0 (M - 1).

[01941] EXAMPLE 358

[01942] Synthesis of 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide

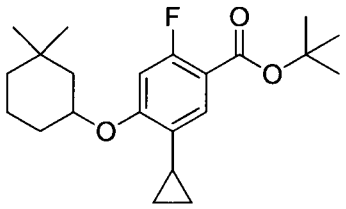


[01943] Step 1. Preparation of *tert*-butyl 5-chloro-4-((3,3-dimethylcyclohexyl)oxy)- 2-fluorobenzoate



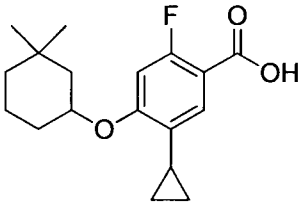
[01944] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with 3,3-dimethylcyclohexanol, the title compound was obtained as a colorless gum (1.33 g, 48%): MS (ES +) *m/z* 357.04 (M + 1).

[01945] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluorobenzoate



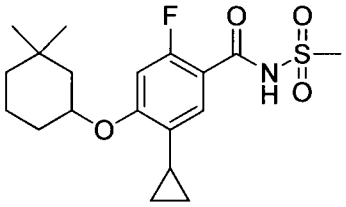
[01946] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1- ylmethoxy)-5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-4-((3,3-dimethyl- cyclohexyl)oxy)-2-fluorobenzoate, the title compound was obtained as an orange oil (1.29 g, 82 %): MS (ES +) *m/z* 385.1 (M + 23).

[01947] Step 3. Preparation of 5-cyclopropyl-4-((3,3- dimethylcyclohexyl)oxy)-2-fluorobenzoic acid



[01948] Following the procedure as described in Example 332 Step 6 and making non-critical variations to replace *tert*-butyl 4-((2-cyanoadamantan- 2-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4- ((3,3-dimethylcyclohexyl)oxy)-2-fluorobenzoate, the title compound was obtained as a beige solid (0.87 g, 80 %): MS (ES+) *m/z* 307.10 (M + 1).

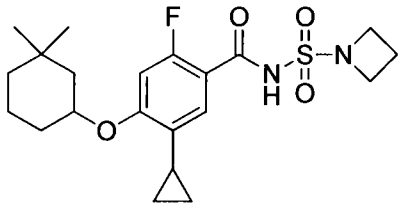
[01949] Step 4. Preparation of 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluoro-*N*-(methylsulfonyl)benzamide



[01950] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2- yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((3,- -dimethylcyclohexyl)oxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid (0.027 g, 13 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 13.3 Hz, 1H), 4.67-4.57 (m, 1H), 2.74-2.54 (m, 2H), 2.45-2.25 (m, 1H), 2.05-1.97 (m, 2H), 1.77-1.70 (m, 1H), 1.65-1.55 (m, 2H), 1.38-1.23 (m, 4H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90-0.84 (m, 2H), 0.69-0.64 (m, 2H); MS (ES +) *m/z* 384.1 (M + 1).

[01951] EXAMPLE 359

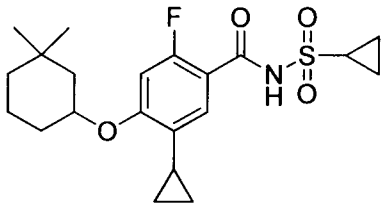
[01952] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluorobenzamide



[01953] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methane sulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid (0.035 g, 15 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 13.3 Hz, 1H), 4.67-4.58 (m, 1H), 4.04 (t, J = 7.7 Hz, 4H), 2.21-2.11 (m, 2H), 2.06-1.96 (m, 2H), 1.76-1.70 (m, 1H), 1.65-1.53 (m, 2H), 1.38-1.14 (m, 4H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90-0.84 (m, 2H), 0.69-0.64 (m, 2H); MS (ES +) *m/z* 425.1 (M + 1).

[01954] EXAMPLE 360

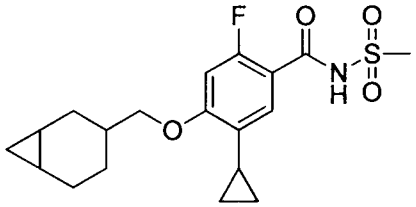
[01955] Synthesis of 5-cyclopropyl-N-(cyclopropylsulfonyl)-4-((3,3-dimethyl-cyclohexyl)oxy)-2-fluorobenzamide



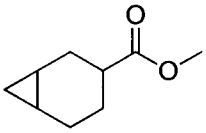
[01956] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methane sulfonamide with cyclopropane sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((3,3-dimethylcyclohexyl)oxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid (0.07 g, 31 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 13.3 Hz, 1H), 4.67-4.58 (m, 1H), 3.11-3.03 (m, 1H), 2.06-1.95 (m, 2H), 1.76-1.70 (m, 1H), 1.65-1.54 (m, 2H), 1.37-1.17 (m, 4H), 1.13-1.08 (m, 4H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90-0.84 (m, 2H), 0.68-0.63 (m, 2H); MS (ES +) *m/z* 410.0 (M + 1).

[01957] EXAMPLE 361

[01958] Synthesis of 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

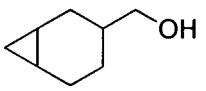


[01959] Step 1. Preparation of methyl bicyclo[4.1.0]heptane-3-carboxylate



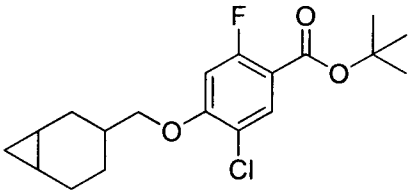
[01960] To a solution of diethyl zinc (1.0 M in hexanes, 35 mL, 35.00 mmol) in anhydrous dichloromethane (34 mL) was added trifluoroacetic acid (3.99 g, 35.0 mmol) in 17.2 mL anhydrous dichloromethane at 0 °C. The reaction mixture was stirred at the same temperature for 1 hour, and then added a solution of diidomethane (9.37 g, 35.00 mmol) in anhydrous dichloromethane (17 mL) at 0 °C. The reaction mixture was further stirred at the same temperature for another 1 hour. To this mixture was added a solution of methyl cyclohex-3-enecarboxylate (2.45 g, 17.50 mmol) in anhydrous dichloromethane 17 mL) at 0 °C. The resulting mixture was warmed to ambient temperature and further stirred for 4 hours. The mixture was quenched with a saturated solution of ammonium chloride (50 mL) and separated the organic layer. The aqueous layer was extracted with dichloromethane (15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate in hexanes (30%) to afford the title compound as yellow oil (2.56 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.31-1.92 (m, 3H), 1.84-1.65 (m, 2H), 1.54 (t, J = 12.9 Hz, 1H), 1.19-1.04 (m, 1H), 0.93-0.86 (m, 2H), 0.63-0.55 (m, 1H), 0.05-0.00 (m, 1H).

[01961] Step 2. Preparation of bicyclo[4.1.0]heptan-3-ylmethanol



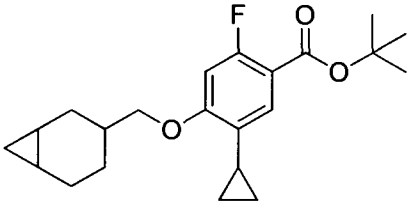
[01962] To a mixture of lithium aluminum hydride (0.74 g, 19.50 mmol) in anhydrous diethyl ether (11 mL) was added a solution of methyl bicyclo[4.1.0]heptane-3-carboxylate (1.00 g, 6.50 mmol) in anhydrous diethyl ether (4.6 mL) at 0 °C. The resulting mixture stirred at 0 °C for 0.5 hour. The mixture was slowly quenched with water (1 mL) at 0 °C and warmed to ambient temperature. The mixture was filtered through diatomaceous earth and washed with diethyl ether. The filtrate was concentrated *in vacuo* to afford the title compound as colorless oil (0.70 g, 85%): MS (ES +) *m/z* 127.0 (M + 1).

[01963] Step 3. Preparation of *tert*-butyl 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-chloro-2-fluorobenzoate



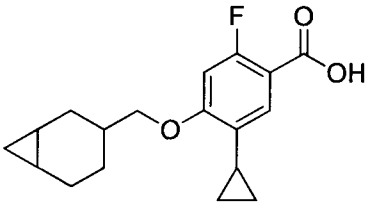
[01964] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with bicyclo[4.1.0]heptan-3-ylmethanol, the title compound was obtained as a gum (1.15 g, 58%): MS (ES +) *m/z* 355.0, 357.0 (M + 1).

[01965] Step 4. Preparation of *tert*-butyl 4-(bicyclo[4.1.0]heptan-3-ylmethoxy) -5-cyclopropyl-2-fluorobenzoate



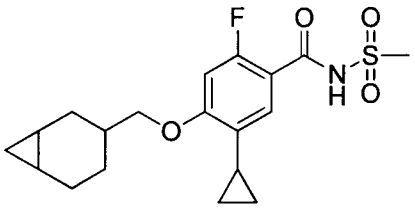
[01966] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-chloro-2-fluorobenzoate with *tert*-butyl 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-chloro-2-fluorobenzoate, the title compound was obtained as a brown oil (1.29 g, 99 %, crude yield): MS (ES +) *m/z* 361.1 (M + 1).

[01967] Step 5. Preparation of 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5- cyclopropyl-2-fluorobenzoic acid



[01968] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)- 5-cyclopropyl-2-fluorobenzoate, the title compound was obtained as a yellow solid (1.06 g, 99 %): MS (ES+) *m/z* 305.1 (M + 1).

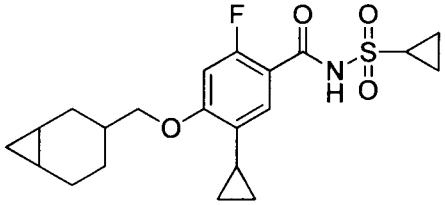
[01969] Step 6. Preparation of 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[01970] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoic acid, the title compound was obtained as a yellow solid (0.031 g, 17 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, J = 16.4 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 6.59 (d, J = 14.5 Hz, 1H), 5.79-5.54 (m, 2H), 3.96-3.87 (m, 2H), 3.42 (s, 2H), 2.37-1.68 (m, 7H), 1.42-1.19 (m, 2H), 1.06-0.99 (m, 2H), 0.96-0.91 (m, 2H), 0.69-0.64 (m, 2H); MS (ES -) *m/z* 380.1 (M - 1).

[01971] EXAMPLE 362

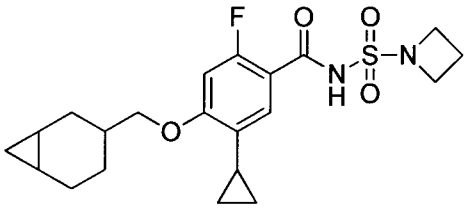
[01972] Synthesis of 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide



[01973] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a solid (0.043 g, 21 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 16.4 Hz, 1H), 7.58 (d, J = 9.1 Hz, 1H), 6.59 (d, J = 14.5 Hz, 1H), 5.78-5.54 (m, 2H), 3.94-3.84 (m, 2H), 3.15-3.06 (m, 1H), 1.96-1.68 (m, 7H), 1.48-1.40 (m, 2H), 1.26-1.11 (m, 2H), 1.06-0.99 (m, 2H), 0.96-0.90 (m, 2H), 0.69-0.64 (m, 2H); MS (ES +) *m/z* 408.0 (M +1).

[01974] EXAMPLE 363

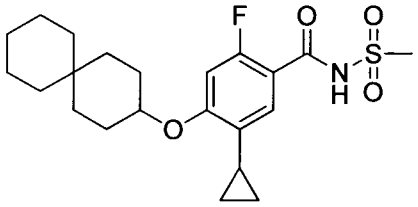
[01975] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide



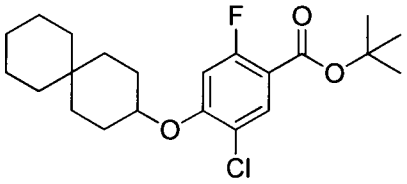
[01976] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[4.1.0]heptan-3-ylmethoxy)-5-cyclopropyl-2- fluorobenzoic acid and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as solid (0.026 g, 5 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 16.5 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 6.59 (d, *J* = 14.5 Hz, 1H), 5.78-5.54 (m, 2H), 4.25 (t, *J* = 7.7 Hz, 4H), 3.96-3.85 (m, 2H), 2.35-2.17 (m, 4H), 2.11-1.64 (m, 5H), 1.28-1.23 (m, 1H), 1.06-1.00 (m, 2H), 0.96-0.91 (m, 2H), 0.70-0.66 (m, 2H); MS (ES +) *m/z* 423.1 (M + 1).

[01977] EXAMPLE 364

[01978] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[5.5]undecan-3-yloxy)benzamide

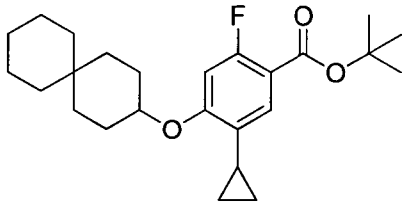


[01979] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-(spiro[5.5]undecan- 3-yloxy)benzoate



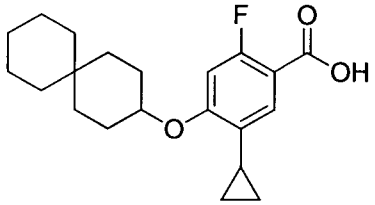
[01980] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with spiro[5.5]undecan-3-ol, the title compound was obtained as a colourless gum (0.41 g, 35%): MS (ES +) *m/z* 397.1, 399.1 (M + 1).

[01981] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan- 3-yloxy)benzoate



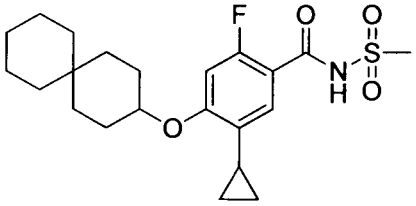
[01982] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5- chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-2-fluoro-4-(spiro[5.5]undecan-3- yloxy)benzoate, the title compound was obtained as an orange oil (0.33 g, 79 %): MS (ES +) *m/z* 403.1 (M + 1).

[01983] Step 3. Preparation of 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan-3 yloxy)benzoic acid



[01984] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan- 3-yloxy)benzoate, the title compound was obtained as a beige solid (0.23 g, 82 %): MS (ES+) *m/z* 347.1 (M + 1).

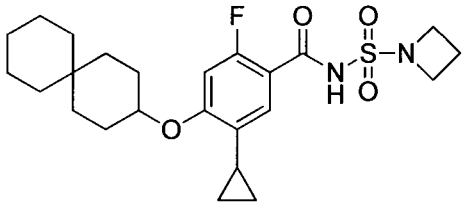
[01985] Step 4. Preparation of 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)-4-(spiro[5.5]undecan-3-yloxy)benzamide



[01986] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan-3- yloxy)benzoic acid, the title compound was obtained as a white solid (0.022 g, 23 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 13.3 Hz, 1H), 4.62-4.53 (m, 1H), 2.74-2.55 (m, 2H), 2.45-2.25 (m, 1H), 2.07-1.98 (m, 2H), 1.83-1.72 (m, 2H), 1.68-1.49 (m, 4H), 1.39-1.23 (m, 11H), 0.91-0.83 (m, 2H), 0.69-0.64 (m, 2H); MS (ES +) *m/z* 424.1 (M + 1).

[01987] EXAMPLE 365

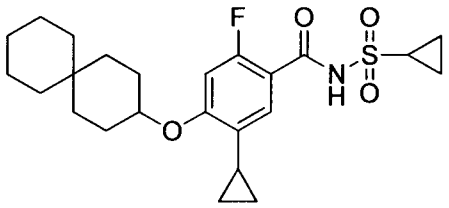
[01988] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan-3-yloxy)benzamide



[01989] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan-3- yloxy)benzoic acid and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a white solid (0.045 g, 44 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 13.3 Hz, 1H), 4.62-4.54 (m, 1H), 4.04 (t, J = 7.8 Hz, 4H), 2.74-2.55 (m, 2H), 2.29-1.97 (m, 2H), 1.84-1.73 (m, 2H), 1.69-1.51 (m, 4H), 1.38-1.23 (m, 11H), 0.90-0.86 (m, 2H), 0.70-0.65 (m, 2H); MS (ES+) *m/z* 465.1 (M + 1).

[01990] EXAMPLE 366

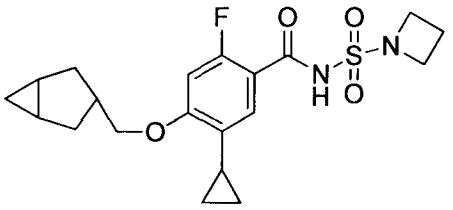
[01991] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-(spiro[5.5]undecan-3-yloxy)benzamide



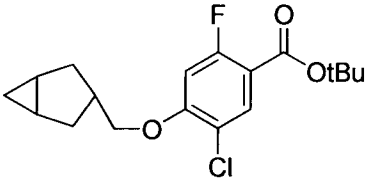
[01992] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-(spiro[5.5]undecan-3-yloxy)benzoic acid, and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a white solid (0.034 g, 34 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 13.3 Hz, 1H), 4.61-4.55 (m, 1H), 3.11-3.03 (m, 1H), 2.08-1.99 (m, 1H), 1.84-1.73 (m, 2H), 1.68-1.50 (m, 4H), 1.38-1.23 (m, 11H), 1.12-1.07 (m, 5H), 0.92-0.85 (m, 2H), 0.69-0.64 (m, 2H); MS (ES+) *m/z* 450.1 (M + 1).

[01993] EXAMPLE 367

[01994] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide

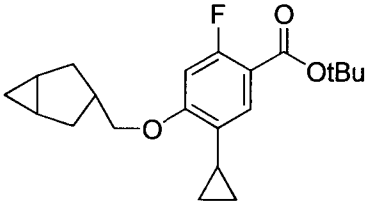


[01995] Step 1. Preparation of *tert*-butyl 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5- chloro-2-fluorobenzoate



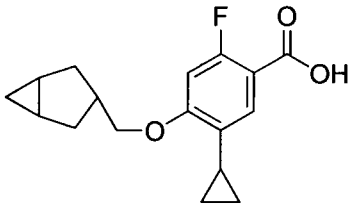
[01996] Following the procedure as described in Example 342 step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with bicyclo[3.1.0]hexan-3-ylmethanol, the title compound was obtained as a colorless gum (1.70 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 6.8 Hz, 1H), 6.55 (d, J = 12.2 Hz, 1H), 3.75 (d, J = 7.3 Hz, 2H), 2.29-2.12 (m, 2H), 1.55 (s, 9H), 1.37-1.26 (m, 4H), 0.70-0.58 (m, 1H), 0.04-0.03 (m, 1H); MS (ES+) *m/z* 341.0, 343.0 (M + 1).

[01997] Step 2. Preparation of *tert*-butyl 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate



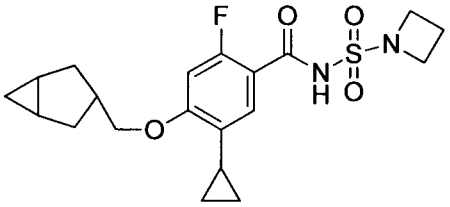
[01998] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)-5-chloro- 2-fluorobenzoate with *tert*-butyl 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-2-fluorobenzoate, the title compound was obtained as a colourless solid (1.20 g, 70 % yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 12.7 Hz, 1H), 3.78 (d, J = 7.4 Hz, 2H), 2.88-2.74 (m, 2H), 2.16-2.07 (m, 1H), 1.98-1.89 (m, 1H), 1.55 (s, 9H), 1.50 (d, J = 4.5 Hz, 1H), 1.46 (d, J = 4.5 Hz, 1H), 1.30-1.25 (m, 2H), 0.88-0.82 (m, 2H), 0.58-0.53 (m, 2H), 0.09-0.05 (m, 1H); MS (ES +) *m/z* 369.1 (M +23).

[01999] Step 3. Preparation of 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5- cyclopropyl-2-fluorobenzoic acid



[02000] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5 -cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl- 2-fluorobenzoate, the title compound was obtained as a solid (0.32 g, 22 % yield): MS (ES+) *m/z* 291.1 (M + 1).

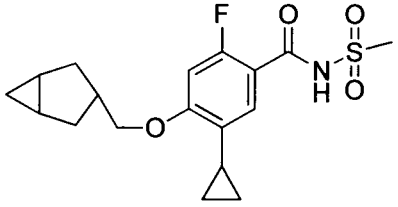
[02001] Step 4. Preparation of *N*-(azetidin-1-ylsulfonyl)-4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzamide



[02002] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a white solid (0.037 g, 27 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (br, s, 1H), 7.13 (d, J = 8.31 Hz, 1H), 6.94 (d, J = 12.98 Hz, 1H), 4.11-3.96 (m, 4H), 3.83 (d, J = 7.42 Hz, 2H), 2.83-2.67 (m, 1H), 2.25-2.07 (m, 4H), 2.05-1.92 (m, 1H), 1.58-1.45 (m, 2H), 1.37-1.26 (m, 2H), 0.94-0.82 (m, 2H), 0.72-0.54 (m, 3H), 0.14-0.06 (m, 1H); MS (ES +) *m/z* 409.1 (M +1).

[02003] EXAMPLE 368

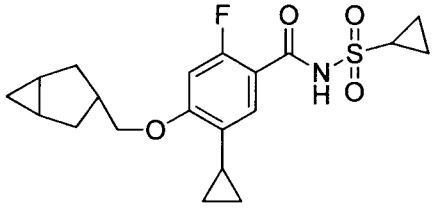
[02004] Synthesis of 4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02005] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was

obtained as a white solid (0.040 g, 32 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.85 (br, s, 1H), 7.09 (d, J = 8.37 Hz, 1H), 6.90 (d, *J* = 13.11 Hz, 1H), 3.3 (s, 3H), 3.79 (d, *J* = 7.43 Hz, 2H), 2.78-2.63 (m, 1H), 2.20-2.03 (m, 2H), 2.03-1.88 (m, 1H), 1.55-1.40 (m, 2H), 1.34-1.22 (m, 2H), 0.90-0.78 (m, 2H), 0.68-0.49 (m, 3H), 0.11-0.02 (m, 1H); MS (ES +) *m/z* 368.1 (M +1).

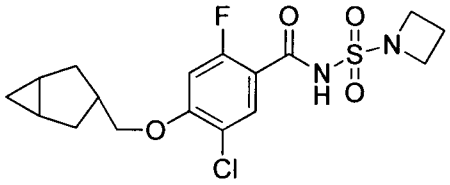
[02006] EXAMPLE 369 Synthesis of 4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide



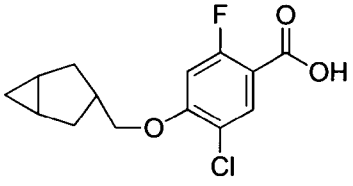
[02007] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a white solid (0.046 g, 34 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, 1H), 7.08 (d, J = 8.35 Hz, 1H), 6.90 (d, J = 13.11 Hz, 1H), 3.83-3.74 (m, 2H), 3.08-2.97 (m, 1H), 2.78-2.64 (m, 1H), 2.19-2.04 (m, 2H), 2.02-1.88 (m, 1H), 1.54-1.42 (m, 2H), 1.33-1.22 (m, 2H), 1.13-1.01 (m, 4H), 0.90-0.79 (m, 2H), 0.67-0.51 (m, 3H), 0.10-0.03 (m, 1H); MS (ES +) *m/z* 394.1 (M +1).

[02008] EXAMPLE 370

[02009] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-2-fluorobenzamide



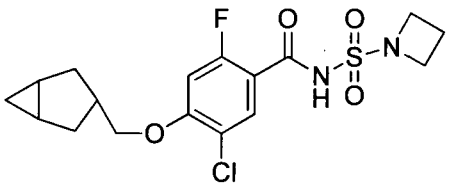
[02010] Step 1. Preparation of 4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-2-fluorobenzoic acid



[02011] Following the procedure as described in Example 342 Step 6, and making variations as required to replace *tert*-butyl 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate

with *tert*-butyl 4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy) -5-chloro-2-fluorobenzoate, the title compound was obtained as a solid (0.048 g, 4 %): MS (ES-) *m/z* 283.2 (M - 1).

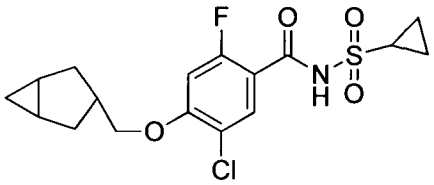
[02012] Step 2. Preparation of *N*-(azetidin-1-ylsulfonyl)-4-((1R,3r,5S)-bicyclo[3.1.0]-hexan-3-ylmethoxy)-5-chloro-2-fluorobenzamide



[02013] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a white solid (0.044 g, 22 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.83 (br s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 12.4 Hz, 1H), 4.12-3.97 (m, 3H), 3.90 (d, *J* = 7.37 Hz, 1H), 3.3 (m, 2H), 2.81-2.66 (m, 1H), 2.25-2.07 (m, 3H), 1.55-1.44 (m, 2H), 1.37-1.26 (m, 2H), 1.05-1.15 (m, 1H), 0.65-0.52 (m, 1H), 0.18-0.10 (m, 1H); MS (ES +) *m/z* 403.1, 405.1 (M +1).

[02014] EXAMPLE 371

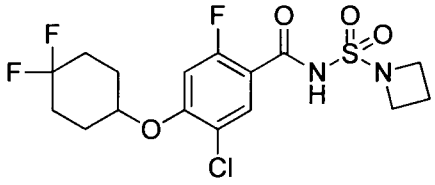
[02015] Synthesis of 4-((1R,3r,5S)-bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-N-(cyclopropylsulfonyl)-2-fluorobenzamide



[02016] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoic acid with 4-(bicyclo[3.1.0]hexan-3-ylmethoxy)-5-chloro-2-fluorobenzoic acid and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a white solid (0.0035 g, 18 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.04 (br, s, 1H), 7.75 (d, J = 7.53 Hz, 1H), 7.23 (d, J = 12.55 Hz, 1H), 3.96-3.84 (m, 2H), 3.13-2.99 (m, 1H), 2.82-2.65 (m, 1H), 2.23-2.05 (m, 2H), 1.56-1.44 (m, 2H), 1.38-1.20 (m, 2H), 1.18-1.05 (m, 3H), 0.94-0.77 (m, 1H), 0.67-0.52 (m, 1H), 0.18-0.09 (m, 1H); MS (ES +) *m/z* 388.0 (M +1).

[02017] Example 372

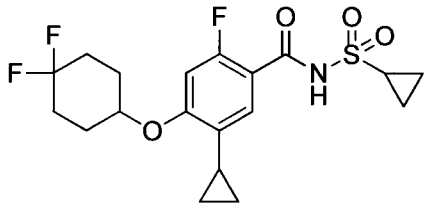
[02018] Synthesis of N-(azetidin-1-ylsulfonyl)-5-chloro-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzamide



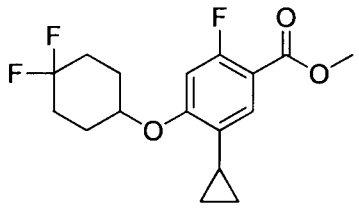
[02019] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.028 g, 19%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 12.4 Hz, 1H), 4.85 (br s, 1H), 4.00 (t, J = 7.7, 7.7 Hz, 4H), 2.18-1.86 (m, 10H); ^{19}F NMR (282 MHz, DMSO-d_6) δ – 92.2 (d, J = 231 Hz, 1F), -98.5 (d, J = 231 Hz, 1F), -110.1 (s, 1F); MS (ES-) *m/z* 425.1, 427.1 (M - 1).

[02020] EXAMPLE 373

[02021] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4- ((4,4-difluorocyclohexyl)oxy)-2-fluorobenzamide



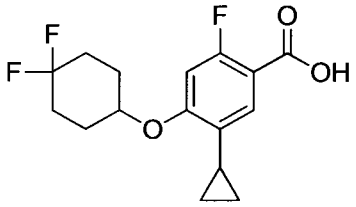
[02022] Step 1. Preparation of methyl 5-cyclopropyl-4-((4,4-difluorocyclohexyl)oxy)- 2-fluorobenzoate



[02023] To an argon-degassed solution of methyl 5-chloro-4-((4,4-difluoro-cyclohexyl)oxy)-2-fluorobenzoate (0.394 g, 1.22 mmol) in toluene (15 mL) and water (3 mL) was added cyclopropylboronic acid (0.639 g, 7.44 mmol), tribasic potassium phosphate (0.826 g, 3.89 mmol), tricyclohexylphosphine tetrafluoroborate (0.30 g, 0.97 mmol), and palladium acetate trimer (0.108 g, 0.481 mmol Pd). The mixture was heated to reflux under an argon atmosphere for 21 hours, cooled to ambient temperature. The mixture was filtered through a pad of diatomaceous earth that was rinsed with ethyl acetate (100 mL). The filtrate was washed with a 2:1 mixture of saturated aqueous ammonium chloride and water (150 mL), brine (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in*

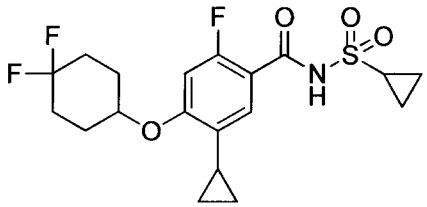
vacuo to dryness. The residue was purified by column chromatography with a gradient of ethyl acetate in hexanes (0-10%) to afford the title compound as a light yellow syrup (0.30 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 12.6 Hz, 1H), 4.57 (br s, 1H), 3.86 (s, 3H), 2.44-1.88 (m, 9H), 0.93-0.86 (m, 2H), 0.64-0.59 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -92.3 (d, J = 238 Hz, 1F), -102.3 (d, J = 237 Hz, 1F), -109.4 (s, 1F); MS (ES+) *m/z* 329.1 (M + 1).

[02024] Step 2. Preparation of 5-cyclopropyl-4-((4,4-difluorocyclohexyl)oxy)- 2-fluorobenzoic acid



[02025] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoate with methyl 5-cyclopropyl-4-((4,4-difluorocyclohexyl)oxy)- 2-fluorobenzoate, the title compound was obtained as a colorless solid (0.32 g, quant. yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 12.7 Hz, 1H), 4.60 (br s, 1H), 2.20-1.92 (m, 9H), 0.94-0.88 (m, 2H), 0.65-0.60 (m, 2H); MS (ES-) *m/z* 313.2 (M - 1).

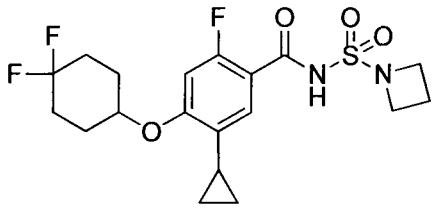
[02026] Step 3. Preparation of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzamide



[02027] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)oxy)- 2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a colorless solid (0.093 g, 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.13-7.06 (m, 2H), 4.78 (br s, 1H), 3.08-2.99 (m, 1H), 2.08-1.86 (m, 9H), 1.09-1.06 (m, 4H), 0.88-0.82 (m, 2H), 0.66-0.60 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ - 92.1 (d, J = 231 Hz, 1F), -98.5 (d, J = 231 Hz, 1F), -112.5 (s, 1F); MS (ES-) *m/z* 416.10 (M - 1).

[02028] Example 373a

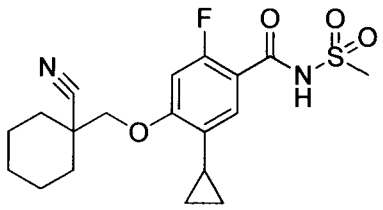
[02029] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4- ((4,4-difluorocyclohexyl)oxy)-2-fluorobenzamide



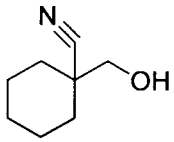
[02030] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with cyclopropanesulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide , the title compound was obtained as a colorless solid (0.092 g, 46%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.58 (br s, 1H), 7.14-7.06 (m, 2H), 4.80 (br s, 1H), 4.00 (t, J = 7.7, 7.7 Hz, 4H), 2.18-1.87 (m, 11H), 0.89-0.82 (m, 2H), 0.67-0.61 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -92.0 (d, J = 232 Hz, 1F), -98.5 (d, J = 231 Hz, 1F), -112.7 (s, 1F); MS (ES-) *m/z* 431.1 (M - 1).

[02031] EXAMPLE 374

[02032] Synthesis of 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



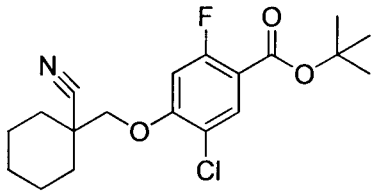
[02033] Step 1. Preparation of 1-(hydroxymethyl)cyclohexanecarbonitrile



[02034] To a solution of methyl 1-cyanocyclohexanecarboxylate (prepared according to Fleming et. al, *J. Org. Chem.* **2005**, *70*, 2200) (8.54 g, 51.10 mmol) in anhydrous tetrahydrofuran (300 mL) was added anhydrous methanol (3.1 mL, 78.00 mmol) and lithium borohydride (4.0 M solution in tetrahydrofuran 19 mL, 76 mmol). The reaction solution was heated to reflux under a nitrogen atmosphere for 4 hours, cooled to ambient temperature. The mixture was quenched by the slow addition of saturated aqueous ammonium chloride (5 mL). The mixture was diluted with ethyl acetate (400 mL), washed with a 2:1 mixture of saturated aqueous ammonium chloride and water (2 × 300 mL), dried over anhydrous magnesium sulfate,

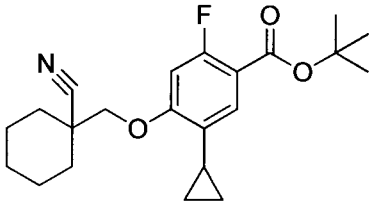
filtered and concentrated *in vacuo* to afford the title compound as a colorless oil (6.30 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (s, 2H), 2.78 (br s, 1H), 1.98-1.93 (m, 2H), 1.74-1.69 (m, 4H), 1.63-1.48 (m, 4H).

[02035] Step 2. Preparation of *tert*-butyl 5-chloro-4-((1-cyanocyclohexyl)methoxy) 2-fluorobenzoate



[02036] To a solution of 1-(hydroxymethyl)cyclohexanecarbonitrile (3.04 g, 21.80 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (6.30 g, 25.30 mmol) in dimethylsulfoxide (40 mL) was added cesium carbonate (14.35 g, 44.00 mmol). The mixture was heated at 80 °C under a nitrogen atmosphere for 3.5 hours, cooled to ambient temperature. The mixture was quenched with 1 M hydrochloric acid (70 mL), then diluted with ethyl acetate (350 mL), washed with 1 M hydrochloric acid (2 × 350 mL), brine (2 × 350 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography, with a gradient of ethyl acetate in hexanes from 0-10% to afford the title compound as a colorless solid (3.87 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 11.6 Hz, 1H), 3.97 (s, 2H), 2.16-2.11 (m, 2H), 1.82-1.63 (m, 5H), 1.59-1.42 (m, 11H), 1.29-1.21 (m, 1H); MS (ES+) *m/z* 368.0, 370.0 (M + 1).

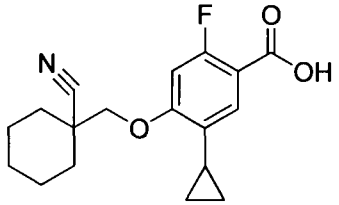
[02037] Step 3. Preparation of tert-butyl 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluorobenzoate



[02038] To an argon-degassed solution of tert-butyl 5-chloro-4-((1-cyano-cyclohexyl)methoxy)-2-fluorobenzoate (0.571 g, 1.55 mmol) in toluene (8 mL) and water (1 mL) was added cyclopropylboronic acid (0.66 g, 7.71 mmol), tribasic potassium phosphate (1.02 g, 4.80 mmol), tricyclohexylphosphine tetrafluoroborate (0.28 g, 0.92 mmol), and palladium acetate trimer (0.11 g, 0.47 mmol Pd). The mixture was heated at 150 °C in a microwave reactor for 0.5 hour, then diluted with ethyl acetate (150 mL), washed with a 3:1 mixture of saturated aqueous ammonium chloride and water (2 × 150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with a gradient of ethyl acetate in hexanes from 0-10% to afford the title compound as a yellow syrup (0.50 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 12.2 Hz, 1H), 3.93 (s, 2H), 2.18-2.13 (m, 2H), 2.07-1.98 (m, 1H), 1.82-1.63 (m, 5H), 1.55 (s,

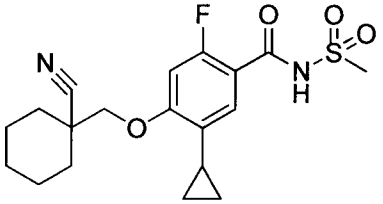
9H), 1.48-1.39 (m, 2H), 1.29-1.21 (m, 1H), 0.94-0.88 (m, 2H), 0.65-0.60 (m, 2H); MS (ES+) *m/z* 374.0 (M + 1).

[02039] Step 4. Preparation of 4-((1-cyanocyclohexyl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid



[02040] To a solution of tert-butyl 4-((1-cyanocyclohexyl)methoxy)-5- cyclopropyl-2-fluorobenzoate (0.498 g, 1.33 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (5 mL). The solution was stirred at ambient temperature for 1 hour and the solvent was concentrated *in vacuo* to dryness. The residue was triturated with diethyl ether (10 mL) to afford the title compound as a colorless solid (0.32 g, 75%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 12.8 Hz, 1H), 4.14 (s, 2H), 2.02-1.95 (m, 3H), 1.72-1.65 (m, 3H), 1.51-1.43 (m, 4H), 1.24-1.18 (m, 1H), 0.91-0.85 (m, 2H), 0.61-0.56 (m, 2H); MS (ES-) *m/z* 316.2 (M - 1).

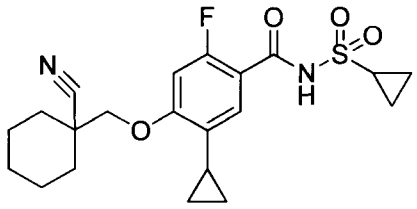
[02041] Step 5. Preparation of 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02042] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.087 g, 67%): ^{1}H NMR (300 MHz, DMSO-d_6) δ11.93 (br s, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 12.8 Hz, 1H), 4.15 (s, 2H), 3.31 (s, 3H), 2.04-1.96 (m, 3H), 1.73-1.66 (m, 3H), 1.51-1.38 (m, 4H), 1.24-1.16 (m, 1H), 0.91-0.85 (m, 2H), 0.69-0.64 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ -112.6 (s, 1F); MS (ES-) *m/z* 393.2 (M - 1).

[02043] Example 375

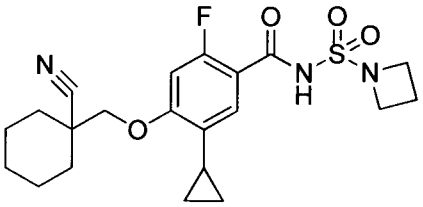
[02044] Synthesis of 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide



[02045] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and making variations as required to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a colorless solid (0.092 g, 66% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 12.8 Hz, 1H), 4.15 (s, 2H), 3.08-3.00 (m, 1H), 2.03-1.95 (m, 3H), 1.73-1.66 (m, 3H), 1.51-1.38 (m, 4H), 1.23-1.15 (m, 1H), 1.09-1.05 (m, 4H), 0.91-0.85 (m, 2H), 0.69-0.64 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ – 112.3 (s, 1F); MS (ES-) *m/z* 419.2 (M - 1).

[02046] Example 376

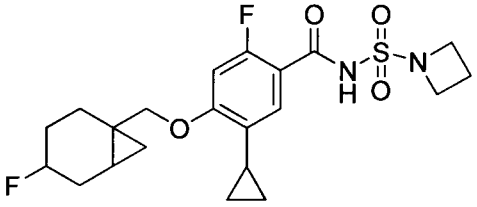
[02047] Synthesis of *N*-(azetidin-1-ylsulfonyl)-4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluorobenzamide



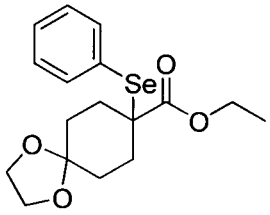
[02048] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 4-((1-cyanocyclohexyl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.061 g, 42%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (br s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 12.6 Hz, 1H), 4.15 (s, 2H), 4.02 (t, J = 7.6, 7.6 Hz, 4H), 2.18-2.08 (m, 2H), 2.03-1.97 (m, 3H), 1.73-1.66 (m, 3H), 1.51-1.39 (m, 4H), 1.20 (br s, 1H), 0.91-0.85 (m, 2H), 0.69-0.64 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ – 112.6 (s, 1F); MS (ES-) *m/z* 434.1 (M - 1).

[02049] EXAMPLE 377

[02050] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((4-fluorobicyclo[4.1.0]heptan-1-yl)methoxy)benzamide

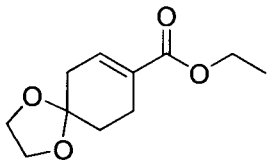


[02051] Step 1. Preparation of ethyl 8-(phenylselanyl)-1,4- dioxaspiro[4.5]decane-8-carboxylate



[02052] To a solution of *diiso*propylethyl amine (5.59 g, 55.30 mmol) in anhydrous tetrahydrofuran (150 mL) was added a solution of butyllithium (1.6 M in hexanes, 34.5 mL, 55.30 mmol) at 0 °C. The reaction solution was stirred at the same temperature for 1 hour, then added a solution of ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate (10.80 g, 50.00 mmol) in anhydrous tetrahydrofuran (20 mL) at -78 °C. The reaction mixture was stirred at the same temperature for 1 h then added phenylselenium bromide (11.90 g, 50.70 mmol). The mixture was continued to stir at -78 °C for 5 hour, then at ambient temperature for 16 hour. The reaction was quenched with saturated sodium hydrogencarbonate (200 mL), diluted with ethyl acetate (200 mL), saturated ammonium chloride (3 x 150 mL), brine (3 x 100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate in hexanes (10%) to afford the title compound as a viscous liquid (14.10 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.37-7.32 (m, 1H), 7.26 (dd, J = 7.0, 7.0 Hz, 2H), 4.05 (dd, J = 7.1 Hz, 2H), 3.90 (d, J = 3.4 Hz, 4H), 2.20-2.12 (m, 2H), 2.00-1.88 (m, 2H), 1.82-1.70 (m, 2H), 1.57-1.46 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H).

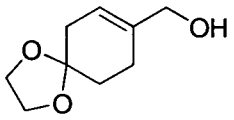
[02053] Step 2. Preparation of ethyl 1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate



[02054] To a solution of ethyl 8-(phenylselanyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (14.00 g, 38.00 mmol) in dichloromethane (100 mL) was added 30% hydrogen peroxide solution (11.6 mL, 380.0 mmol). The reaction mixture was stirred at ambient temperature for 16 h then diluted with dichloromethane (100 mL), washed with saturated sodium hydrogencarbonate (100 mL), saturated ammonium chloride (3 x 75 mL), and brine (3 x 75 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate

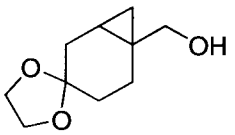
in hexanes (10%) to afford the title compound as a colorless liquid (6.10 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 1H), 4.11 (dd, J = 7.1 Hz, 2H), 3.92 (s, 4H), 2.49-2.43 (m, 2H), 2.34-2.29 (m, 2H), 1.76-1.65 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H).

[02055] Step 3. Preparation of 1,4-dioxaspiro[4.5]dec-7-en-8-ylmethanol



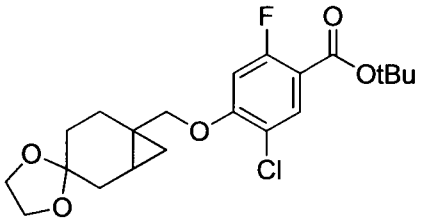
[02056] Following the procedure as described in Example 361 Step 2 and making non-critical variations to replace methyl bicyclo[4.1.0]heptane-3-carboxylate with ethyl 1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate, the title compound was obtained as a colourless liquid (5.0 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62-5.57 (m, 1H), 4.04-3.91 (m, 6H), 3.47 (d, J = 6.4 Hz, 1H), 2.31-2.20 (m, 4H), 1.82-1.71 (m, 4H).

[02057] Step 4. Preparation of spiro[bicyclo[4.1.0]heptane-3,2'- [1,3]dioxolane]-6-ylmethanol



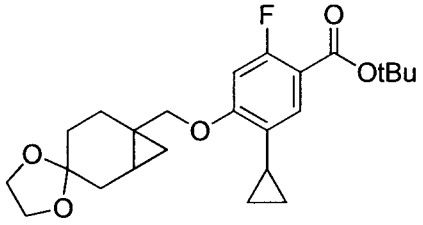
[02058] Following the procedure as described in Example 342 Step 2 and making non-critical variations to replace cyclohexenylmethanol with 1,4-dioxaspiro[4.5]dec-7-en-8-ylmethanol, the title compound was obtained as a colourless liquid (4.0 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92-3.84 (m, 4H), 3.48 (d, J = 10.8 Hz, 1H), 3.26 (d, J = 10.9 Hz, 1H), 2.21-2.0 (m, 2H), 1.94-1.86 (m 1H), 1.77-1.65 (m, 1H), 1.60-1.51 (m, 1H), 1.40-1.30 (m, 1H), 0.58 (dd, J = 9.2, 4.8 Hz, 1H), 0.40 (t, J = 5.0 Hz, 1H).

[02059] Step 5. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-(spiro[bicycle- [4.1.0]heptane-3,2'-[1,3]dioxolan]-6-ylmethoxy)benzoate



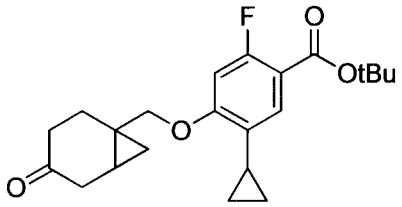
[02060] Following the procedure as described in Example 342 step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol spiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolane]-6-ylmethanol, the title compound was obtained as a colorless gum (1.40 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 6.54 (d, J = 12.2 Hz, 1H), 3.99-3.82 (m, 6H), 3.73 (d, J = 9.2 Hz, 1H), 2.14-2.04 (m 2H), 1.80-1.72 (m, 2H), 1.64-1.57 (m, 2H), 1.55 (s, 9H), 1.46-1.34 (m, 2H), 1.12-1.03 (m, 1H), 0.81-0.76 (m, 1H), 0.59 (t, J = 5.3 Hz, 1H); MS (ES+) *m/z* 435.0, 437.0 (M + 23).

[02061] Step 6. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-(spiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolan]-6-ylmethoxy)benzoate



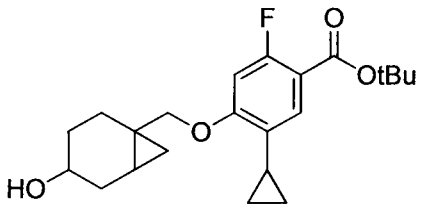
[02062] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1- ylmethoxy)-5-chloro-2-fluorobenzoate of *tert*-butyl 5-chloro-2-fluoro-4- (spiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolan]-6-ylmethoxy)benzoate, the title compound was obtained as a colorless solid (1.30 g, 93 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 12.7 Hz, 1H), 3.95-3.86 (m, 4H), 3.84-3.70 (m, 2H), 2.22-1.98 (m, 4H), 1.82-1.72 (m, 2H), 1.64-1.57 (m, 2H), 1.56 (s, 9H), 1.49-1.35 (m, 2H), 1.11-1.04 (m, 1H), 0.80-0.75 (m, 1H), 0.65-0.60 (m, 1H), 0.56 (t, J = 5.3 Hz, 1H) ; MS (ES+) *m/z* 419.2 (M + 1).

[02063] Step 7. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-oxobicyclo[4.1.0]-heptan-1-yl)methoxy)benzoate



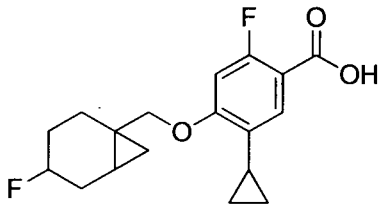
[02064] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-(spiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolan]-6-ylmethoxy)benzoate (0.61 g, 1.86 mmol) in tetrahydrofuran (2.0 mL) was added water (2.0 mL) followed by trifluoroacetic acid (0.75 g, 6.56 mmol). The reaction solution was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (20 mL), washed with a solution of aqueous sodium hydroxide (2.0 mL, 3 M). The organic layer was separated and concentrated *in vacuo* to afford the title compound as a colorless gum (0.63 g, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 12.6 Hz, 1H), 3.91 (d, J = 9.3 Hz, 1H), 3.71 (d, J = 9.3 Hz, 1H), 2.72 (dd, J = 18.4, 5.4 Hz, 1H), 2.56-2.32 (m, 4H), 2.20 -2.07 (m, 2H), 1.99-1.92 (m, 1H), 1.53 (s, 9H), 1.21-0.79 (m, 5H), 0.70 (t, J = 5.3 Hz, 1H), 0.63-0.58 (m, 2H); MS (ES+) *m/z* 397.2 (M + 23).

[02065] Step 8. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-hydroxybicyclo-[4.1.0]heptan-1-yl)methoxy)benzoate



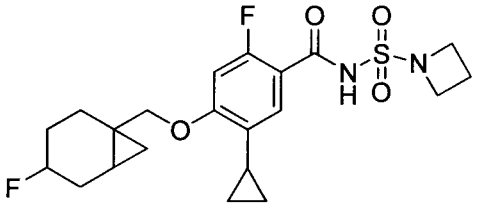
[02066] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-oxobicyclo[4.1.0]heptan-1-yl)methoxy)benzoate (0.63 g, 1.70 mmol) was dissolved in 1,2- dimethoxyethane (5 mL), sodium borohydride (0.13 g, 3.40 mmol) was added. The reaction mixture was stirred for 0.5 hour and quenched with slow addition of water (5 mL) followed by ethyl acetate (10 mL). To this reaction mixture was added concentrated hydrochloride (37%, 1.0 mL) and stirred for 10 minutes. The organic layer was separated and the solvent was concentrated *in vacuo* to afford the title compound as a solid (0.13 g, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 12.7 Hz, 1H), 3.78 (d, J = 9.2 Hz, 1H), 3.62 (d, J = 9.4 Hz, 1H), 2.40-2.30 (m, 4H), 2.20 -2.07 (m, 2H), 1.99-1.92 (m, 1H), 1.53 (s, 9H), 1.42-1.33 (m, 1H), 1.29-1.09 (m, 2H), 0.89-0.82 (m, 4H), 0.76-0.71 (m, 1H, 0.65-0.60 (m, 2H), 0.47(t, J = 5.3 Hz, 1H); MS (ES+) *m/z* 377.2 (M + 1).

[02067] Step 9. Preparation of 5-cyclopropyl-2-fluoro-4-((4-fluorobicyclo[4.1.0]heptan-1-yl)methoxy)benzoic acid



[02068] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-hydroxybicyclo-[4.1.0]heptan-1-yl)methoxy)benzoate (0.13 g, 0.41 mmol) in chloroform (2 mL) was added diethylaminosulfur trifluoride (0.11 mL, 0.89 mmol). The reaction solution was stirred at ambient temperature for 16 h and quenched with slow addition of aqueous saturated sodium hydrogencarbonate. The reaction mixture was extracted with dichloromethane. The solvent was concentrated *in vacuo* to dryness. The residue (0.10 g) was dissolved in dichloromethane (1 mL) and trifluoroacetic acid (0.15 g, 1.30 mmol) was added. The reaction mixture was stirred for 2 h and the solvent was concentrated *in vacuo* to obtain the title compound as a gum (0.080 g, 95%). The residue was carried forward without any further purification in next reaction: MS (ES-) *m/z* 321.1 (M - 1).

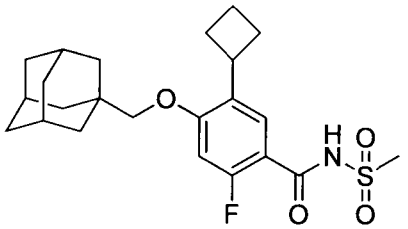
[02069] Step 10. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-((4-fluorobicyclo[4.1.0]heptan-1-yl)methoxy)benzamide



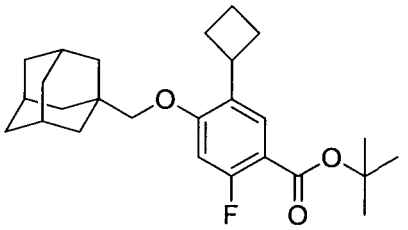
[02070] Following the procedure as described in Example 339 Step 4 and making non-critical variations to replace 5-chloro-4-(cyclohexyloxymethyl)-2-fluorobenzoic acid with 5-cyclopropyl-2-fluoro-4-((4-fluorobicyclo[4.1.0]heptan-1-yl)methoxy)benzoic acid, the title compound was obtained following purification by reverse-phase HPLC as a colorless powder (0.007 g, 6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 16.3 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 6.51 (d, J = 14.1 Hz, 1H), 4.80-4.42 (m, 2H), 4.35-4.09 (m, 3H), 4.31-4.14 (m, 1H), 3.86-3.78 (m, 1H), 2.40-1.61 (m, 7H), 1.61-1.13 (m, 1H), 1.14-0.58 (m, 7H), 0.44-0.31 (m, 1H); MS (ES-) *m/z* 441.1 (M + 1).

[02071] EXAMPLE 378

[02072] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclobutyl- 2-fluoro-*N*-(methylsulfonyl)benzamide

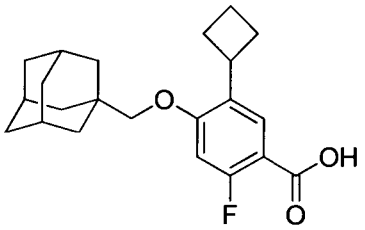


[02073] Step 1. Synthesis of *tert*-butyl 4-(adamantan-1-ylmethoxy)- 5-cyclobutyl-2-fluorobenzoate



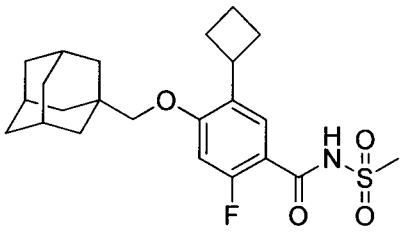
[02074] Following the procedure as described in Example 373 Step 1 and making non-critical variations to replace *tert*-butyl 5-chloro-4-((1-cyanocyclohexyl)- methoxy)-2-fluorobenzoate with *tert*-butyl 4-(adamantan-1-ylmethoxy)- 5-chloro-2-fluorobenzoate, to replace cyclopropylboronic acid with cyclobutylboronic acid, and to replace tricyclohexylphosphine tetrafluoroborate with 2-dicyclohexylphosphino- 2',6'-diisopropoxybiphenyl (RuPhos), the title compound was obtained as a colorless syrup containing ~25% *tert*-butyl 4-(adamantan-1-ylmethoxy)-2-fluorobenzoate (1.01 g, 97%): MS (ES+) *m/z* 359.1 (M - 55).

[02075] Step 2. Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluorobenzoic acid



[02076] Following the procedure as described in Example 373 Step 2 making non-critical variations to replace *tert*-butyl 4-((1-cyanocyclohexyl)methoxy)-5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 4-(adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluorobenzoate, the title compound was obtained as a yellow solid (0.65 g, 76%). The solid was carried forward without further purification and analytical characterization.

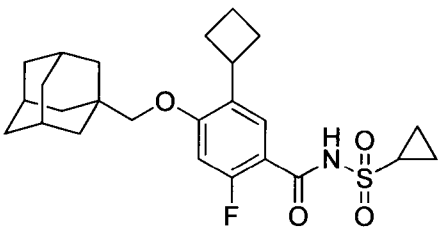
[02077] Step 3. Preparation of 4-(adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluoro-*N*-(methylsulfonyl)benzamide



[02078] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-((3*r*,5*r*,7*r*)-adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluorobenzoic acid, the title compound was obtained as a colorless solid (0.017 g, 4%): ^{1}H NMR (300 MHz, DMSO-d_6) δ11.89 (br s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 13.2 Hz, 1H), 3.56 (s, 3H), 3.31 (s, 3H), 2.33–2.21 (m, 2H), 2.15-1.96 (m, 6H), 1.81-1.60 (m, 13H); MS (ES-) *m/z* 434.2 (M - 1).

[02079] EXAMPLE 379

[02080] Synthesis of 4-(adamantan-1-ylmethoxy)-5-cyclobutyl-*N*-(cyclopropylsulfonyl)-2-fluorobenzamide

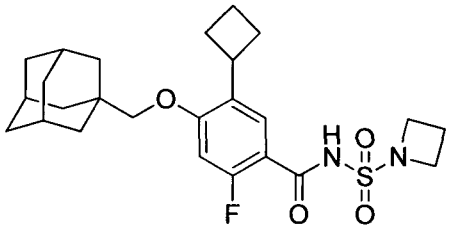


[02081] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5-cyclobutyl-2-fluorobenzoic acid and to replace methanesulfonamide with

cyclopropanesulfonamide, the title compound was obtained as a colorless solid (0.090 g, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 16.3 Hz, 1H), 7.87 (d, J = 9.3 Hz, 1H), 6.53 (d, J = 14.7 1H), 3.69-3.56 (m, 1H), 3.49 (s, 2H), 3.15-3.06 (m, 1H), 2.39-2.29 (m, 2H), 2.18-1.98 (m, 6H), 1.87-1.65 (m, 13H), 1.48-1.42 (m, 2H), 1.17-1.10 (m, 2H); MS (ES-) *m/z* 460.2 (M - 1).

[02082] EXAMPLE 380

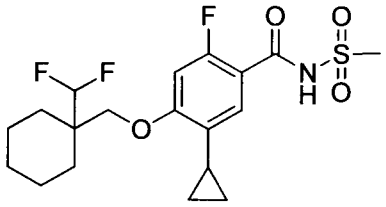
[02083] Synthesis of 4-(adamantan-1-ylmethoxy)-*N*-(azetidin-1-ylsulfonyl)-5-cyclobutyl-2-fluorobenzamide



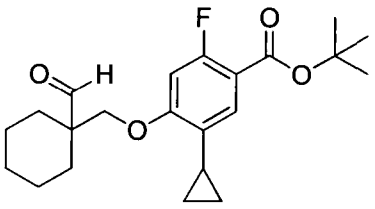
[02084] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 4-(adamantan-1-ylmethoxy)-5- cyclobutyl-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.043 g, 13%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 16.5 Hz, 1H), 7.88 (d, J = 9.3 Hz, 1H), 6.54 (d, J = 14.6 Hz, 1H), 4.24 (t, J = 7.7 Hz, 4H), 3.69-3.58 (m, 1H), 3.49 (s, 2H), 2.39-1.99 (m, 10H), 1.87-1.64 (m, 13H); MS (ES-) *m/z* 475.2 (M - 1).

[02085] EXAMPLE 381

[02086] Synthesis of 5-cyclopropyl-4-((1-(difluoromethyl)cyclohexyl)methoxy)-2-fluoro-N-(methylsulfonyl)benzamide



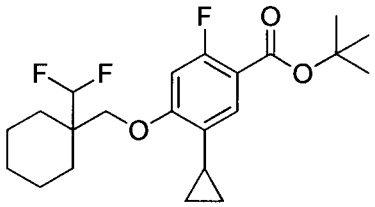
[02087] Step 1. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-formylcyclohexyl)-methoxy)benzoate



[02088] To a mixture of *tert*-butyl 4-((1-cyanocyclohexyl)methoxy)-5- cyclopropyl-2-fluorobenzoate (1.00 g, 2.70 mmol) in anhydrous toluene (11 mL) was added di*iso*butylaluminum hydride (1.0 M in

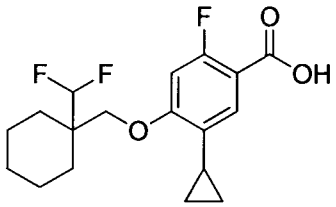
toluene, 2.9 mL, 2.90 mmol) at -78 °C. The resulting mixture stirred at -78 °C for 2.5 hours. The mixture was slowly quenched with water (20 mL) at -78 °C and warmed to ambient temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with ethyl acetate in hexanes (0 - 20 %) to afford the title compound as a yellow oil (0.315 g, 31%): MS (ES+) *m/z* 321.0 (M - 55).

[02089] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-4-((1- (difluoromethyl)cyclohexyl)-methoxy)-2-fluorobenzoate



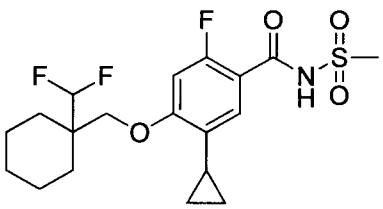
[02090] Following the procedure as described in Example 357 Step 5 and making variations as required to replace methyl 5-cyclopropyl-2-fluoro-4-((4-oxocyclohexyl)- methoxy)benzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-formyl- cyclohexyl)methoxy)benzoate, the title compound was obtained as an yellow oil (0.21 g, 98 %): MS (ES +) *m/z* 421.1 (M + 23).

[02091] Step 3. Preparation of 5-cyclopropyl-4-((1-(difluoromethyl)-cyclohexyl)methoxy)-2-fluorobenzoic acid



[02092] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4-((1-(difluoromethyl)- cyclohexyl)methoxy)-2-fluorobenzoate, the title compound was obtained as a beige solid (0.16 g, 96 %): MS (ES+) *m/z* 343.1 (M + 1).

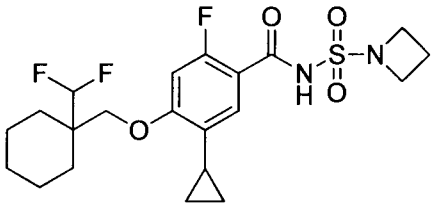
[02093] Step 4. Preparation of 5-cyclopropyl-4-((1-(difluoromethyl)cyclohexyl)methoxy)-2-fluoro-N-(methylsulfonyl)benzamide



[02094] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((1-(difluoromethyl)cyclohexyl)- methoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid (0.074 g, 75 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 13.0 Hz, 1H), 6.04 (t, J = 56.4 Hz, 1H), 4.14 (s, 2H), 2.07-2.00 (m, 1H), 1.73-1.23 (m, 13H), 0.91-0.85 (m, 2H), 0.67-0.62 (m, 2H); MS (ES +) *m/z* 420.0 (M + 1).

[02095] EXAMPLE 382

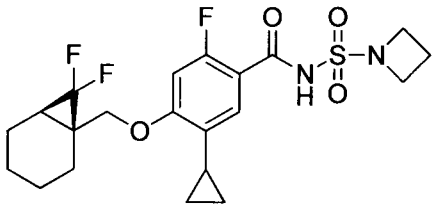
[02096] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((1-(difluoromethyl)-cyclohexyl)methoxy)-2-fluorobenzamide



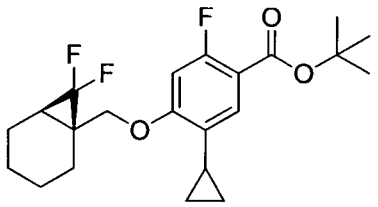
[02097] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((1-(difluoromethyl)cyclohexyl)- methoxy)-2-fluorobenzoic acid, and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a yellow oil (0.085 g, 79 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.17-7.10 (m, 2H), 6.04 (t, J = 56.4 Hz, 1H), 4.14 (s, 2H), 4.05 (t, J = 7.7 Hz, 4H), 2.22-2.08 (m, 2H), 2.06-1.98 (m, 1H), 1.74-1.65 (m, 2H), 1.59-1.44 (m, 7H), 1.32-1.21 (m, 1H), 0.92-0.85 (m, 2H), 0.68-0.63 (m, 2H); MS (ES +) *m/z* 461.1 (M + 1).

[02098] EXAMPLE 383

[02099] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide

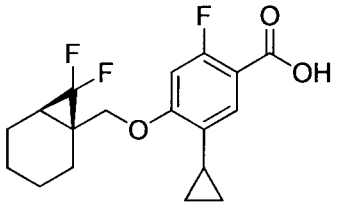


[02100] Step 1. Preparation of *tert*-butyl 5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo[4.1.0]-heptan-1-yl)methoxy)-2-fluorobenzoate



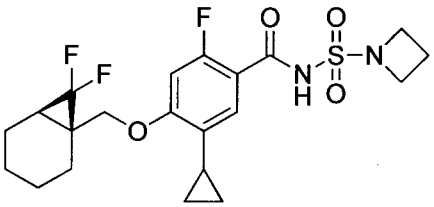
[02101] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)- 5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-4-(((1SR,6RS)-7,7- difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoate (stereochemistry arbitrarily assigned), the title compound was obtained as a yellow oil (0.18 g, 58 %): MS (ES +) *m/z* 341.0 (M - 55).

[02102] Step 2. Preparation of 5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluoro-bicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid (stereochemistry arbitrarily assigned)



[02103] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7- difluorobicyclo[4.1.0]heptan- 1-yl)methoxy)-2-fluorobenzoate (stereochemistry arbitrarily assigned) the title compound was obtained as a beige solid (0.12 g, 79 %): MS (ES+) *m/z* 341.0 (M + 1).

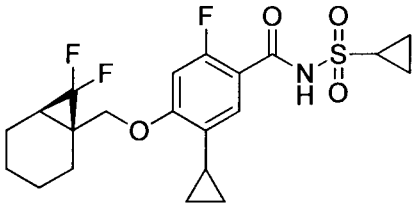
[02104] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide



[02105] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo- [4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a white gum (0.051 g, 81 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.64 (d, J = 9.1 Hz, 1H), 6.54 (d, J = 14.1 Hz, 1H), 4.25 (t, J = 7.9 Hz, 4H), 3.98 (s, 2H), 2.32-2.22 (m, 2H), 2.09-2.00 (m, 1H), 1.96-1.57 (m, 4H), 1.49-1.25 (m, 5H), 0.98-0.92 (m, 2H), 0.72-0.67 (m, 2H); MS (ES +) *m/z* 459.1 (M + 1).

[02106] EXAMPLE 384

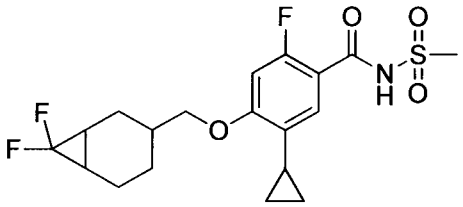
[02107] Synthesis of 5-cyclopropyl-N-(cyclopropylsulfonyl)-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide (stereochemistry arbitrarily assigned)



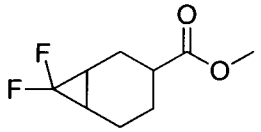
[02108] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-(((1*SR*,6*RS*)-7,7-difluorobicyclo- [4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a white gum (0.053 g, 87 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 14.5 Hz, 1H), 7.63 (d, J = 9.1 Hz, 1H), 6.53 (d, J = 14.1 Hz, 1H), 3.98 (s, 2H), 3.14-3.06 (m, 1H), 2.08-1.99 (m, 1H), 1.95-1.92 (m, 2H), 1.87-1.71 (m, 2H), 1.49-1.43 (m, 2H),1.40-1.25 (m, 5H), 1.17-1.13 (m, 2H), 0.98-0.91 (m, 2H), 0.71-0.66 (m, 2H); MS (ES+) *m/z* 444.0 (M + 1).

[02109] EXAMPLE 385

[02110] Synthesis of 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-3-yl)-methoxy)-2-fluoro-N-(methylsulfonyl)benzamide

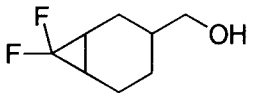


[02111] Step 1. Preparation of methyl 7,7-difluorobicyclo[4.1.0]heptane-3-carboxylate



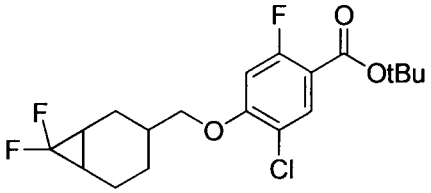
[02112] Following the procedure as described in Example 347 Step 2 and making non-critical variations to replace 1-((cyclohexenylmethoxy)methyl)-4-methoxybenzene with methyl cyclohex-3-enecarboxylate, the title compound was obtained as a colorless liquid (0.50 g, 52 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.36-1.85 (m, 3H), 1.87-1.41 (m, 5H), 1.40-1.15 (m, 1H);

[02113] Step 2. Preparation of (7,7-difluorobicyclo[4.1.0]heptan-3-yl)methanol



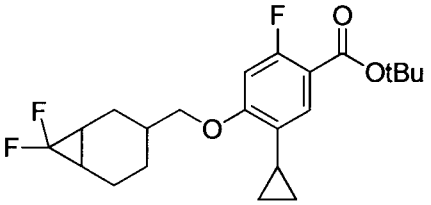
[02114] Following the procedure as described in Example 342 Step 1 and making non-critical variations to replace methyl cyclohex-1-enecarboxylate with 7,7-difluorobicyclo[4.1.0]- heptane-3-carboxylate, the title compound was obtained as a colorless liquid (0.30 g, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50-3.23 (m, 2H), 2.50-2.25 (m, 1H), 2.15-1.76 (m, 2H), 1.74-0.96 (m, 5H), 0.96-0.54 (m, 1H).

[02115] Step 3. Preparation of *tert*-butyl 5-chloro-4-((7,7-difluorobicyclo[4.1.0]heptan-3-yl)methoxy)-2-fluorobenzoate



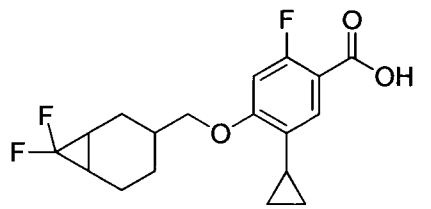
[02116] Following the procedure as described in Example 342 Step 3 and making variations as required to replace bicyclo[4.1.0]heptan-1-ylmethanol with (7,7-difluorobicyclo[4.1.0]heptan- 3-yl)methanol, the title compound was obtained as a colorless gum (0.48 g, 61%): MS (ES+) m/z 391.22 (M + 1).

[02117] Step 4. Preparation of *tert*-butyl 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-3-yl)methoxy)-2-fluorobenzoate



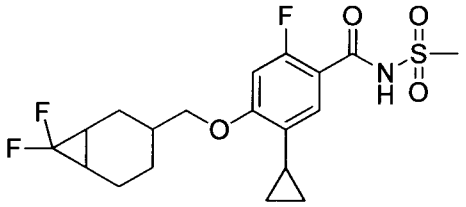
[02118] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1-ylmethoxy)- 5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-4-((7,7-difluorobicyclo[4.1.0]heptan-3-yl)methoxy)-2-fluorobenzoate, the title compound was obtained as oil (0.35 g, 48 %): MS (ES +) *m/z* 341.07 (M - 55).

[02119] Step 5. Preparation of 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan-3-yl)methoxy)-2-fluorobenzoic acid



[02120] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-(((1*r*,3*r*,5*r*,7*r*)-2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl- 2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4-((7,7-difluorobicyclo- [4.1.0]heptan- 3-yl)methoxy)-2-fluorobenzoate, the title compound was obtained as solid (0.24 g, 78 %): MS (ES+) *m/z* 341.10 (M + 1).

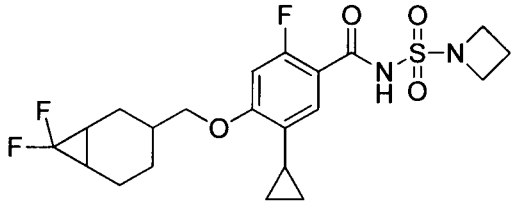
[02121] Step 6. Preparation of 5-cyclopropyl-4-((7,7-difluorobicyclo- [4.1.0]heptan-3-yl)methoxy) 2-fluoro-N-(methylsulfonyl)benzamide



[02122] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]- heptan-3-yl)methoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid (0.035 g, 35 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (br s, 1H), 7.11 (d, J = 8.33 Hz, 1H), 7.03-6.85 (m, 1H), 4.21-3.68 (m, 2H), 2.97-2.51 (m, 3H), 2.36-1.05 (m, 10H), 0.93-0.77 (m, 2H), 0.69-0.56 (m, 2H); MS (ES +) *m/z* 418.1 (M + 1).

[02123] EXAMPLE 386

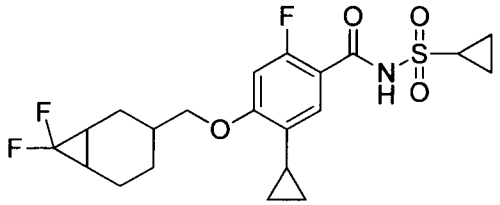
[02124] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((7,7-difluorobicyclo[4.1.0]- heptan-3-yl)methoxy)-2-fluorobenzamide



[02125] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan- 3-yl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.025 g, 22 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.59 (br s, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.03-6.87 (m, 1H), 4.14-3.77 (m, 6H), 2.94-2.50 (m, 1H), 2.43-1.49 (m, 8H), 1.48-1.06 (m, 2H), 1.06-0.75 (m, 3H), 0.75-0.56 (m, 2H); MS (ES +) *m/z* 459.07 (M + 1).

[02126] EXAMPLE 387

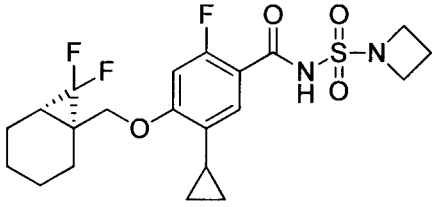
[02127] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)- 4-((7,7-difluorobicyclo[4.1.0]-heptan-3-yl)methoxy)-2-fluorobenzamide



[02128] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-((7,7-difluorobicyclo[4.1.0]heptan- 3-yl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a colorless solid (0.012 g, 11 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (br s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.02-6.87 (m, 1H), 4.14-3.78 (m, 2H), 3.12-2.50 (m, 2H), 2.42-2.05 (m, 2H), 2.05-1.27 (m, 5H), 1.28-1.14 (m, 2H), 1.15-0.95 (m, 4H), 0.95-0.74 (m, 2H), 0.70-0.54 (m, 2H); MS (ES +) *m/z* 444.1 (M + 1).

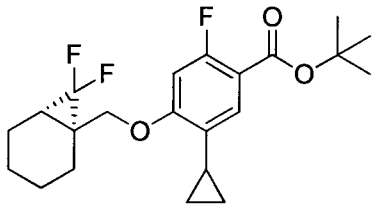
[02129] EXAMPLE 388

[02130] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide



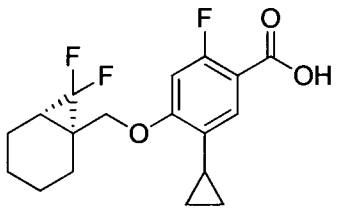
[02131]

[02132] Step 1. Preparation of *tert*-butyl 5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7- difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoate



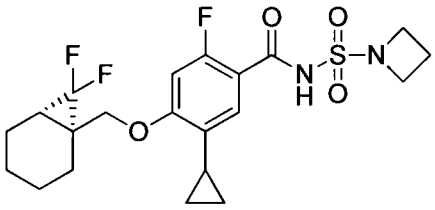
[02133] Following the procedure as described in Example 342 Step 4 and making variations as required to replace *tert*-butyl 4-(bicyclo[4.1.0]heptan-1- ylmethoxy)-5-chloro-2-fluorobenzoate with *tert*-butyl 5-chloro-4-(((1*RS*,6*SR*)-7,7- difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoate (stereochemistry arbitrarily assigned), the title compound was obtained as a yellow oil (0.23 g, 81 %): MS (ES +) *m/z* 341.0 (M - 55).

[02134] Step 2. Preparation of 5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo[4.1.0]- heptan-1-yl)methoxy)-2-fluorobenzoic acid



[02135] Following the procedure as described in Example 332 Step 6, and making variations as required to replace *tert*-butyl 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)- methoxy)-2-fluorobenzoate, the title compound was obtained as a beige solid (0.12 g, 79 %): MS (ES+) *m/z* 341.0 (M + 1).

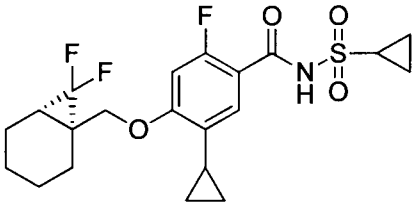
[02136] Step 3. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide



[02137] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo- [4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid and to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained as a white gum (0.040 g, 30 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (br s, 1H), 7.14 (d, J = 8.25 Hz, 1H), 6.92 (d, J = 12.76 Hz, 1H), 4.17-3.92 (m, 6H), 2.21-2.05 (m, 2H), 2.04-1.54 (m, 6H), 1.36-1.14 (m, 4H), 0.92-0.80 (m, 2H), 0.72-0.63 (m, 2H); MS (ES +) *m/z* 459.1 (M + 1).

[02138] EXAMPLE 389

[02139] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo[4.1.0]heptan-1-yl)methoxy)-2-fluorobenzamide

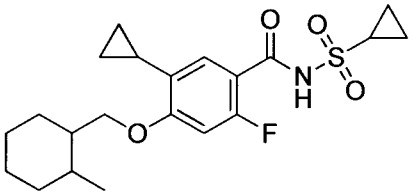


[02140] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace 4-((2-cyanoadamantan-2-yl)methoxy)- 5-cyclopropyl-2-fluorobenzoic acid with 5-cyclopropyl-4-(((1*RS*,6*SR*)-7,7-difluorobicyclo- [4.1.0]heptan-1-yl)methoxy)-2-fluorobenzoic acid and

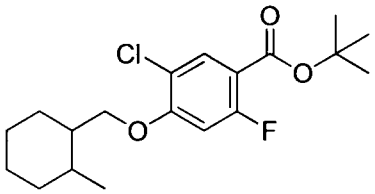
to replace methanesulfonamide with cyclopropanesulfonamide, the title compound was obtained as a white gum (0.030 g, 23 %): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 12.9 Hz, 1H), 4.17-3.92 (m, 2H), 3.10-2.97 (m, 1H), 2.04-1.54 (m, 6H), 1.34-1.15 (m, 4H), 1.14-1.02 (m, 4H), 0.92-0.80 (m, 2H), 0.72-0.62 (m, 2H); MS (ES+) *m/z* 444.1 (M + 1).

[02141] EXAMPLE 390

[02142] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((2-methylcyclohexyl)methoxy)-benzamide

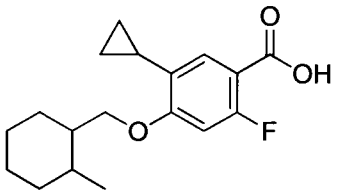


[02143] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((2-methylcyclohexyl)-methoxy)benzoate



[02144] To a solution of (2-methylcyclohexyl)methanol (1.28 g, 9.99 mmol) in anhydrous dimethylsulfoxide (20 mL) was added cesium carbonate (5.87 g, 18.06 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (2.23 g, 8.96 mmol). The reaction mixture was stirred at 70 °C for 16 hours; cooled to ambient temperature and acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with ethyl acetate (2 x 15 mL), the combined organics were washed with brine (15 mL); dried over anhydrous sodium sulfate; filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (0 to 10% ethyl acetate in hexanes) afforded the title compound (2.30 g, 72%); MS(ES+) *m/z* 303.2, 301.2 (M - 54); MS(ES-) *m/z* 301.2, 299.2 (M - 56).

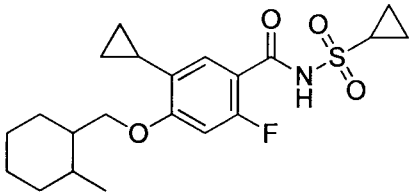
[02145] Step 2. Preparation of 5-cyclopropyl-2-fluoro-4-((2-methyl- cyclohexyl)methoxy)benzoic acid



[02146] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((2-methylcyclohexyl)- methoxy)benzoate (1.50 g, 4.30 mmol), cyclopropylboronic acid (0.55 g, 6.41 mmol), potassium phosphate (3.60 g, 17.2 mmol) and tricyclohexylphosphine tetrafluoroborate (0.31 g, 0.86 mmol) in toluene (15 mL) and water (1.5 mL) under a nitrogen atmosphere was added palladium acetate (0.09 g, 0.43 mmol). The reaction mixture was

heated at 130 °C for 30 minutes in the microwave, and then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate, the combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded *tert*-butyl 5-cyclopropyl-2-fluoro-4-((2-methylcyclohexyl)- methoxy)benzoate (1.5 g, 4.3 mmol), which was used directly for the next step. To a solution of this compound (1.50 g, 4.30 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (20 mL). The reaction mixture was stirred at 0 °C for 1 hour and then concentrated in *vacuo*. The residue was triturated in diethyl ether (10 mL), the solid was filtered, rinsed with diethyl ether (2 x 10 mL) and dried to give the title compound (0.63 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 12.9 Hz, 1H), 3.87 (dd, J = 6.7, 2.3 Hz, 2H), 2.17-1.91 (m, 3H), 1.76-1.31 (m, 8H), 0.98-0.84 (m, 5H), 0.67-0.58 (m, 2H).

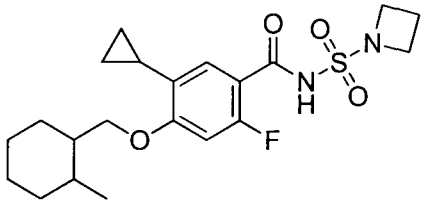
[02147] Step 3. Preparation of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro-4-((2-methylcyclohexyl)methoxy)benzamide



[02148] To a stirred solution of 5-cyclopropyl-2-fluoro-4-((2-methylcyclohexyl)- methoxy)benzoic acid (0.093 g, 0.305 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen was added carbonyldiimidazole (0.074 g, 0.457 mmol) and the reaction mixture was stirred at 70 °C for 1 hour. The mixture was cooled to room temperature and 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.07 mL, 0.45 mmol) was added followed by cyclopropanesulfonamide (0.06 mg, 0.52 mmol). Stirring was continued at ambient temperature for 18 hours. 5% aqueous hydrochloric acid solution (0.15 mL) was added and the mixture was concentrated and directly purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.05 g, 43%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79-8.58 (m, 1H), 7.56 (d, J = 9.1 Hz, 1H), 6.57 (d, J = 14.5 Hz, 1H), 3.87 (dd, J = 7.0, 2.7 Hz, 2H), 3.08 (tt, J = 8.1, 8.1, 4.8, 4.8 Hz, 1H), 2.21-1.93 (m, 3H), 1.76-1.35 (m, 9H), 1.13 (dq, J = 6.20, 6.08, 1.31 Hz, 2H), 0.98-0.86 (m, 5H), 0.68-0.59 (m, 2H); MS(ES+) *m/z* 410.1 (M + 1) ; MS(ES-) *m/z* 408.2 (M - 1).

[02149] EXAMPLE 391

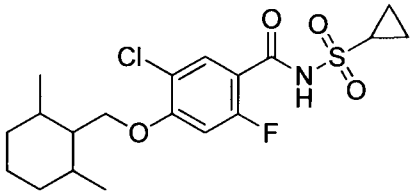
[02150] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4- ((2-methylcyclohexyl)-methoxy)benzamide



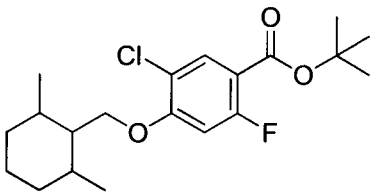
[02151] Following the procedure as described in Example 390 step 3, and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.034 g, 26%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (m, 1H), 7.56 (d, *J* = 9.1 Hz, 1H), 6.58 (d, *J* = 14.4 Hz, 1H), 4.23 (t, *J* = 7.7 Hz, 4H), 3.87 (dd, *J* = 6.9, 2.5 Hz, 2H), 2.25 (p, *J* = 7.7 Hz, 2H), 2.17-1.96 (m, 3H), 1.77-1.21 (m, 8H), 0.98-0.84 (m, 5H), 0.68-0.60 (m, 2H); MS(ES+) *m/z* 425.1 (M + 1) ; MS(ES-) *m/z* 423.2 (M - 1).

[02152] EXAMPLE 392

[02153] Synthesis of 5-chloro-N-(cyclopropylsulfonyl)-4-((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



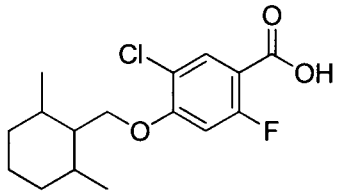
[02154] Step 1. Preparation of *tert*-butyl 5-chloro-4-((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzoate.



[02155] To a solution of (2,6-dimethylcyclohexyl)methanol (0.34 g, 2.40 mmol) in anhydrous dimethylsulfoxide (5 mL) were added cesium carbonate (1.56 g, 4.80 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (0.53 g, 2.16 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was cooled down and acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with ethyl acetate (2 x 15 mL), the combined organics were washed with brine (15 mL); dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue

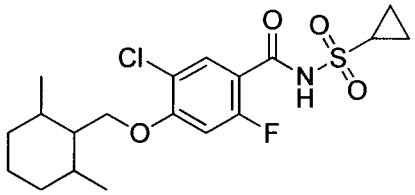
by column chromatography (0 to10% ethyl acetate in hexanes) afforded the title compound (0.43 g, 54%): MS (ES+) *m/z* 317.2, 315.2 (M - 54); MS(ES-) *m/z* 315.1, 313.1, (M - 56).

[02156] Step 2. Preparation of 5-chloro-4-((2,6-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid.



[02157] To a solution of *tert*-butyl 5-chloro-4-((2,6-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate (0.21 g, 0.58 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at 0 °C for 1 hour and then concentrated in *vacuo*. The residue was purified by column chromatography (0 to 30% gradient ethyl acetate in hexanes) to afford the title compound (0.071 g, 38%): MS (ES-) *m/z* 315.2, 313.2 (M - 1).

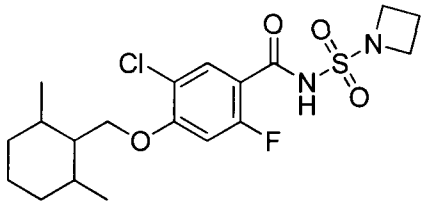
[02158] Step 3. Preparation of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-4- ((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



[02159] To a stirred solution of 5-chloro-4-((2,6-dimethylcyclohexyl)methoxy)- 2-fluorobenzoic acid (0.07 g, 0.22 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen was added carbonyldiimidazole (0.053 g, 0.33 mmol). The reaction mixture was stirred at 70 °C for 1 hour. The mixture was cooled to room temperature and 1,8-diazabicyclo[5.4.0]undec- 7-ene (0.07 mL, 0.45 mmol) was added followed by cyclopropanesulfonamide (0.045 mg, 0.374 mmol). Stirring continued at room temperature for 18 hours. 5% aqueous hydrochloric acid solution (0.15 mL) was added and the mixture was concentrated and directly purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.026 g, 28%) as a colorless solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09-11.90 (m, 1H), 7.71 (d, J = 7.07 Hz, 1H), 7.35 (d, J = 12.32 Hz, 1H), 4.12-4.06 (m, 2H), 3.11-2.96 (m, 1H), 1.98-0.80 (m, 19H); MS(ES-) *m/z* 416.2, 418.2 (M - 1).

[02160] EXAMPLE 393

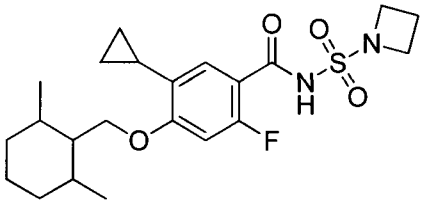
[02161] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-4-((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



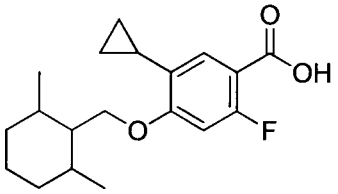
[02162] Following the procedure as described in Example 392 step 3, and making variations as required to replace methanesulfonamide with azetidine-1-sulfonamide, the title compound was obtained (0.009 g, 10%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73-8.55 (m, 1H), 7.57 (d, J = 9.1 Hz, 1H), 6.62 (d, J = 14.5 Hz, 1H), 4.23 (t, J = 7.7 Hz, 4H), 4.01 (d, J = 4.5 Hz, 2H), 2.34-2.17 (m, 2H), 2.07-1.96 (m, 2H), 1.85-0.58 (m, 13H); MS (ES+) *m/z* 433.1, 435.1 (M + 1); MS(ES-) *m/z* 433.2, 431.2 (M - 1).

[02163] EXAMPLE 394

[02164] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



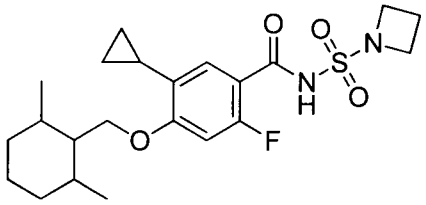
[02165] Step 1. Preparation of 5-cyclopropyl-4-((2,6-dimethylcyclohexyl)- methoxy)-2-fluorobenzoic acid.



[02166] To a solution of *tert*-butyl 5-chloro-4-((2,6-dimethylcyclohexyl)- methoxy)-2-fluorobenzoate (0.43 g, 1.16 mmol), cyclopropylboronic acid (0.14 g, 1.74 mmol), potassium phosphate (1.48 g, 7.00 mmol) and tricyclohexylphosphine tetrafluoroborate (0.085 g, 0.230 mmol) in toluene (5 mL) and water (0.5 mL) under a nitrogen atmosphere was added palladium acetate (0.04 g, 0.12 mmol). The reaction mixture was heated at 130 °C for 30 minutes in the microwave then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL), the combined organics were washed with brine; dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded *tert*-butyl

5-cyclopropyl-4-((2,6-dimethylcyclohexyl)methoxy)-2-fluorobenzoate (0.43 g, 1.16 mmol) which was used directly into the next step. To a solution of this compound (0.43 g, 1.16 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at 0 °C for 1 hour and then concentrated in *vacuo*. The residue was purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.142 g, 38%). MS (ES-) *m/z* 319.2 (M - 1).

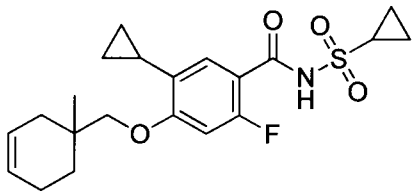
[02167] Step 2. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl- 4-((2,6-dimethylcyclohexyl)-methoxy)-2-fluorobenzamide



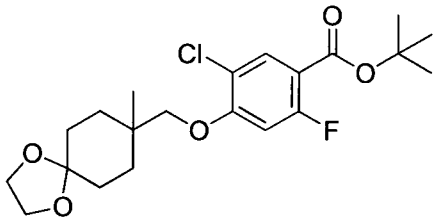
[02168] To a stirred solution of 5-cyclopropyl-4-((2,6-dimethylcyclohexyl)methoxy)- 2-fluorobenzoic acid (0.07 g, 0.22 mmol) in tetrahydrofuran (2 mL) and under an atmosphere of nitrogen was added carbonyldiimidazole (0.053 g, 0.33 mmol) and the reaction mixture was stirred at 70 °C for 1 hour. The mixture was cooled down to ambient temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.07 mL, 0.45 mmol) was added followed by azetidine-1-sulfonamide (0.051 g, 0.37 mmol) and the stirring continued at ambient temperature for 18 hours. 5% aqueous hydrochloric acid solution (0.15 mL) was added and the mixture was concentrated and directly purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.022 g, 22%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.55 (m, 1H), 7.57 (d, J = 9.1 Hz, 1H), 6.62 (d, J = 14.5 Hz, 1H), 4.23 (t, J = 7.7 Hz, 4H), 4.01 (d, J = 4.5 Hz, 2H), 2.35-2.17 (m, 2H), 2.07-1.95 (m, 2H), 1.86-0.56 (m, 20H); MS(ES+) *m/z* 439.1 (M + 1); MS(ES-) *m/z* 437.2 (M - 1).

[02169] EXAMPLE 395

[02170] Synthesis of 5-cyclopropyl-*N*-(cyclopropylsulfonyl)-2-fluoro- 4-((1-methylcyclohex-3-en-1-yl)methoxy)benzamide

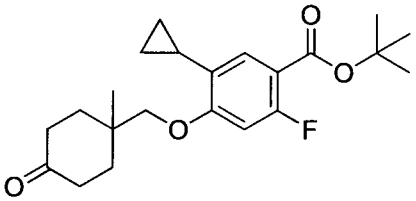


[02171] Step 1. Preparation of *tert*-butyl 5-chloro-2-fluoro-4-((8-methyl-1,4- dioxaspiro[4.5]decan-8-yl)methoxy)benzoate.



[02172] To a solution of (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (0.301 g, 1.65 mmol) in anhydrous dimethylsulfoxide (3 mL) were added cesium carbonate (1.07 g, 3.30 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (0.37 g, 1.49 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was cooled down to room temperature and acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL); dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (0 to 10% ethyl acetate in hexanes) afforded the title compound (0.28 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 7.67 Hz, 1H), 6.60 (d, J = 12.13 Hz, 1H), 3.96-3.89 (m, 4H), 3.72 (s, 1H), 1.98-1.37 (m, 17H), 1.12 (s, 1H).

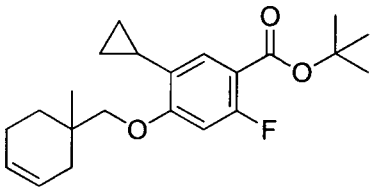
[02173] Step 2. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4- oxocyclohexyl)-methoxy)benzoate.



[02174] To a solution of *tert*-butyl 5-chloro-2-fluoro-4-((8-methyl-1,4- dioxaspiro[4.5]decan-8-yl)-methoxy)benzoate (0.28 g, 0.67 mmol), cyclopropylboronic acid (0.08 g, 1.00 mmol), potassium phosphate (0.57 g, 2.68 mmol) and tricyclohexylphosphine tetrafluoroborate (0.05 g, 0.14 mmol) in toluene (3 mL) and water (0.3 mL) under a nitrogen atmosphere was added palladium acetate (0.016 g, 0.07 mmol). The reaction mixture was heated at 130 °C for 30 minutes in the microwave and then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate (2 x 15 mL), the combined organics were washed with brine (10 mL); dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded *tert*-butyl 5-cyclopropyl-2-fluoro-4-((8-methyl-1,4-dioxaspiro[4.5]-decan-8-yl)methoxy)benzoate (0.28 g, 0.67 mmol) which was used directly into the next step. To a solution of this compound (0.28 g, 0.67 mmol) in dichloromethane (5 mL), was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at ambient temperature for 20 minutes and then directly purified by

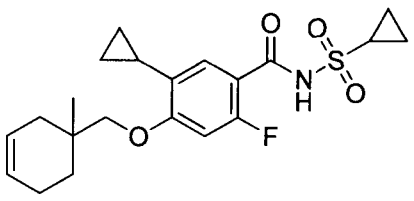
column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.071 g, 28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 12.5 Hz, 1H), 3.85-3.76 (m, 2H), 2.58-2.29 (m, 4H), 2.06-1.73 (m, 5H), 1.55 (s, 9H), 1.28 (s, 3H), 0.91-0.82 (m, 2H), 0.64-0.57 (m, 2H).

[02175] Step 3. Preparation of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methylcyclohex- 3-en-1-yl)-methoxy)benzoate.



[02176] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methyl-4-oxocyclohexyl)-methoxy)benzoate (0.071 g, 0.190 mmol) in (3 mL) and methanol(1 mL) was added sodium borohydride (0.014 g, 0.38 mmol) and the reaction mixture was stirred 20 minutes at ambient temperature. The mixture was then quenched by addition of 1N hydrochloric acid until reaching pH = 1. The mixture was extracted with dichloromethane (3 x 10 mL), the organic layers were combined and washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to afford *tert*-butyl 5-cyclopropyl-2-fluoro-4-((4-hydroxy-1- methylcyclohexyl)methoxy)benzoate (0.071 g, 99%) which was used directly for next step. To a solution of the previous compound in dichloromethane (3 mL) at -78 °C was added dropwise diethylaminosulfur trifluoride (0.15 g, 0.94 mmol) dissolved in dichloromethane (1 mL) and the reaction mixture was stirred 1 hour at -78 °C, then slowly warmed up to ambient temperature during 2 hours. The mixture was then stirred at ambient temperature for a further 1 hour and then cooled down to -78 °C and quenched by addition of methanol (1 mL), followed by a saturated aqueous solution of sodium bicarbonate (2 mL). The mixture was warmed up to ambient temperature and extracted with dichloromethane (3 x 10 mL). The organic layers were combined and washed with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by chromatography (0 to 30% ethyl acetate in hexanes) to give the title compound (0.048 g, 70%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.43 Hz, 1H), 6.49 (d, J = 12.75 Hz, 1H), 5.73-5.56 (m, 2H), 3.76-3.61 (m, 2H), 2.14-1.43 (m, 16H), 1.08 (s, 3H), 0.92-0.78 (m, 2H), 0.66-0.57 (m, 2H).

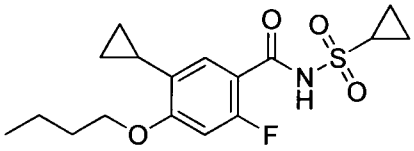
[02177] Step 4. Preparation of *5*-cyclopropyl-*N*-(cyclopropylsulfonyl)- 2-fluoro-4-((1-methylcyclohex-3-en-1-yl)methoxy)benzamide



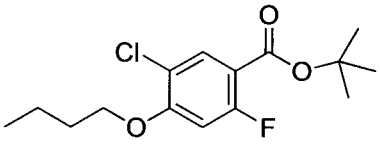
[02178] To a solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-((1-methylcyclohex-3-en-1-yl)methoxy)benzoate (0.041 g, 0.11 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 1 hour and then concentrated in *vacuo* to afford 5-cyclopropyl-2-fluoro-4-((1-methylcyclohex-3-en-1- yl)methoxy)benzoic acid (0.033 g, 0.11 mmol) which was used directly in the next step. This compound was dissolved in tetrahydrofuran (2 mL) under an atmosphere of nitrogen and carbonyldiimidazole (0.024 g, 0.15 mmol) was added to the solution and the reaction mixture was stirred at 70 °C for 1 hour. The mixture was cooled to ambient temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 mg, 0.17 mmol) was added, followed by cyclopropanesulfonamide (0.021 mg, 0.170 mmol) and stirring continued at ambient temperature for 18 hours. 5% aqueous hydrochloric acid solution (0.15 mL) was added and the mixture was concentrated and purified by column chromatography (0 to 30% ethyl acetate in hexanes) to afford the title compound (0.012 g, 24%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18-8.28 (br, 1H), 7.60 (s, 1H), 6.56 (d, J = 14.4 Hz, 1H), 5.75-5.57 (m, 2H), 3.76 (d, J = 8.5 Hz, 1H), 3.69 (d, J = 8.6 Hz, 1H), 3.17-3.00 (m, 1H), 2.18-1.95 (m, 4H), 1.95-1.81 (m, 1H), 1.78-1.63 (m, 1H), 1.57-1.36 (m, 3H), 1.23 (s, 3H), 1.18-1.05 (m, 2H), 0.96-0.85 (m, 2H), 0.68-0.59 (m, 2H); MS(ES+) *m/z* 408.2 (M + 1) ; MS(ES-) *m/z* 406.2 (M - 1).

[02179] EXAMPLE 396

[02180] Synthesis of 4-butoxy-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide

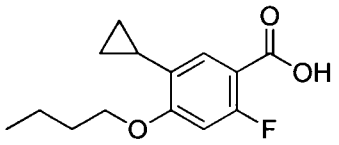


[02181] Step 1. Preparation of *tert*-butyl 4-butoxy-5-chloro-2-fluorobenzoate



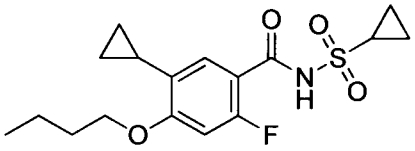
[02182] To a solution of butanol (0.07 g, 0.99 mmol) in anhydrous dimethylsulfoxide (2 mL) were added cesium carbonate (0.59 g, 1.81 mmol) and *tert*-butyl 5-chloro-2,4-difluorobenzoate (0.22 g, 0.90 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was cooled down to room temperature and acidified to pH = 1 with 5% aqueous hydrochloric acid solution and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine (15 mL); dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by column chromatography (0 to 10% ethyl acetate in hexanes) afforded the title compound (0.23 g, 72%); MS (ES+) *m/z* 303.2, 305.2 (M + 1).

[02183] Step 2. Preparation of 4-butoxy-5-cyclopropyl-2-fluorobenzoic acid.



[02184] To a solution of *tert*-butyl 4-butoxy-5-chloro-2-fluorobenzoate (0.23 g, 0.76 mmol), cyclopropylboronic acid (0.10 g, 1.14 mmol), potassium phosphate (0.64 g, 3.10 mmol) and tricyclohexylphosphine tetrafluoroborate (0.05 g, 0.15 mmol) in toluene (3 mL) and water (0.3 mL) under a nitrogen atmosphere was added palladium acetate (0.005 g, 0.076 mmol). The reaction mixture was heated at 130 °C for 30 minutes in the microwave then cooled to ambient temperature. Water (20 mL) was added and the mixture extracted with ethyl acetate (2 x 15 mL). The combined organics were washed with brine; dried over anhydrous sodium sulfate and concentrated in *vacuo*. Purification of the residue by column chromatography (5% ethyl acetate in hexanes) afforded *tert*-butyl 4-butoxy-5-cyclopropyl-2-fluorobenzoate (0.15 g, 67%), which was used directly in the next step. To a solution of this compound (0.15 g, 0.48 mmol) in dichloromethane (2 mL), was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 1 hour and then concentrated in *vacuo*. The residue was triturated in diethyl ether (10 mL) and the solid was filtered, rinsed with diethyl ether (2 x 10 mL) and dried to give the title compound (0.048 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 1H), 6.56 (d, J = 12.7 Hz, 1H), 4.08-3.95 (m, 2H), 2.18-0.39 (m, 14H).

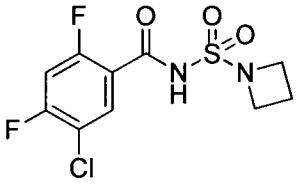
[02185] Step 3. Preparation of 4-butoxy-5-cyclopropyl-*N*-(cyclopropyl- sulfonyl)-2-fluorobenzamide



[02186] To a stirred solution of 4-butoxy-5-cyclopropyl-2-fluorobenzoic acid (0.039 g, 0.15 mmol) in tetrahydrofuran (1 mL) and under an atmosphere of nitrogen was added carbonyldiimidazole (0.030 g, 0.18 mmol) and the reaction mixture was stirred at 70 °C for 1 hour. The mixture was cooled down to room temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.02 mmol) was added followed by cyclopropanesulfonamide (0.024 g, 0.20 mmol) and the stirring continued at ambient temperature for 18 hours. 5% aqueous hydrochloric acid solution (0.15 mL) was added and the mixture was concentrated and directly purified by column chromatography (0 to 30% gradient ethyl acetate in hexanes) to afford the title compound (0.011 g, 20%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82-8.57 (m, 1H), 7.57 (d, J = 9.24 Hz, 1H), 6.58 (d, J = 14.42 Hz, 1H), 4.04 (t, J = 6.30, 6.30 Hz, 2H), 3.16-3.05 (m, 1H), 2.18-1.74 (m, 3H), 0.72-0.61 (m, 2H), 1.71-0.84 (m, 13H), 0.74-0.60 (m, 2H); MS (ES+) *m/z* 356.1 (M + 1); MS(ES-) *m/z* 354.2 (M - 1).

[02187] EXAMPLE 397

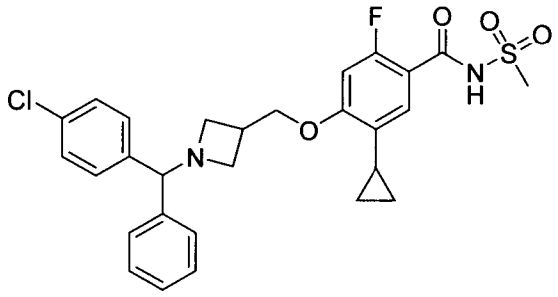
[02188] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-chloro-2,4-difluorobenzamide



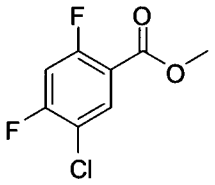
[02189] Following the procedure as described in Example 332 Step 7 and making non-critical variations to replace methanesulfonamide with azetidine-1-sulfonamide and to replace 4-((2-cyanoadamantan-2-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2,4-difluorobenzoic acid, the title compound was obtained as a colorless powder (7.0 g, 70%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.71 (t, J = 9.8 Hz, 1H), 4.03 (t, J = 7.7 Hz, 4H), 2.20-2.10 (m, 2H); MS (ES-) *m/z* 309.1, 311.1 (M - 1).

[02190] EXAMPLE 398

[02191] Synthesis of 4-((1-((4-chlorophenyl)(phenyl)methyl)azetidin-3-yl)-methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

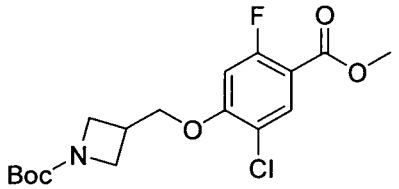


[02192] Step 1. Preparation of methyl 5-chloro-2,4-difluorobenzoate



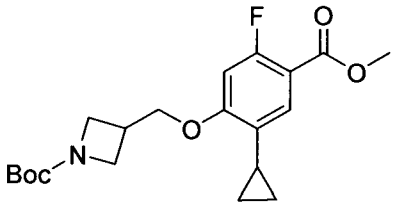
a. To a stirred solution of 5-chloro-2,4-difluorobenzoic acid (10.0 g, 52 mmol) in MeOH (150 mL) was added sulfuric acid (1 mL). After stirring at 90 °C for 16 h, the solvent was removed in vacuo and the crude product was quenched by saturated aqueous sodium bicarbonate and extracted with DCM (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give target compound (10.0 g, 94%) as a white solid.

[02193] Step 2. Preparation of *tert*-butyl 3-((2-chloro-5-fluoro-4-(methoxycarbonyl)-phenoxy)methyl)azetidine-1-carboxylate



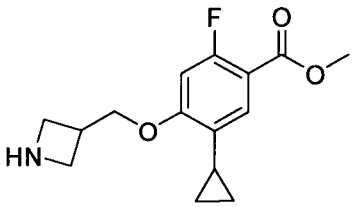
[02194] A mixture of methyl 5-chloro-2,4-difluorobenzoate (2.2 g, 10.7 mmol), *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (2.0 g, 10.7 mmol) and potassium carbonate (4.43 g, 32.1 mmol) in DMF (30 mL) was stirred at 30 °C for 16 h. The mixture was quenched by water and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column (eluting with petroleum ether/ethyl acetate, from 20/1 to 3/1) to give *tert*-butyl 3-((2-chloro-5-fluoro-4-(methoxycarbonyl)phenoxy)methyl)azetidine-1-carboxylate (1.2 g, 30%) as a pale yellow oil. LCMS (ESI) m/z: 318.0 $[M-56+H]^+$.

[02195] Step 3. Preparation of *tert*-butyl 3-((2-cyclopropyl-5-fluoro-4-(methoxycarbonyl)-phenoxy)methyl)azetidine-1-carboxylate



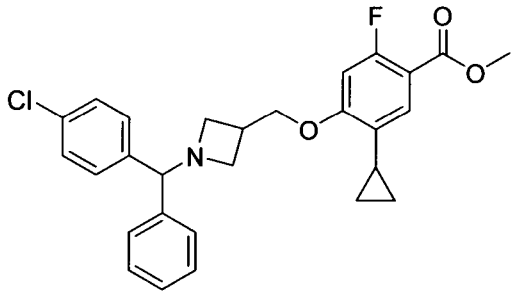
[02196] To a mixture of *tert*-butyl 3-((2-chloro-5-fluoro-4-(methoxycarbonyl)- phenoxy)methyl)-azetidine-1-carboxylate (1.2 g, 3.2 mmol), cyclopropylboronic acid (415 mg, 4.8 mmol), potassium phosphate (2.04 g, 9.6 mmol) and tricyclohexylphosphine tetrafluoroborate (118 mg, 0.32 mmol) in toluene (20 mL) and water (1 mL) under a nitrogen atmosphere was added palladium acetate (36 mg, 0.16 mmol). The reaction mixture was heated to 100 °C for 16 h and then cooled to ambient temperature. The mixture was quenched by water (50 mL) and extracted with ethyl acetate (50 mL × 3), the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column (eluting with petroleum ether/ethyl acetate, from 10/1 to 2/1) to afford target compound (1.0 g, 83%) as a pale yellow solid. LCMS (ESI) m/z: 324.3 $[M-56+H]^+$.

[02197] Step 4. Preparation of methyl 4-(azetidin-3-ylmethoxy)-5- cyclopropyl-2-fluorobenzoate



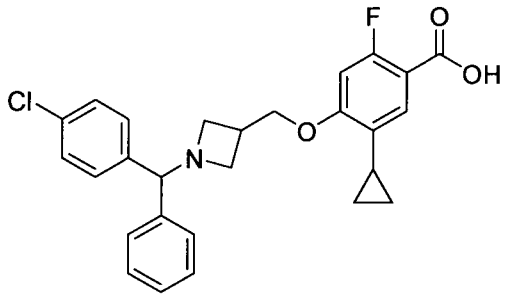
[02198] A solution of *tert*-butyl 3-((2-cyclopropyl-5-fluoro-4-(methoxycarbonyl)phenoxy)
[02199] methyl)azetidine-1-carboxylate (1.0 g, 2.6 mmol) in DCM (5 mL) and trifluoroacetic acid (5 mL) was stirred at room temperature for 1 h. The reaction was quenched by saturated aqueous $NaHCO_3$ and extracted with DCM (30 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to give methyl 4-(azetidin-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate (700 mg, crude) as a solid which was used in the next step without purification. LCMS (ESI) m/z: 280.1$[M+H]^+$.

[02200] Step 5. Preparation of methyl 4-((1-((4-chlorophenyl)(phenyl)-methyl)azetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate



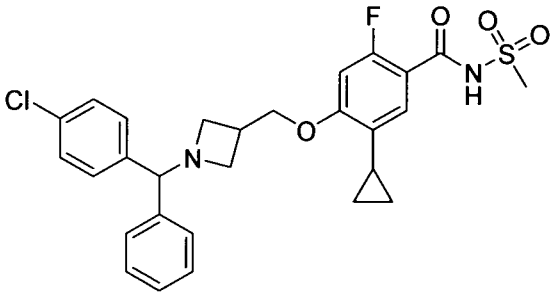
[02201] A mixture of methyl 4-(azetidin-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate (58 mg, 0.21 mmol), 1-chloro-4-(chloro(phenyl)methyl)benzene (74 mg, 0.31 mmol), potassium carbonate (86 mg, 0.62 mmol) and sodium iodide (32 mg, 0.21 mmol) in MeCN (10 mL) was stirred at 80 °C for 16 h. The reaction mixture was diluted with EtOAc (100 mL) and brine (50 mL). The organic layer was separated and washed with brine (50 × 2 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (eluting with petroleum ether/EtOAc = 4/1) to give the target compound (50 mg, 50%) as a pale yellow oil. LCMS (ESI) m/z: 480.1 $[M+H]^+$.

[02202] Step 6. Preparation of 4-((1-((4-chlorophenyl)(phenyl)methyl)azetidin-3-yl)-methoxy)-5-cyclopropyl-2-fluorobenzoic acid



[02203] A mixture of methyl 4-((1-((4-chlorophenyl)(phenyl)methyl)azetidin 3-yl)-methoxy)-5-cyclopropyl-2-fluorobenzoate (50 mg, 0.10 mmol) and lithium hydroxide (13 mg, 0.31mmol) in THF (10 mL) and H_2O (10 mL) was stirred at 50 °C for 3 h. The mixture was diluted with EtOAc (100 mL), washed with HCl (2.0 M, 20 mL), brine (50 × 2 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the target product (50 mg) as oil which was used in the next step without further purification. LCMS (ESI) m/z: 466.1 $[M+H]^+$.

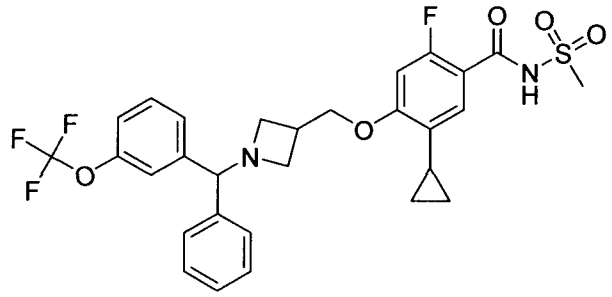
[02204] Step 7. Preparation of 4-((1-((4-chlorophenyl)(phenyl)methyl)azetidin- 3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



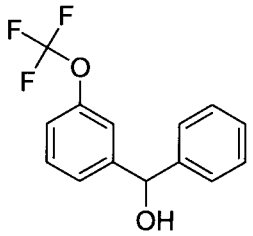
[02205] A mixture of 4-((1-((4-chlorophenyl)(phenyl)methyl)azetidin-3-yl)-methoxy)-5-cyclopropyl-2-fluorobenzoic acid (50 mg, 0.11 mmol), methanesulfonamide (15 mg, 0.16 mmol), EDCI (31 mg, 0.16 mmol) and DMAP (20 mg, 0.16 mmol) in DCM (20 mL) was stirred at 25 °C for 16 h. The reaction mixture was diluted with EtOAc (100 mL), washed with HCl (2.0 M, 20 mL) and brine (50 × 2 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase Combiflash (35%-38% MeCN in 0.5% NH_4HCO_3) to give the target product (11.0 mg, 19%) as an off-white solid. LCMS (ESI) Method A: RT = 5.83 min, m/z: 543.5 $[M+H]^+$. ^{1}H-NMR (500 MHz, MeOH-d_4): δ 7.31-7.29 (m, 4H), 7.23-7.19 (m, 5H), 7.14-7.11 (m, 1H), 6.69-6.66 (m, 1H), 4.51 (s, 1H), 4.08 (d, J = 6.5 Hz, 2H), 3.39-3.34 (m, 2H), 3.32-3.13 (m, 5H), 2.94-2.90 (m, 1H), 1.99-1.96 (m, 1H), 0.84-0.80 (m, 2H), 0.58-0.54 (m, 2H).

[02206] EXAMPLE 399

[02207] Synthesis of 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)-4-((1-(phenyl(3-(trifluoromethoxy)phenyl)methyl)azetidin-3-yl)methoxy)benzamide

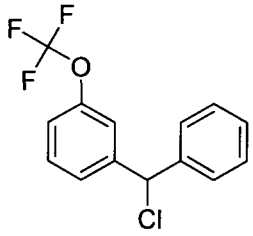


[02208] Step 1. Preparation of phenyl(3-(trifluoromethoxy)phenyl)methanol



[02209] To a solution of 3-(trifluoromethoxy)benzaldehyde (1.30 g, 6.84 mmol) in anhydrous THF (50 mL) was added phenylmagnesium bromide (1.0 M, 17 mL, 17 mmol) dropwise at 0 °C. The resulting mixture was stirred at 80 °C for 3 h. The mixture was cooled to room temperature and diluted with EtOAc (100 mL). The organic layer was washed with saturated NH_4Cl (50 mL) and brine (50 × 2 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase Combiflash (50%-55% MeCN in 0.5% NH_4HCO_3) to give target product (1.36 g, 74%) as a pale yellow oil. LCMS (ESI) m/z: 267.1 $[M-H]^-$. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.44-7.40 (m, 5H), 7.33-7.30 (m, 2H), 7.23-7.18 (m, 2H), 6.13 (d, J = 4.0 Hz, 1H), 5.79 (d, J = 4.0 Hz, 1H).

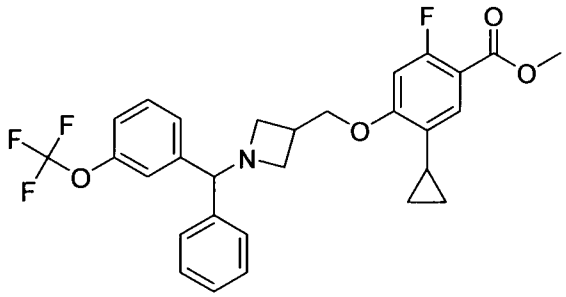
[02210] Step 2. Preparation of 1-(chloro(phenyl)methyl)-3-(trifluoromethoxy)benzene



[02211] A solution of phenyl(3-(trifluoromethoxy)phenyl)methanol (300 mg, 1.12 mmol) in thionyl chloride (50 mL) was refluxed for 5 h. The solvent was removed and the residue was purified by silica gel chromatography (eluting with petroleum ether/EtOAc = 100/1) to give the target compound (140 mg, 44%)

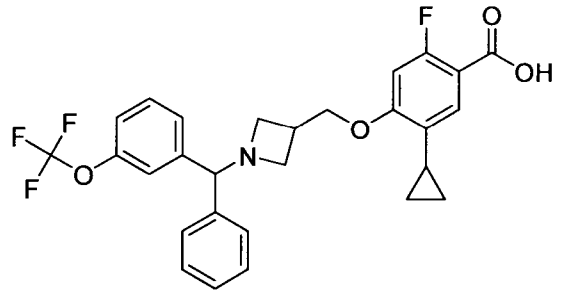
as a pale yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.56-7.49 (m, 5H), 7.42-7.40 (m, 2H), 7.35-7.32 (m, 2H), 6.62 (m, 1H).

[02212] Step 3. Preparation of methyl 5-cyclopropyl-2-fluoro-4-((1-(phenyl(3- (trifluoromethoxy)-phenyl)methyl)azetidin-3-yl)methoxy)benzoate



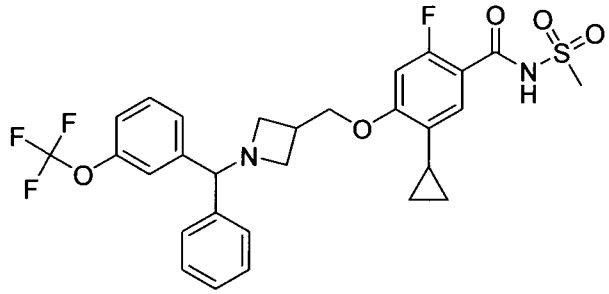
[02213] The synthetic procedure was similar to step 5 of Example 398. LCMS (ESI) m/z: 530.1 $[M+H]^+$.

[02214] Step 4. Preparation of 5-cyclopropyl-2-fluoro-4-((1-(phenyl(3-(trifluoromethoxy)-phenyl)methyl)azetidin-3-yl) methoxy)benzoic acid



[02215] The synthetic procedure was similar to step 6 of Example 398. LCMS (ESI) m/z: 516.0 $[M+H]^+$.

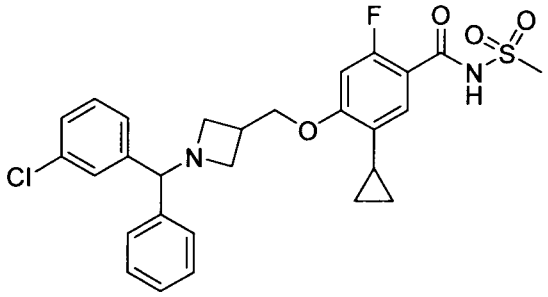
[02216] Step 5. Preparation of 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)- 4-((1-(phenyl(3-(trifluoromethoxy)phenyl)methyl)azetidin-3-yl)methoxy)benzamide



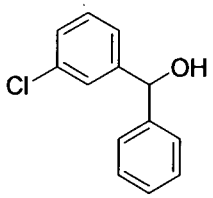
[02217] The synthetic procedure was similar to step 7 of Example 398. LCMS (ESI) Method A: RT = 6.04 min, m/z: 590.8 $[M-H]^-$. ^{1}H-NMR (500 MHz, MeOH-d_4): δ 7.33-7.29 (m, 4H), 7.25-7.23 (m, 1H), 7.22-7.20 (m, 3H), 7.15-7.12 (m, 1H), 7.04-7.02 (m, 1H), 6.72-6.70 (m, 1H), 4.53 (s, 1H), 4.10 (d, J = 6.0 Hz, 2H), 3.39-3.31 (m, 2H), 3.17 (s, 3H), 3.15-3.11 (m, 2H), 2.94-2.91 (m, 1H), 2.00-1.97 (m, 1H), 0.85-0.81 (m, 2H), 0.58-0.54 (m, 2H).

[02218] EXAMPLE 400

[02219] Synthesis of 4-((1-((3-chlorophenyl)(phenyl)methyl)azetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

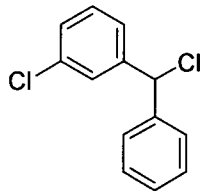


[02220] Step 1. Preparation of (3-chlorophenyl)(phenyl)methanol



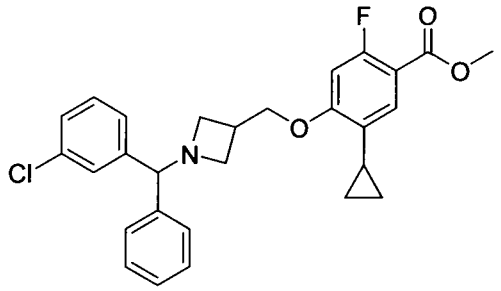
[02221] A mixture of methyl (3-chlorophenyl)(phenyl)methanone (1 g, 4.63 mmol) and sodium borohydride (352 mg, 9.26 mmol) in EtOH (6 mL) was stirred at 25°C for 2 h. After removal of the solvent, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the desired product (950 mg, 94%) as yellow oil which was used in the next step without further purification.

[02222] Step 2. Preparation of 1-chloro-3-(chloro(phenyl)methyl)benzene



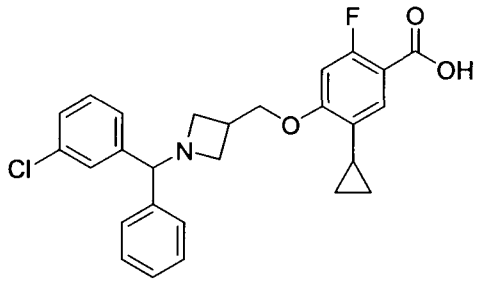
[02223] A solution of (3-chlorophenyl)(phenyl)methanol(500 mg, 2.3 mmol) in thionyl chloride (3 mL) was stirred at 80°C for 16 h. After cooling to room temperature, the reaction mixture was concentrated and purified by silica gel column (eluting with petroleum ether/ethyl acetate = 100/1) to give the desired product (200 mg, 37%) as yellow oil.

[02224] Step 3. Preparation of Methyl4-((1-((3-chlorophenyl)(phenyl)methyl)azetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate



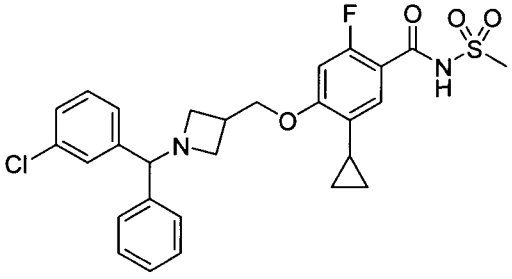
[02225] The synthetic procedures were similar to Example 398. LCMS (ESI) m/z: 480.1 $[M+H]^+$.

[02226] Step 4. Preparation of 4-((1-((3-chlorophenyl)(phenyl)methyl)azetidin-3-yl)-methoxy)-5-cyclopropyl-2-fluorobenzoic acid



[02227] The synthetic procedures were similar to those of Example 398. LCMS (ESI) m/z: 466.1 $[M+H]^+$.

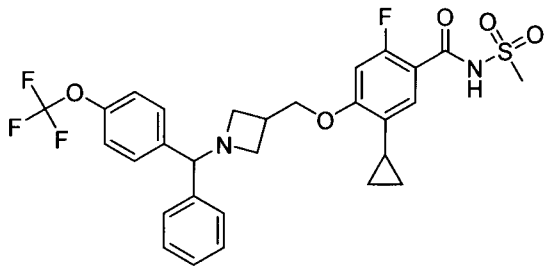
[02228] Step 5. Preparation of 4-((1-((3-chlorophenyl)(phenyl)methyl)azetidin- 3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02229] The synthetic procedures were similar to those of Example 398. LCMS (ESI) Method A: RT = 5.77 min, m/z: 543.1 $[M+H]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47-7.40 (m, 4H), 7.32-7.18 (m, 7H), 6.86 (d, J = 10.0 Hz, 1H), 4.50 (s, 1H), 4.18 (d, J = 6.5 Hz, 2H), 3.27-3.23 (m, 2H), 3.08 (s, 3H), 3.02-2.99 (m, 2H), 2.87-2.85 (m, 1H), 2.08-2.04 (m, 1H), 0.91-0.87 (m, 2H), 0.62-0.61 (m, 2H).

[02230] EXAMPLE 401

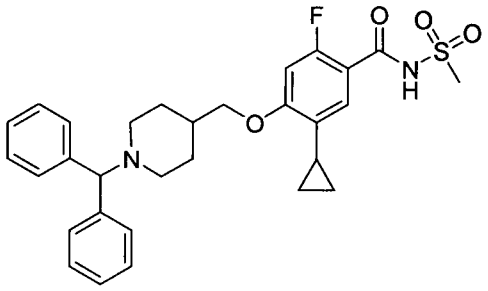
[02231] Synthesis of 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)-4-((1-(phenyl(4-(trifluoromethoxy)phenyl)methyl)azetidin-3-yl)methoxy)benzamide



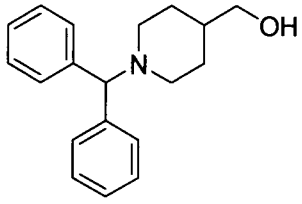
[02232] The synthetic procedures were similar to those of Example 399. LCMS (ESI) Method A: RT = 4.69 min, m/z: 593.2 $[M+H]^+$. ^1H NMR (500 MHz, MeOD): δ 7.54-7.52 (m, 2H), 7.43-7.41 (m, 3H), 7.33-7.30 (m, 3H), 7.24-7.21 (m, 2H), 6.72-6.69 (m, 1H), 4.56 (s, 1H), 4.16 (d, J = 6.0 Hz, 2H), 3.44-3.38 (m, 2H), 3.20-3.16 (m, 2H), 3.10 (s, 3H), 3.02-2.97 (m, 1H), 2.11-2.06 (m, 1H), 0.92-0.89 (m, 2H), 0.67-0.66 (m, 2H).

[02233] EXAMPLE 402

[02234] Synthesis of 4-((1-benzhydrylpiperidin-4-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



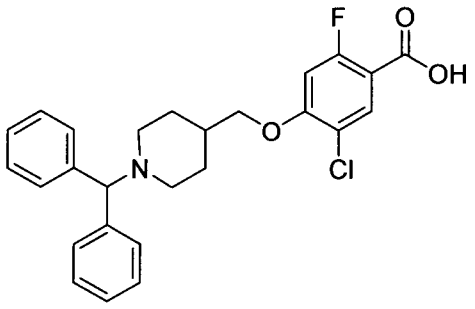
Step 1. Preparation of (1-benzhydrylpiperidin-4-yl)methanol



[02235] To a solution of (bromomethylene)dibenzene (115 mg, 1.0 mmol) and piperidin-4-ylmethanol (247 mg, 1.0 mmol) in DMF (5 mL) was added potassium carbonate (276 mg, 2.0 mmol), and the reaction mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the mixture was quenched with water (50 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was

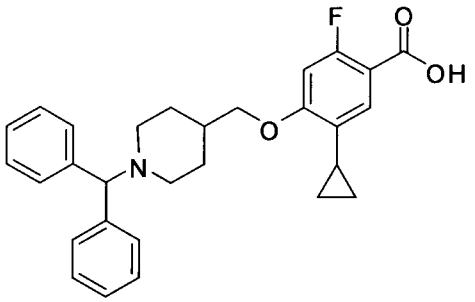
purified by silica column chromatography (eluting with petroleum ether/ethyl acetate = 3/1) to give (1-benzhydrylpiperidin-4-yl)methanol (280 mg, 99% yield) as white solid. LCMS (ESI) m/z: 281.9 $[M+H]^+$.

[02236] Step 2. Preparation of 4-((1-benzhydrylpiperidin-4-yl)methoxy)- 5-chloro-2-fluorobenzoic acid



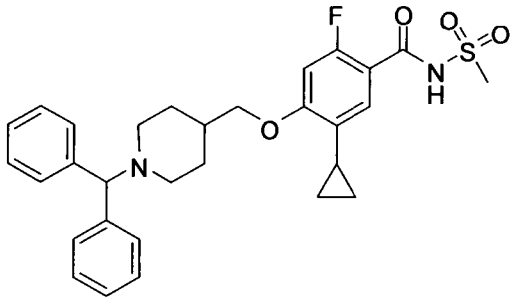
[02237] A mixture of (1-benzhydrylpiperidin-4-yl)methanol (370 mg, 1.3 mmol), *tert*-butyl 5-chloro-2,4-difluorobenzoate (328 mg, 1.3 mmol) and potassium *tert*-butanolate (295 mg, 2.6 mmol) in DMSO (4 mL) was stirred at room temperature for 16 h. The reaction mixture was quenched by water (50 mL) and extracted with ethyl acetate (10 mL × 4). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was washed with ethyl acetate (5 mL) and filtered to afford 4-((1-benzhydrylpiperidin-4-yl)methoxy)-5-chloro-2-fluorobenzoic acid (480 mg, 82%) as a white solid. LCMS (ESI) m/z: 454.2 $[M+H]^+$.

[02238] Step 3. Preparation of 4-((1-benzhydrylpiperidin-4-yl)methoxy) 5-cyclopropyl-2-fluorobenzoic acid



[02239] A mixture of 4-((1-benzhydrylpiperidin-4-yl)methoxy)-5-chloro-2-fluorobenzoic acid (480 mg, 0.94 mmol), cyclopropylboronic acid (162 mg, 1.88 mmol), potassium phosphate (797 mg, 3.67 mmol), palladium acetate (21 mg, 0.047 mmol) and tricyclohexylphosphine tetrafluoroborate (36 mg, 0.094 mmol) in toluene (10 mL) and water (0.5 mL) was stirred under a nitrogen atmosphere at 100 °C for 18 h. The reaction mixture was cooled down, quenched with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford product (320 mg, 46%, crude) as oil which was used in the next step without further purification. LCMS (ESI) m/z: 458.1 $[M+H]^+$.

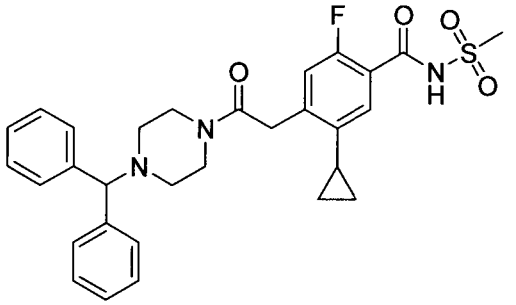
[02240] Step 4. Preparation of 4-((1-benzhydrylpiperidin-4-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



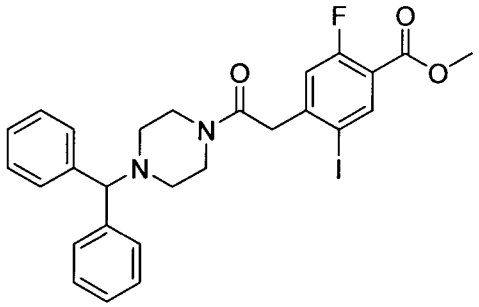
[02241] A solution of 4-((1-benzhydrylpiperidin-4-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid (270 mg, 0.59 mmol), methanesulfonamide (84 mg, 0.88 mmol), EDCI (169 mg, 0.88 mmol) and DMAP (107 mg, 0.88 mmol) in DCM (5 mL) was stirred at room temperature for 16 h. The reaction was quenched with water (5 mL) then adjusted pH to 1 with HCl (1 M). The resulting mixture was extracted with DCM (5mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by reverse phase Combiflash (20%-50% CH_3CN/H_2O in 0.1% NH_4HCO_3) to afford the target compound (15 mg, 5%) as a white solid. LCMS (ESI) Method A: RT = 6.10 min, m/z: 537.2 $[M+H]^+$. ^{1}H-NMR (500 MHz, MeOD-d_4,): δ 7.40-7.42 (m, 4H), 7.15-7.30 (m, 7H), 6.67 (d, J = 13 Hz, 1H), 4.30 (s, 1H), 3.87 (d, J=6 Hz, 2H), 2.82 (s, 3H), 1.73-1.98 (m, 7H), 1.37-1.40 (m, 3H), 0.83-0.86 (m, 2H), 0.50-0.53 (m, 2H).

[02242] EXAMPLE 403

[02243] Synthesis of 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

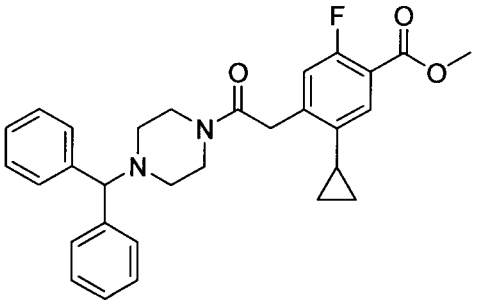


[02244] Step 1. Preparation of methyl 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-2-fluoro-5-iodobenzoate



[02245] A mixture of 2-(5-fluoro-2-iodo-4-(methoxycarbonyl)phenyl)acetic acid (100 mg, 0.30 mmol), 1-benzhydrylpiperazine (82 mg, 0.33 mmol), 1-(3-Dimethylaminopropyl)- 3-ethylcarbodiimide hydrochloride (86 mg, 0.45 mmol), 1H-benzo[d][1,2,3]triazol-4-ol (61 mg, 0.45 mmol) and triethylamine (91 mg, 0.90 mmol) in DCM (5.0 mL) was stirred at room temperature for 16 h. The mixture was diluted with DCM (20 mL), washed with HCl (2M, 10 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Combiflash (60%-70% CH_3CN in 0.1% HCOOH) to afford methyl 4-(2-(4-benzhydrylpiperazin-1-yl)-2- oxoethyl)-2-fluoro-5-iodobenzoate (70 mg, 41%) as a white solid. LCMS (ESI): m/z: 572.8 $[M+H]^+$.

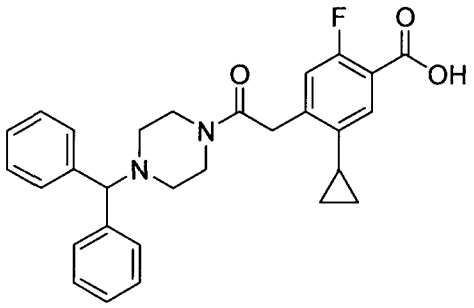
[02246] Step 2. Preparation of methyl 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-5-cyclopropyl-2-fluorobenzoate



[02247] To a solution of methyl 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)- 2-fluoro-5-iodobenzoate (70 mg, 0.12 mmol), cyclopropylboronic acid (16 mg, 0.18 mmol), potassium phosphate (102 mg, 0.48 mmol) and tricyclohexylphosphine tetrafluoroborate (9 mg, 0.024 mmol) in toluene (2mL) and water (0.1 mL) under a nitrogen atmosphere was added palladium acetate (8 mg, 0.037 mmol). The reaction mixture was heated to 100 °C for 18 hours then cooled to ambient temperature. The reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the target

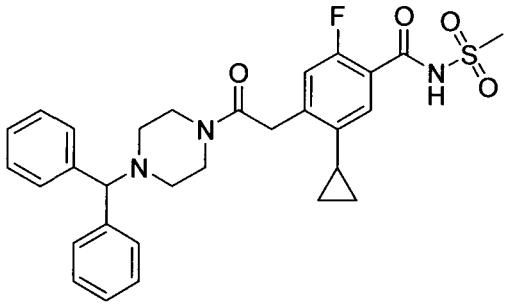
compound (70 mg, crude) which was used in the next step without purification. LCMS (ESI): m/z: 486.9 $[M+H]^+$.

[02248] Step 3. Preparation of 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-5-cyclopropyl-2-fluorobenzoic acid



[02249] To a solution of methyl 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-5- cyclopropyl-2-fluorobenzoate (70 mg, 0.14 mmol) in THF (2 mL) and methanol (2 mL), lithium hydroxide (2M, 2 mL) was added. After stirring at room temperature for 16 h, the mixture pH was adjusted to 2-3 with HCl (2 M) and extracted by ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Combiflash (30%-40% CH_3CN in 0.1% HCOOH) to afford target compound (35 mg, 53%) as a white solid. LCMS (ESI): m/z: 473.2 $[M+H]^+$.

[02250] Step 4. Preparation of 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)- 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

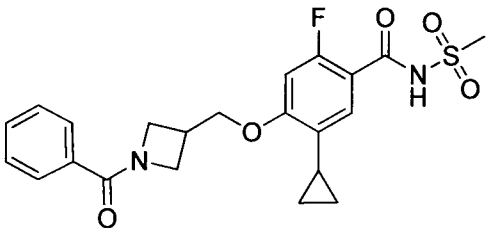


[02251] A mixture of 4-(2-(4-benzhydrylpiperazin-1-yl)-2-oxoethyl)-5- cyclopropyl-2-fluorobenzoic acid (35 mg, 0.074 mmol), methanesulfonamide (11 mg, 0.11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28 mg, 0.15 mmol) and 4-dimethylaminopyridine (18 mg, 0.15 mmol) in dichloromethane (2 mL) was stirred at room temperature for 16 h. The mixture was diluted with DCM (10 mL), washed with HCl (2M, 8 mL) and brine (8 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Combiflash (30%-40% CH_3CN in 0.1% NH_4HCO_3) to afford target compound (5 mg, 12.3%) as a white solid. LCMS (ESI) Method A: RT = 5.17 min, m/z: 550.2 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 7.44-7.43 (m, 4H), 7.31-7.26 (m, 5H), 7.21-7.18 (m, 2H), 6.82

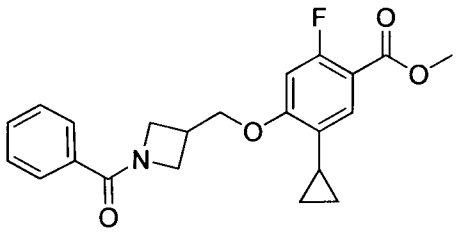
(d, J = 11.0 Hz, 1H), 4.34 (s, 1H), 3.81 (s, 2H), 3.53 (brs, 4H), 2.88 (s, 3H), 2.28 (brs, 4H), 1.76-1.75 (m, 1H), 0.83-0.81 (m, 2H), 0.51-0.49 (m, 2H).

[02252] EXAMPLE 404

[02253] Synthesis of 4-((1-benzoylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

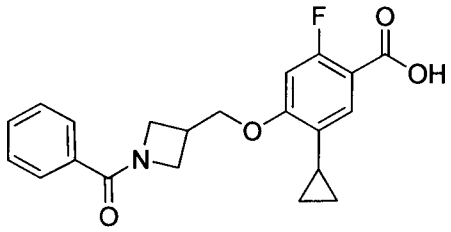


[02254] Step 1. Preparation of methyl 4-((1-benzoylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate



[02255] To a mixture of methyl 4-(azetidin-3-ylmethoxy)-5-cyclopropyl-2-fluorobenzoate (50 mg, 0.18 mmol), benzoyl chloride (28 mg, 0.20 mmol), and triethylamine (36 mg, 0.36 mmol) in DCM (10 mL) was stirred at 20 °C for 1 hour. The mixture was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to get a crude product (70 mg, 99%) which was used in the next step without further purification. LCMS(ESI) m/z: 384.1 $[M+H]^+$.

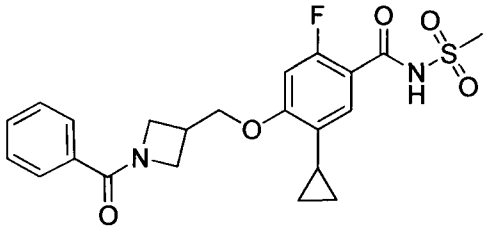
[02256] Step 2. Preparation of 4-((1-benzoylazetidin-3-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid



[02257] A mixture of methyl 4-((1-benzoylazetidin-3-yl)methoxy)-5- cyclopropyl-2-fluorobenzoate (70 mg, 0.18 mmol) and lithium hydroxide (22mg, 0.91 mmol) in THF (5 mL) and H_2O (10ml) was stirred at room temperature for 18 h. The mixture was quenched with HCl (1N, 2 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium

sulfate, filtered and concentrated to get the target compound (50 mg, 74%) as a yellow solid. LCMS(ESI) m/z: 370.1 $[M+H]^+$.

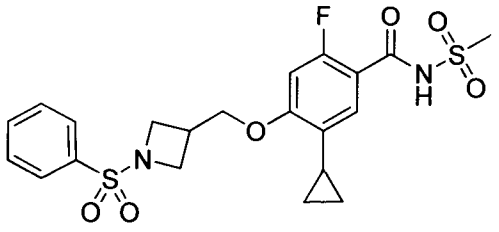
[02258] Step 3. Preparation of 4-((1-benzoylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02259] A mixture of 4-((1-benzoylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid (20 mg, 0.05 mmol), EDCI (21 mg, 0.10 mmol), DMAP (12mg, 0.10 mmol) and methanesulfonamide (9 mg, 0.10 mmol) in DCM (5 mL) was stirred at room temperature for 18 h. The mixture was diluted with DCM (10 mL) and washed with HCl (2 N, 15 mL × 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by HPLC (20%-30% CH_3CN in 0.1% NH_4HCO_3) to give target compound (4 mg, 17%) as a pale yellow solid. LCMS (ESI) Method A: RT = 3.86 min, m/z: 446.5 $[M+H]^+$. ^{1}H-NMR (500 MHz, MeOH-d_4,): δ 7.67- 7.31 (m, 5H), 7.30 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 13.0 Hz, 1H), 4.65-3.62 (m, 1H), 4.61-4.22 (m, 5H), 3.36 (s, 3H), 3.25-3.23 (m, 1H), 1.99-1.95 (m, 1H), 0.94- 0.61 (m, 4H).

[02260] EXAMPLE 405

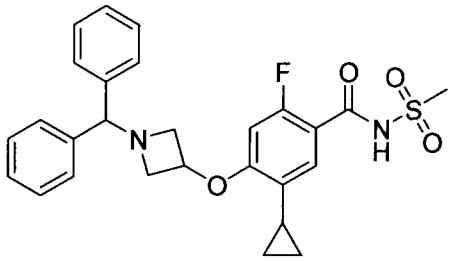
[02261] Synthesis of 5-cyclopropyl-2-fluoro-N-(methylsulfonyl)-4- ((1-(phenylsulfonyl)azetidin-3-yl)methoxy)benzamide



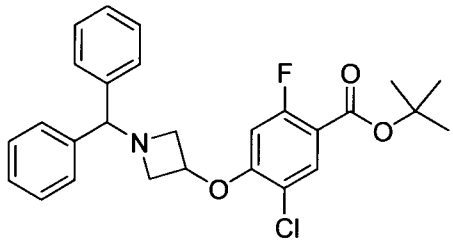
[02262] The synthetic procedure was same as Example 404. LCMS (ESI) Method A: RT = 4.26 min, m/z: 483.2 $[M+H]^+$. ^{1}H-NMR (500 MHz, MeOH-d_4,): δ 7.90-7.66 (m, 5H), 7.26 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 12.5 Hz, 1H), 4.02 (d, J = 5.5 Hz, 1H), 3.98-3.80(m, 5H), 3.36(s, 3H), 2.99-2.96 (m, 1H), 1.91-1.88 (m, 1H), 0.91-0.88 (m, 2H), 0.63-0.60 (m, 2H).

[02263] EXAMPLE 406

[02264] Synthesis of 4-(1-benzhydrylazetidin-3-yloxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

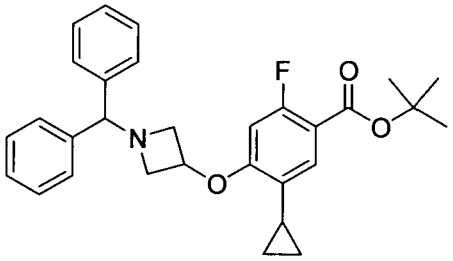


[02265] Step 1. Preparation of *tert*-butyl 4-(1-benzhydrylazetidin-3- yloxy)-5-chloro-2-fluorobenzoate



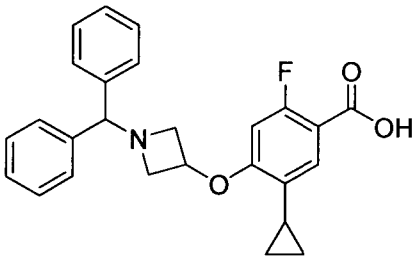
[02266] A mixture of 1-benzhydrylazetidin-3-ol (500 mg, 2.08 mmol), *tert*-butyl 5-chloro-2,4-difluorobenzoate (568 mg, 2.29 mmol) and potassium *tert*-butoxide (349 mg, 3.12 mmol) in DMSO (30 mL) was stirred at 20 °C for 1 h. The mixture was quenched with water and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to get the target compound (700 mg, 72%) which was used in the next step without further purification. LCMS(ESI) m/z: 468.2 $[M+H]^+$.

[02267] Step 2. Preparation of *tert*-butyl 4-(1-benzhydrylazetidin-3-yloxy)- 5-cyclopropyl-2-fluorobenzoate



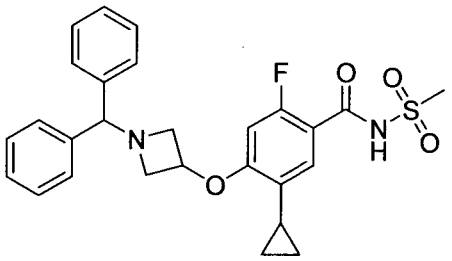
[02268] A mixture of *tert*-butyl 4-(1-benzhydrylazetidin-3-yloxy)-5- chloro-2-fluorobenzoate (700 mg, 1.50 mmol), cyclopropylboronic acid (258 mg, 3.00 mmol), tricyclohexylphosphine tetrafluoroborate (57 mg, 0.15 mmol), potassium phosphate (954 mg, 4.5 mmol) and palladium acetate (224 mg, 0.15 mmol) in toluene (20 mL) and H_2O (1 mL) was stirred at 100 °C for 18 h. The mixture was filtered and diluted with ethyl acetate, washed with brine and concentrated. The residue was purified by silica gel chromatography (eluting with ethyl acetate/ petroleum ether from 0/10 to 1/10) to give target product (650 mg, 92%) as a yellow oil. LCMS(ESI) m/z: 474.2 $[M+H]^+$.

[02269] Step 3. Preparation of 4-(1-benzhydrylazetidin-3-yloxy)-5- cyclopropyl-2-fluorobenzoic acid



[02270] A solution of *tert*-butyl 4-(1-benzhydrylazetidin-3-yloxy)-5-cyclopropyl- 2-fluorobenzoate (650 mg, 1.37mmol) in DCM (10 mL) and trifluoroacetic acid (5 mL) was stirred at room temperature for 2 h. The solvent was removed and the residue was used in the next step without further purification.

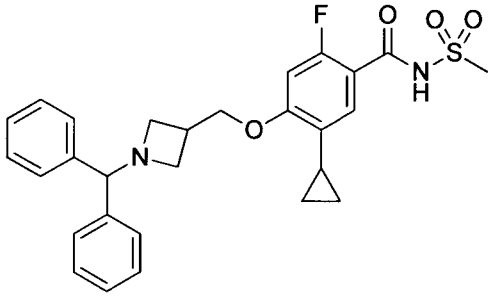
[02271] Step 4. Preparation of 4-(1-benzhydrylazetidin-3-yloxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02272] A mixture of 4-(1-benzhydrylazetidin-3-yloxy)-5-cyclopropyl-2-fluorobenzoic acid (100 mg, 0.24 mmol), EDCI (69 mg, 0.36 mmol), DMAP (44mg, 0.36 mmol) and methanesulfonamide (34 mg, 0.36 mmol) in DCM (15 mL) was stirred at room temperature for 18 h. The mixture was diluted with DCM (10 mL) and washed with HCl (2 N, 15 mL × 2). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Combiflash (20%-50% CH_3CN/H_2O in 0.1% NH_4HCO_3) to give target compound (40 mg, 34%) as a pale yellow solid. LCMS (ESI) Method A: RT = 5.29 min, m/z: 495.1 $[M+H]^+$. ^{1}H-NMR (500 MHz, MeOH-d_4,): δ 7.54-7.46 (m, 10H), 7.29 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 12.0 Hz, 1H), 5.83 (s, 1H), 5.29-5.26 (m, 1H), 4.75-4.71 (m, 2H), 4.41-4.38 (m, 2H), 3.37 (s, 3H), 2.22-2.18 (m, 1H), 1.03-0.99 (m, 2H), 0.75-0.42 (m, 2H).

[02274] EXAMPLE 407

[02275] Synthesis of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide



[02276] Step 1. Preparation of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-chloro-2-fluoro-N-(methylsulfonyl)benzamide.

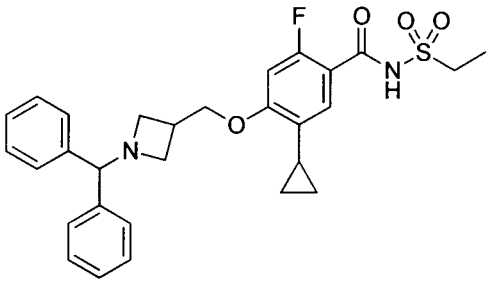
[02277] To a solution of (1-benzhydrylazetidin-3-yl)methanol (40.4 mg, 0.159 mmol) and 5-chloro-2,4-difluoro-N-methylsulfonyl-benzamide (43.0 mg, 0.159 mmol) in DMSO (0.80 mL) at rt was added potassium tert-butoxide in 1:10 THF-DMSO (0.38 mL, 0.93 M). The mixture was stirred at rt for 1 hr. LCMS showed major product. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (2x) and brine (1x), dried (Na_2SO_4). After filtration and concentration, the crude was purified with HPLC (55.7 mg).

[02278] Step 2. Preparation of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(methylsulfonyl)benzamide

[02279] A mixture of product from step 1 (29.1 mg), cyclopropylboronic acid (31.4 mg), potassium phosphate (188 mg), palladium acetate (2.8 mg) and tricyclohexylphosphine tetrafluoroborate (8.8 mg) in toluene (1.2 mL) and water (0.06 mL) was heated at 95 °C for 16 hours. The contents were concentrated. The residue was diluted with EtOAc and washed with 1M NaH_2PO_4 and brine, and dried (Na_2SO_4). After filtration and concentration, the crude was purified with HPLC (10.3 mg). LCMS (Method D): RT=5.44 min, m/z: 509.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 7.46 – 7.38 (m, 4H), 7.29 (t, J = 7.5 Hz, 4H), 7.18 (dd, J = 18.0, 7.9 Hz, 3H), 6.96 (d, J = 12.9 Hz, 1H), 4.54 (s, 1H), 4.22 (d, J = 6.2 Hz, 2H), 3.07 (s, 2H), 2.89 (s, 1H), 2.13 – 1.98 (m, 1H), 0.96 – 0.83 (m, 2H), 0.72 – 0.61 (m, 2H).

[02280] EXAMPLE 408

[02281] Synthesis of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-N-(ethylsulfonyl)-2-fluorobenzamide



[02282] Step 1. Preparation of tert-butyl 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-chloro-2-fluorobenzoate

[02283] To solution of (1-benzhydrylazetidin-3-yl)methanol (368 mg) and tert-butyl 5-chloro-2,4-difluoro-benzoate (397 mg) in DMSO (7.3 mL) at 14°C (bath) was added potassium tert-butoxide (196 mg). The mixture was stirred at rt for 1 hr. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (2x) and brine (1x), dried (Na_2SO_4). After filtration and concentration, the crude was purified with flash chromatography (0-40% EtOAc/heptane) to give the product (511 mg).

[02284] Step 2. Preparation of tert-butyl 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate

[02285] A mixture of tert-butyl 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-chloro-2-fluorobenzoate (500 mg), cyclopropylboronic acid (188 mg), potassium phosphate (1.12 g) in toluene (6.2 mL) and water (0.31 mL) was purge with nitrogen. Tricyclohexylphosphine tetrafluoroborate (79 mg) and palladium acetate (24 mg) were added. The mixture was heated at 90 °C for 16 hours. The mixture was diluted with EtOAc and filtered. The filtrate was concentrated. The residue was purified with flash chromatography (0-30% EtOAc/heptane) to give the product (276 mg).

[02286] Step 3. Preparation of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5- cyclopropyl-2-fluorobenzoic acid

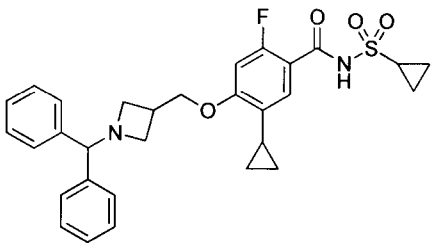
[02287] A mixture of tert-butyl 4-((1-benzhydrylazetidin-3-yl)methoxy)-5- cyclopropyl-2-fluorobenzoate (203 mg) and potassium hydroxide (187 mg) in DMSO (1.7 mL) was stirred at rt for 16 hr. The contents were acidified with 1M NaH_2PO_4. Solid was collected with filtration, washed with water, and dried under vacuum (171 mg).

[02288] Step 4. Preparation of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-N-(ethylsulfonyl)-2-fluorobenzamide

[02289] A mixture of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl- 2-fluorobenzoic acid (35.6 mg), ethanesulfonamide (22.5 mg), HBTU (41.9 mg), and DIPEA (0.073 mL) in DCE (0.83 mL) was heated at 35°C for 16 hr then at 55°C for 1 hr. More ethyanesulfonamide (9 mg) was added. Heating continued for 1 hr. Added with 1M NaH_2PO_4, the contents were extracted with DCM (2x). The combined extracts were dried (Na_2SO_4). The crude was purified with HPLC (23 mg). LCMS (Method D): RT=5.08 min, m/z: 523.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 7.49 – 7.36 (m, 4H), 7.28 (dd, J = 8.3, 6.8 Hz, 4H), 7.22 – 7.09 (m, 3H), 6.95 (d, J = 12.8 Hz, 1H), 4.49 (s, 1H), 4.21 (d, J = 6.2 Hz, 2H), 3.47 – 3.36 (m, 2H), 3.02 (s, 2H), 2.93 – 2.81 (m, 1H), 2.10 – 1.99 (m, 1H), 1.22 (t, J = 7.5 Hz, 3H), 0.95 – 0.82 (m, 2H), 0.71 – 0.61 (m, 2H).

[02290] EXAMPLE 409

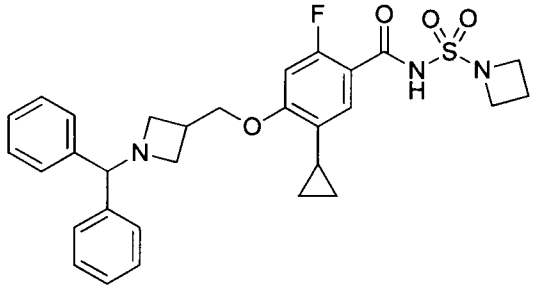
[02291] Synthesis of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-N-(cyclopropylsulfonyl)-2-fluorobenzamide



[02292] The compound was prepared in a similar manner to Example 408 from 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and cyclopropanesulfonamide. LCMS (Method D): RT=4.69 min, m/z: 535.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 7.48 – 7.36 (m, 4H), 7.28 (t, J = 7.4 Hz, 4H), 7.23 – 7.09 (m, 3H), 6.96 (d, J = 12.8 Hz, 1H), 4.50 (s, 1H), 4.22 (d, J = 6.1 Hz, 2H), 3.12 – 2.96 (m, 3H), 2.94 – 2.80 (m, 1H), 2.12 – 1.99 (m, 1H), 1.18 – 0.97 (m, 4H), 0.95 – 0.82 (m, 2H), 0.73 – 0.60 (m, 2H).

[02293] EXAMPLE 410

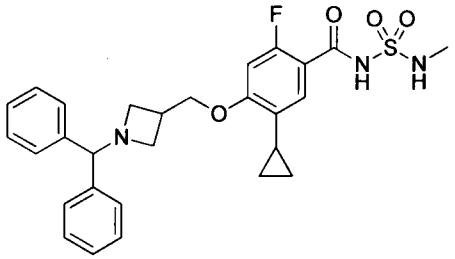
[02294] Synthesis of N-(azetidin-1-ylsulfonyl)-4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzamide



[02295] The compound was prepared in a similar manner to Example 408 from 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and azetidine-1-sulfonamide. LCMS (Method D): RT=4.74 min, m/z: 550.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.46 – 7.38 (m, 4H), 7.28 (dd, J = 8.3, 6.8 Hz, 4H), 7.22 – 7.13 (m, 3H), 6.99 – 6.87 (m, 1H), 4.46 (s, 1H), 4.21 (d, *J* = 6.1 Hz, 2H), 3.97 (s, 3H), 3.28 – 3.21 (m, 2H), 3.07 – 2.94 (m, 2H), 2.91 – 2.81 (m, 1H), 2.20 – 1.99 (m, 3H), 1.25 (d, *J* = 6.9 Hz, 1H), 0.93 – 0.85 (m, 2H), 0.70 – 0.62 (m, 2H).

[02296] EXAMPLE 411

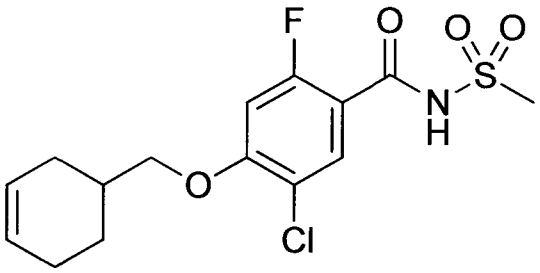
[02297] Synthesis of 4-((1-benzhydrylazetidin-3-yl)methoxy)-5-cyclopropyl-2-fluoro-N-(N-methylsulfamoyl)benzamide



[02298] The compound was prepared in a similar manner to Example 408 from 4-((1-benzhydryl-azetidin-3-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid and N-methylsulfamide. LCMS (Method D): RT=4.48 min, m/z: 524.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.46 – 7.38 (m, 4H), 7.27 (t, *J* = 7.7 Hz, 4H), 7.22 – 7.08 (m, 3H), 6.95 (d, *J* = 12.7 Hz, 1H), 4.46 (s, 1H), 4.21 (d, *J* = 6.2 Hz, 2H), 3.24 (d, *J* = 7.4 Hz, 2H), 3.00 (t, *J* = 6.6 Hz, 2H), 2.92 – 2.79 (m, 1H), 2.53 (d, *J* = 4.9 Hz, 2H), 2.11 – 1.99 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 1H), 0.93 – 0.83 (m, 2H), 0.67 (m, 2H).

[02299] EXAMPLE 412

[02300] Synthesis of 5-chloro-4-(cyclohex-3-en-1-ylmethoxy)-2-fluoro-N- (methylsulfonyl)benzamide



[02301] Step 1. Preparation of 5-chloro-4-(cyclohex-3-en-1-ylmethoxy)-2-fluorobenzoic acid

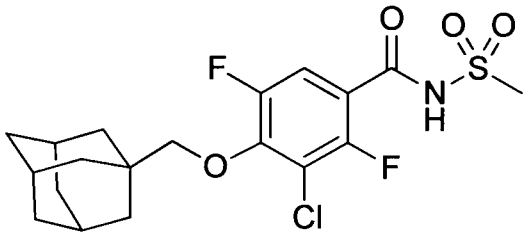
[02302] To a solution of cyclohex-3-en-1-ylmethanol (1.00 g) and 5-chloro-2,4-difluoro-benzoic acid (1.72 g) in DMSO (36 mL) at 14°C (bath) was added potassium tert-butoxide (2.20 g) gradually. The mixture was stirred at that temp for 5 min then at rt for 30 min. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (3x) and brine, and dried (Na_2SO_4). After filtration and concentration, the product was obtained as white solid (2.48 g).

[02303] Step 2. Preparation of 5-chloro-4-(cyclohex-3-en-1-ylmethoxy)-2-fluoro-N-(methylsulfonyl)benzamide

[02304] A mixture of 5-chloro-4-(cyclohex-3-en-1-ylmethoxy)-2-fluorobenzoic acid (53 mg), methanesulfonamide (35 mg), HBTU (95 mg), and DIPEA (0.13 mL) in dichloromethane (0.83 mL) was stirred at rt for 4 hr. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (2x) and brine, and dried (Na_2SO_4). The crude was purified with HPLC. LCMS (Method D): RT=5.62 min, m/z: 362.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 12.07 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 12.4 Hz, 1H), 5.69 (d, J = 2.1 Hz, 2H), 4.06 (dd, J = 6.5, 1.3 Hz, 2H), 2.28 –1.97 (m, 4H), 1.98 – 1.76 (m, 2H), 1.50 – 1.29 (m, 1H).

[02305] EXAMPLE 413

[02306] Synthesis of 4-(adamantan-1-ylmethoxy)-3-chloro-2,5-difluoro-N- (methylsulfonyl)benzamide



[02307] Step 1. Preparation of 4-(adamantan-1-ylmethoxy)-3-chloro-2,5-difluorobenzoic acid

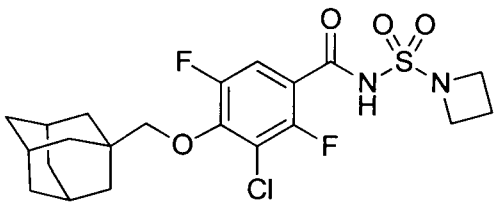
[02308] To a solution of 1-adamantylmethanol (309 mg) and 3-chloro-2,4,5-trifluoro-benzoic acid (391 mg) in DMSO (5.6 mL) at 14°C (bath) was added potassium tert-butoxide (458 mg) gradually. The mixture was stirred at that temp for 30 min. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (3x) and brine, and dried (Na_2SO_4). After filtration and concentration, the product was obtained as white solid (1.00 g).

[02309] Step 2: 4-(adamantan-1-ylmethoxy)-3-chloro-2,5-difluoro-N-(methylsulfonyl)benzamide

[02310] The compound was prepared in a similar manner to step 2 of Example 412 from 4-(adamantan-1-ylmethoxy)-3-chloro-2,5-difluorobenzoic acid and methanesulfonamide. LCMS (Method D): RT=6.97 min, m/z: 434.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.66 (dd, J = 11.6, 6.6 Hz, 1H), 3.82 (d, J = 2.0 Hz, 2H), 1.99 (s, 3H), 1.82 – 1.56 (m, 12H).

[02311] EXAMPLE 414

[02312] Synthesis of 4-(adamantan-1-ylmethoxy)-N-(azetidin-1-ylsulfonyl)-3-chloro-2,5-difluorobenzamide

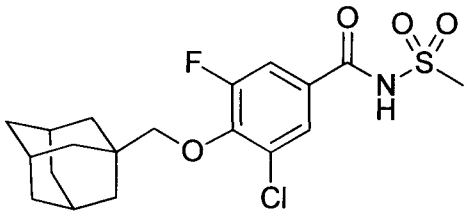


[02313] The compound was prepared in a similar manner to step 2 of Example 412 from 4-(adamantan-1-ylmethoxy)-3-chloro-2,5-difluorobenzoic acid and azetidine-1-sulfonamide. LCMS (Method D): RT=7.35

min, m/z: 475.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.60 (dd, J = 11.7, 6.6 Hz, 1H), 3.86 (t, J = 7.6 Hz, 4H), 3.77 (d, J = 1.7 Hz, 2H), 2.08 (p, J = 7.6 Hz, 2H), 2.02 – 1.93 (m, 3H), 1.77 – 1.59 (m, 12H).

[02314] EXAMPLE 415

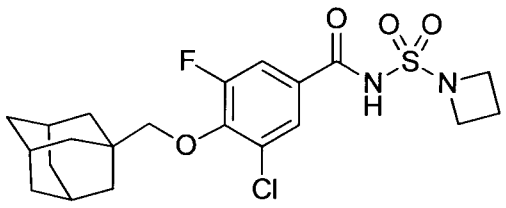
b. Synthesis of 4-(adamantan-1-ylmethoxy)-3-chloro-5-fluoro-N- (methylsulfonyl)benzamide



[02315] The compound was prepared in a similar manner to Example 413from 3-chloro-4,5-difluorobenzoic acid. LCMS (Method D): RT=7.24 min, m/z: 416.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.84 – 7.77 (m, 1H), 7.68 (dd, J = 12.1, 2.0 Hz, 1H), 3.70 (d, J = 1.5 Hz, 2H), 2.96 (s, 3H), 1.99 (t, J = 3.3 Hz, 3H), 1.79 – 1.59 (m, 12H).

[02316] EXAMPLE 416

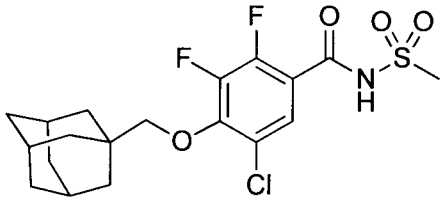
[02317] Synthesis of 4-(adamantan-1-ylmethoxy)-N-(azetidin-1-ylsulfonyl)-3-chloro-5-fluorobenzamide



[02318] The compound was prepared in a similar manner to Example 414 from 3-chloro-4,5-difluorobenzoic acid. LCMS (Method D): RT=7.87 min, m/z: 457.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.85 (t, J = 1.7 Hz, 1H), 7.74 (dd, J = 12.1, 2.1 Hz, 1H), 3.83 (t, J = 7.6 Hz, 4H), 3.71 (d, J = 1.5 Hz, 2H), 2.13 – 1.94 (m, 5H), 1.79 – 1.59 (m, 12H).

[02319] EXAMPLE 417

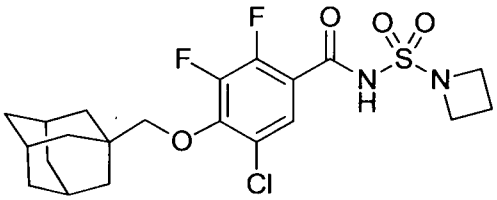
[02320] Synthesis of 4-(adamantan-1-ylmethoxy)-5-chloro-2,3-difluoro-N- (methylsulfonyl)benzamide



[02321] The compound was prepared in a similar manner to Example 413from 5-chloro-2,3,4-trifluorobenzoic acid. LCMS (Method D): RT=7.00 min, m/z: 434.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.58 (dd, J = 7.2, 2.4 Hz, 1H), 3.74 (d, J = 1.5 Hz, 2H), 2.86 (s, 3H), 1.98 (q, J = 3.1 Hz, 3H), 1.77 – 1.58 (m, 12H).

[02322] EXAMPLE 418

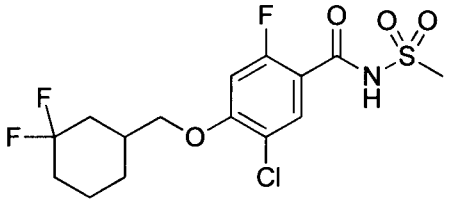
[02323] Synthesis of 4-(adamantan-1-ylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-chloro-2,3-difluorobenzamide



[02324] The compound was prepared in a similar manner to Example 414 from 5-chloro-2,3,4-trifluorobenzoic acid. LCMS (Method D): RT=7.89 min, m/z: 475.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.61 (dd, J = 7.0, 2.4 Hz, 1H), 3.89 – 3.69 (m, 6H), 2.10 – 1.93 (m, 5H), 1.76 – 1.59 (m, 12H).

[02325] EXAMPLE 419

[02326] Synthesis of 5-chloro-4-((3,3-difluorocyclohexyl)methoxy)-2- fluoro-N-(methylsulfonyl) benzamide



[02327] Step 1. Preparation of tert-butyl 5-chloro-2-fluoro-4-((3-oxocyclohexyl)- methoxy)benzoate

[02328] To a solution of 3-(hydroxymethyl)cyclohexanone (575 mg) and tert-butyl 5-chloro-2,4-difluoro-benzoate (1.23 g) in DMSO (13.5 mL) at 14°C (bath) was added potassium

tert-butoxide (604 mg) gradually. After 5 min, the mixture was stirred at rt for 30 min. Diluted with EtOAc, the contents were washed with dilute $NaHCO_3$ (3x) and brine, and dried (Na_2SO_4). After filtration and concentration, the crude was purified with flash chromatography (0->40% EtOAc/heptane) to give the product (445 mg).

[02329] Step 2. Preparation of tert-butyl 5-chloro-4-((3,3-difluorocyclohexyl)-methoxy)-2-fluorobenzoate

[02330] To a solution tert-butyl 5-chloro-2-fluoro-4-((3-oxocyclohexyl)methoxy)benzoate
[02331] (384 mg) in dichloromethane (6.5 mL) at 0°C (bath) was added bis(2-methoxyethyl)aminosulfur trifluoride (0.63 mL) . The mixture was stirred at rt for 18 hr. Diluted with EtOAc, the contents were washed with diluted $NaHCO_3$ and dried (Na_2SO_4). The crude was purified with flash chromatography (0->20% EtOAc/heptane) to give the product (212 mg).

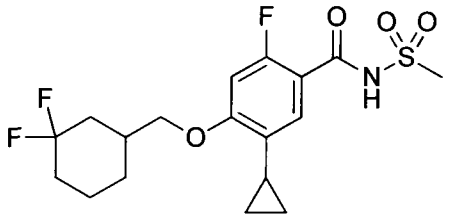
[02332] Step 3. Preparation of 5-chloro-4-((3,3-difluorocyclohexyl)methoxy)- 2-fluorobenzoic acid
[02333] A solution of tert-butyl 5-chloro-4-((3,3-difluorocyclohexyl)methoxy)-2- fluorobenzoate (64.4 mg) in dichloromethane (0.34 mL) and trifluoroacetic acid (0.17 mL) was stirred at 0°C for 10 min then at rt for 2 h. The contents were concentrated. The residue was re-dissolved with dichloromethane and concentrated. The crude was dried under vacuum and used directly.

[02334] Step 4. Preparation of 5-chloro-4-((3,3-difluorocyclohexyl)methoxy)-2-fluoro -N-(methylsulfonyl)benzamide

[02335] A mixture of the product from step 3, methanesulfonamide (32 mg), HBTU (86 mg), and DIPEA (0.18 mL) in dichloromethane (1.7 mL) was stirred at rt for 16 hr. Diluted with EtOAc, the contents were washed with 1:4 mixture of 1M HCl and 1M NaH_2PO_4 (2x) and brine, and dried (Na_2SO_4). The crude was purified with HPLC. LCMS (Method D): RT=5.35 min, m/z: 400.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 12.08 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.14 (d, J= 12.3 Hz, 1H), 4.13 – 3.98 (m, 2H), 3.13 (s, 3H), 2.18 (s, 1H), 2.04 (s, 2H), 1.90 –1.56 (m, 4H), 1.55 – 1.39 (m, 1H), 1.19 (m, 1H).

[02336] EXAMPLE 420

[02337] Synthesis of 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluoro-N-(methylsulfonyl)benzamide



[02338] Step 1. Preparation of tert-butyl 5-cyclopropyl-4-((3,3-difluorocyclohexyl)-methoxy)-2-fluorobenzoate

[02339] The compound was prepared in a similar manner to step 2 of Example 419 from tert-butyl 5-chloro-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoate.

[02340] Step 2. Preparation of 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid

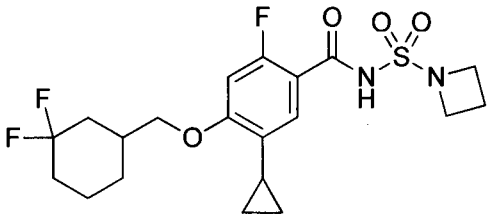
[02341] A solution of tert-butyl 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoate (191 mg) in dichloromethane (1.0 mL) and trifluoroacetic acid (0.5 mL) was stirred at 0°C for 30 min then at rt for 3 h. The contents were concentrated. The residue was suspended in toluene and concentrated. The beige solid was dried under vacuum (162 mg).

[02342] Step 3. Preparation of 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluoro-N-(methylsulfonyl)benzamide

[02343] The compound was prepared in a similar manner to step 4 of Example 419 from 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid. Two enantiomers were separated with chiral chromatography. Enantiomer 1: LCMS (Method D): RT=5.81 min, m/z: 406.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.85 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 13.0 Hz, 1H), 4.08 – 3.92 (m, 2H), 3.25 (s, 3H), 2.20 (s, 1H), 2.14 – 1.95 (m, 3H), 1.89 – 1.60 (m, 4H), 1.56 – 1.40 (m, 1H), 1.30 – 1.14 (m, 1H), 0.95 – 0.84 (m, 2H), 0.70 – 0.58 (m, 2H). Enantiomer 2: LCMS (Method D): RT=5.81 min, m/z: 406.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 12.9 Hz, 1H), 4.07 – 3.92 (m, 2H), 3.24 (s, 3H), 2.20 (s, 1H), 2.02 (m, 3H), 1.89 – 1.59 (m, 4H), 1.56 – 1.38 (m, 1H), 1.30 – 1.14 (m, 1H), 0.94 – 0.84 (m, 2H), 0.70 – 0.59 (m, 2H).

[02344] EXAMPLE 421

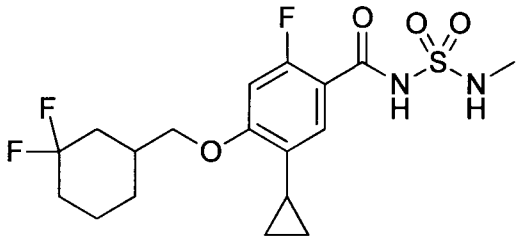
[02345] Synthesis of N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-4-((3,3-difluorocyclohexyl)-methoxy)-2-fluorobenzamide



[02346] The compound was prepared in a similar manner to Example 420 from 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid. Two enantiomers were separated with chiral chromatography. Enantiomer 1: LCMS (Method D): RT=6.19 min, m/z: 447.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.8 Hz, 1H), 4.10 – 3.94 (m, 6H), 2.29 – 1.95 (m, 6H), 1.92 – 1.58 (m, 4H), 1.57 – 1.40 (m, 1H), 1.30 – 1.14 (m, 1H), 0.96 – 0.84 (m, 2H), 0.73 – 0.60 (m, 2H). Enantiomer 2: LCMS (Method D): RT=6.23 min, m/z: 447.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 12.8 Hz, 1H), 4.10 – 3.94 (m, 6H), 2.29 – 1.95 (m, 6H), 1.92 – 1.58 (m, 4H), 1.57 – 1.40 (m, 1H), 1.30 – 1.14 (m, 1H), 0.96 – 0.84 (m, 2H), 0.73 – 0.60 (m, 2H).

[02347] EXAMPLE 422

[02348] Synthesis of 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluoro-N-(N-methylsulfamoyl)benzamide

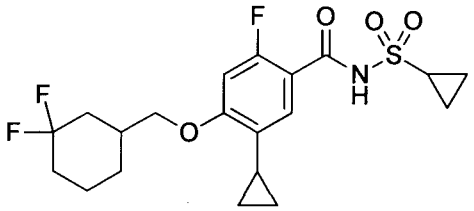


[02349] The compound was prepared in a similar manner to Example 420 from 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid. Two enantiomers were separated with chiral chromatography. Enantiomer 1: LCMS (Method D): RT=5.79 min, m/z: 421.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.44 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 12.8 Hz, 1H), 4.07 – 3.91 (m, 2H), 2.53 (d, J = 4.9 Hz, 2H), 2.20 (s, 1H), 2.14 – 1.96 (m, 3H), 1.89 – 1.40 (m, 5H), 1.35 – 1.09 (m, 2H), 0.95 – 0.86 (m, 2H), 0.70 – 0.61 (m, 2H). ^1H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.44 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 12.8 Hz, 1H), 4.07 – 3.91 (m, 2H), 2.53 (d, J = 4.9 Hz, 2H), 2.20 (s, 1H), 2.14 – 1.96 (m, 3H), 1.89 – 1.40 (m, 5H), 1.35 – 1.09 (m, 2H), 0.95 – 0.86 (m, 2H), 0.70 – 0.61 (m, 2H). Enantiomer 2: LCMS (Method D): RT=5.78 min, m/z: 421.1 $[M+H]^+$. ^1H NMR

(400 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.45 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 12.8 Hz, 1H), 4.08 – 3.92 (m, 2H), 2.54 (d, J = 4.8 Hz, 2H), 2.20 (s, 1H), 2.02 (tt, J = 8.6, 5.3 Hz, 3H), 1.90 – 1.58 (m, 4H), 1.58 – 1.37 (m, 1H), 1.31 – 1.12 (m, 1H), 0.96 – 0.83 (m, 2H), 0.73 – 0.61 (m, 2H).

[02350] EXAMPLE 423

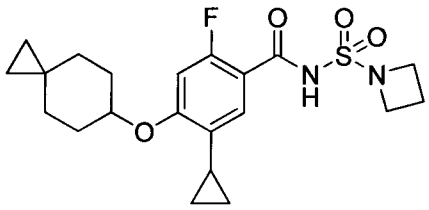
[02351] Synthesis of 5-cyclopropyl-N-(cyclopropylsulfonyl)-4-((3,3-difluorocyclohexyl)-methoxy)-2-fluorobenzamide



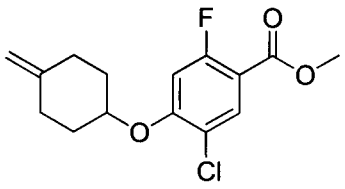
[02352] The compound was prepared in a similar manner to Example 420 from 5-cyclopropyl-4-((3,3-difluorocyclohexyl)methoxy)-2-fluorobenzoic acid. Two enantiomers were separated with chiral chromatography. Enantiomer 1: LCMS (Method D): RT=6.13 min, m/z: 432.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.66 (s, 1H), 7.22 – 7.10 (m, 1H), 6.93 (d, J = 13.0 Hz, 1H), 4.01 (t, J = 6.3 Hz, 2H), 3.11 – 2.97 (m, 1H), 2.28 – 1.92 (m, 4H), 1.91 – 1.59 (m, 4H), 1.49 (d, J = 13.1 Hz, 1H), 1.34 – 1.00 (m, 5H), 0.97 – 0.81 (m, 2H), 0.66 (td, J = 5.0, 2.4 Hz, 2H). Enantiomer 2: LCMS (Method D): RT=6.14 min, m/z: 432.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.78 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 12.9 Hz, 1H), 4.09 – 3.93 (m, 2H), 3.11 – 2.99 (m, 1H), 2.29 – 1.95 (m, 4H), 1.90 – 1.59 (m, 4H), 1.49 (dd, J = 14.5, 11.2 Hz, 1H), 1.30 – 0.99 (m, 5H), 0.95 – 0.83 (m, 2H), 0.71 – 0.60 (m, 2H).

[02353] Example 424

[02354] Synthesis of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzamide

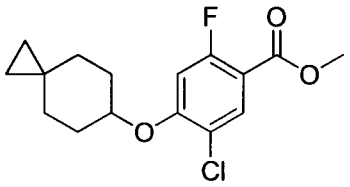


[02355] Step 1. Preparation of methyl 5-chloro-2-fluoro-4-((4-methylenecyclohexyl)oxy)benzoate



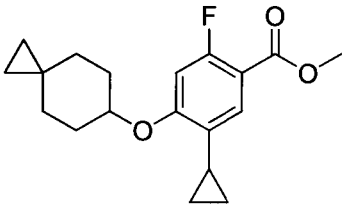
[02356] To a suspension of methyltriphenylphosphonium bromide (1.61 g, 4.51 mmol) in anhydrous tetrahydrofuran (20 mL) was added a solution of potassium *tert*-butoxide (0.541 g, 4.82 mmol) in anhydrous tetrahydrofuran (15 mL) dropwise over 3 minutes at 0 °C. The mixture was stirred under a nitrogen atmosphere at 0 °C for 1 h. To this solution was added a solution of methyl 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoate (1.05 g, 3.48 mmol) in anhydrous tetrahydrofuran (15 mL) dropwise over 3 minutes. The mixture was stirred at ambient temperature for 21 h, then diluted with water (200 mL). The mixture was extracted with ethyl acetate (200 mL) and the organic phase was washed with water (50 mL) and brine (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography with a gradient of 0-10% ethyl acetate in hexanes to afford the title compound as a colorless syrup (0.866 g, 83% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 12.2 Hz, 1H), 4.68 (s, 2H), 4.56-4.50 (m, 1H), 3.87 (s, 3H), 2.48-2.40 (m, 2H), 2.17-2.09 (m, 2H), 1.92-1.86 (m, 4H); MS (ES+) *m/z* 299.00 (M + 1).

[02357] Step 2. Preparation of methyl 5-chloro-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoate



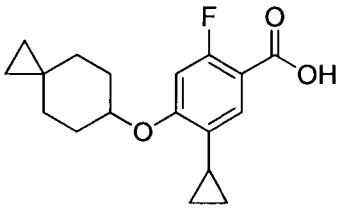
[02358] Following the procedure as described in Example 342 Step 2 and making non-critical variations to replace cyclohexenylmethanol with methyl 5-chloro-2-fluoro-4-((4-methylenecyclohexyl)oxy)benzoate, the title compound was obtained as a colorless syrup (0.769 g, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 12.4 Hz, 1H), 4.49-4.41 (m, 1H), 3.88 (s, 3H), 1.99-1.78 (m, 4H), 1.53-1.32 (m, 4H), 0.33-0.27 (m, 4H).

[02359] Step 3. Preparation of methyl 5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoate



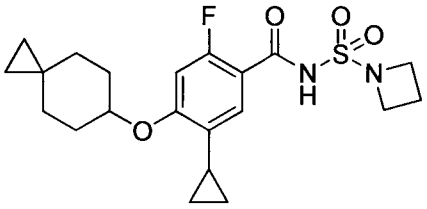
[02360] Following the procedure as described in Example 374 Step 3 and making non-critical variations to replace *tert*-butyl 5-chloro-4-((1-cyanocyclohexyl)methoxy)-2-fluorobenzoate with methyl 5-chloro-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoate, the title compound was obtained as a colorless syrup (0.389 g, 72% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 13.0 Hz, 1H), 4.46-4.39 (m, 1H), 3.86 (s, 3H), 2.10-2.01 (m, 1H), 1.99-1.90 (m, 2H), 1.86-1.76 (m, 2H), 1.54-1.24 (m, 4H), 0.96-0.84 (m, 3H), 0.66-0.60 (m, 2H), 0.32-0.26 (m, 4H); MS (ES+) *m/z* 287.05 (M - 31).

[02361] Step 4. Preparation of 5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoic acid



[02362] Following the procedure as described in Example 357 Step 6 and making non-critical variations to replace methyl 5-chloro-4-((4,4-difluorocyclohexyl)oxy)-2-fluorobenzoate with methyl 5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoate, the title compound was obtained as a colorless syrup that was carried forward without further purification (0.393 g, quant. yield).

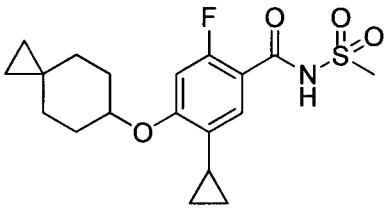
[02363] Step 5. Preparation of *N*-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzamide



[02364] Following the procedure as described in Example 357 Step 4 and making non-critical variations to replace 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoic acid with 5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoic acid and methanol with azetidine-1-sulfonamide, the title compound was obtained as a colorless solid (0.029 g, 12% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ11.57 (br s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 13.2 Hz, 1H), 4.67-4.61 (m, 1H), 4.00 (t, J = 7.7 Hz, 4H), 2.17-1.98 (m, 3H), 1.90-1.83 (m, 2H), 1.72-1.61 (m, 2H), 1.49-1.29 (m, 4H), 0.90-0.84 (m, 2H), 0.68-0.63 (m, 2H), 0.30-0.19 (m, 4H); MS (ES-) *m/z* 421.15 (M - 1).

[02365] Example 425

[02366] Synthesis of 5-cyclopropyl-2-fluoro-*N*-(methylsulfonyl)-4-(spiro[2.5]octan-6-yloxy)benzamide



[02367] Following the procedure as described in Example 357 Step 4 and making non-critical variations to replace 5-chloro-2-fluoro-4-((4-oxocyclohexyl)oxy)benzoic acid with 5-cyclopropyl-2-fluoro-4-(spiro[2.5]octan-6-yloxy)benzoic acid and methanol with methanesulfonamide, the title compound was obtained as a colorless solid (0.121 g, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ8.69 (d, J = 16.2 Hz, 1H),

7.55 (d, J = 9.2 Hz, 1H), 6.58 (d, J = 14.8 Hz, 1H), 4.49-4.42 (m, 1H), 3.39 (s, 3H), 2.11-1.77 (m, 5H), 1.54-1.21 (m, 4H), 0.96-0.89 (m, 2H), 0.67-0.61 (m, 2H), 0.34-0.27 (m, 4H); MS (ES-) *m/z* 380.20 (M - 1).

[02368] EXAMPLE 426

[02369] Using procedures and intermediates similar to those described herein, additional representative compounds of formula (I) were prepared. Biological data for these compounds is provided in Table 2 below.

[02370] EXAMPLE 427

[02371] Electrophysiological Assay (In vitro assay)

[02372] Patch voltage clamp electrophysiology allows for the direct measurement and quantification of block of voltage-gated sodium channels (NaV's), and allows the determination of the time- and voltage-dependence of block which has been interpreted as differential binding to the resting, open, and inactivated states of the sodium channel (Hille, B., Journal of General Physiology (1977), 69: 497-515).

[02373] The following patch voltage clamp electrophysiology studies were performed on representative compounds of the invention using human embryonic kidney cells (HEK), permanently transfected with an expression vector containing the full-length cDNA coding for the desired human sodium channel α-subunit, grown in culture media containing 10% FBS, 1% PSG, and 0.5 mg/mL G418 at 37 °C with 5% CO2. HEK cells used for the electrophysiology (EP) recordings had a passage number of less than 40 for all studies and were used within three days from the time of plating. NaV1.7 and NaV1.5 cDNAs (NM_002977 and AC137587; SCN5A, respectively) were stably expressed in HEK-293 cells. The β1 subunit was coexpressed in both the NaV1.7 and NaV1.5 cell lines.

[02374] Sodium currents were measured using the patch clamp technique in the whole-cell configuration using either a PatchXpress automated voltage clamp or manually using an Axopatch 200B (Axon Instruments) or Model 2400 (A-M systems) amplifier. The manual voltage clamp protocol was as follows: Borosilicate glass micropipettes were fire-polished to a tip diameter yielding a resistance of 2-4 Mohms in the working solutions. The pipette was filled with a solution comprised of: 5 mM NaCl, 10 mM CsCl, 120 mM CsF, 0.1 mM CaCl2, 2 mM MgCl2, 10 mM HEPES, 10 mM EGTA; and adjusted to pH 7.2 with CsOH. The external solution had the following composition: 140 mM NaCl, 5 mM KCl, 2 mM CaCl2, 1 mM MgCl2, 10 mM HEPES; and adjusted to pH 7.4 with NaOH. In some studies, the external sodium was reduced by equimolar replacement with choline. Osmolarity in the CsF internal and NaCl external solutions was adjusted to 300 mOsm/kg and 310 mOsm/kg with glucose, respectively. All recordings were performed at ambient temperature in a bath chamber with a volume of 150 µL. Control sodium currents were measured in 0.5% DMSO. Controls and representative compounds of the invention were applied to the recording chamber through a 4-pinch or 8-pinch valve bath perfusion system manufactured by ALA Scientific Instruments.

[02375] Currents were recorded at 40 kHz sampling frequency, filtered at 5 Hz, and stored using a Digidata-1322A analogue/digital interface with the pClamp software (Axon Instruments). Series resistance compensation was applied (60-80%). Cells were rejected if currents showed inadequate voltage control (as judged by the IV relationship during stepwise activation). All statistics in this study are given as mean ± SD.

[02376] The membrane potential was maintained at a voltage where inactivation of the channel is complete (which was -60 mV for both NaV1.7 and NaV1.5). The voltage is then stepped back to a very negative (Vhold = 150mV) voltage for 20 ms and then a test pulse is applied to quantify the compound block. The 20 ms brief repolarization was long enough for compound-free channels to completely recover from fast inactivation, but the compound-bound channels recovered more slowly such that negligible recovery could occur during this interval. The percent decrease in sodium current following wash-on of compound was taken as the percent block of sodium channels.

[02377] Compounds of the invention, when tested in this model, demonstrated affinities for the inactivated state of NaV1.7 and NaV1.5 as set forth below in Table 2.

[02378] Table 2:

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
1	9.99		
2	6.86		
3	10.0		
4	10.0		
5	0.15		0.0201
6	0.029	1.9	0.0055
7	10.0		
8	0.012	1.07	0.0038
9	0.040		0.0052
10	0.26		0.0082
11	0.029		0.0087
12	0.074		0.0069
13	0.41		0.123
14	0.32		0.0377
15	0.77		0.171
16	0.12		0.0312
17	10.0		
18	1.2		0.356
19	0.092		0.0386
20	0.09		0.0563
21	1.06		0.107
22	0.19		0.0134
23	0.013		0.0229
24	10.0		
25	0.22		0.027

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
26	0.12	0.772	0.0281
27	10.0		10.0
28	10.0		2.25
29	10.0		
30	0.14		0.0099
31	1.4		0.146
32	0.14		
33	0.19		0.0937
34	0.038		0.0658
35	10.0		
36	0.12		0.0077
37	10.0		
38	0.603		
39	0.009		
40	0.14 or 0.04		0.013 or 0.0423
41	0.14 or 0.04		0.013 or 0.0423
42	0.044		
43	0.072	2.58	0.0179
44	0.005		
45	0.005		
46	0.005		0.0033
47	0.007	0.0606	0.0107
48	0.007		0.0046
49	0.003	0.101	0.0022
50	0.029		
51	0.009		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
52	0.006		
53	0.10		
54	0.058		
55	0.009		0.0031
56	0.48		
57	0.077	0.653	0.0154
58	0.026		
59	0.065		
60	0.001	0.159	0.00030
61	0.051	1.95	0.0076
62	0.058		
63	0.0021		0.0030
64	0.002	0.0515	0.00040
65	0.17		
66	0.18		
67	0.13		
68	0.73		
69	0.097		0.0343
70	0.021		0.0368
71	0.37		
72	0.076		0.0154
73	0.19		
74	0.055		
75	0.77		
76	0.19		
77	0.086		
78	0.033		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
79	0.16		0.0854
80	1.68		
81	0.122		
82	0.294		0.0416
83	0.106		
84	0.0162		
85	0.016		
86	0.003	0.70	0.00131
87	0.081		
88	0.121		
89	0.234		
90	0.094		
91	1.21		
92	0.221	3.76	0.0531
93	0.086		
94	0.224		
95	0.017		
96	0.164		
97	0.051		0.0073
98	0.382		
99	0.558		
100	0.299		
101	0.322		
102	0.672		
103	0.603		
104	0.053		
105	0.264		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
106	0.158		0.0847
107	0.044		
108	0.803		
109	0.017		
110	0.086		
111	0.181		
112	0.117		
113	0.080		
114	0.044		
115	0.009		
116	0.167		
117	7.12		
118	1.32		
119	0.491		
120	0.205		
121	0.057		
122	0.093		
123	0.166		
124	0.738		
125	0.23		
126	0.392		
127	0.339		
128	0.291		0.0303
129	0.283		
130	0.542		
131	0.138		
132	0.419		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
133	0.125		
134	0.067		
135	0.535	7.82	0.0304
136	0.21		
137	0.295		
138	1.12		
139	0.281		
140	0.885		
141	0.273		
142	3.52		
143	0.30		
144	0.166		
145	0.009	0.743	0.0036
146	0.00432	0.427	0.0153
147	0.010	0.11	0.0067
148	0.001	0.026	0.0014
149	0.353		
150	0.001	0.422	0.0043
151	0.021		
152	0.027		0.0106
153	0.001	0.714	
154	0.004		
155	0.005	0.014	
156	0.003		
157	0.012		
158	0.002		
159	0.010	0.326	

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
160	1.64		
161	0.014		
162	0.010		
163	0.001		
164	0.003		
165	0.152		
166	0.027	5.23	0.0040
167	0.012		
168	0.023	0.022	0.0092
169	0.003	0.144	0.0249
170	0.004		0.006
171	0.002		0.002
172	0.12		
173	0.29		
174	1.1		
175	0.006	0.67	0.001
176	0.05		
177	0.07		
178	0.25		
179	1.7		
180	1.2		
181	0.004		
182	0.89		
183	21.5		
184	0.012		
185	0.006	0.04	0.001
186	0.018	0.14	0.004

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
187	0.99		
188	0.88		
189	0.31		
190	0.0031		
191	0.001	0.13	0.009
192	0.005		
193	0.066		
194	1.2		
195	0.008		
196	0.012		
197	0.022		
198	0.014	3.5	0.02
199	0.015		
200	0.005		
201	0.007		
202	0.04		
203	0.54		
204	0.012		
205	0.022		
206	0.16		
207	0.012		
208	0.007		
209	0.016		
210	0.008		
211	0.002		
212	2.3		
213	1.1		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
214	0.9		
215	0.99		
216	0.043		
217	0.006	0.63	0.008
218	0.01		
219	0.007	0.95	0.005
220	0.005		
221	0.003	0.35	0.003
222	0.009		
223	0.18		
224	0.009		0.005
225	0.1		
226	0.03		
227	0.06		
228	0.046		
229	0.63		
230	0.03		
231	0.036		
232	0.08		
233	0.005	0.43	0.02
234	0.03		
235	0.003		
236	0.035		
237	0.067		
238	0.02		
239	0.004		0.008
240	0.004		0.008

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
241	0.13		
242	0.02		
243	0.1		
244	0.077		
245	0.004		0.01
246	0.01		0.004
247	0.018		
248	0.005		
249	0.004	0.09	0.002
250	0.010		
251	0.004		0.006
252			
253	0.036		
254			
255	0.047		
256	0.038		
257	0.09		
258	0.011		
259	0.02		
260	0.61		
261	0.04		
262	0.003	0.13	0.008
263			
264			
265	0.13		
266	0.049		
267	0.06		

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
268	0.21		
269	0.006	0.16	0.002
270	0.002		0.002
271			
272			
273			
274			
275			
276			
277			
278			
279			
280	0.29	7.5	0.063
281	0.72	15.3	0.37
282	0.009		0.02
283	0.009	21.6	0.03
284	0.019		0.01
285	0.026		0.023
286	0.004		0.006
287	1.5		1
288	0.007		0.013
289	0.14		0.062
290	0.016		0.02
291	0.043		0.035
292	0.12		0.088
293	0.18		0.14
294	0.005		0.046

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
295	0.01		0.021
296	0.16		0.31
297	0.011		0.10
298	0.014		0.041
299	0.031		0.08
300	0.045		0.23
301	0.014		0.36
302	0.23		0.08
303	0.07		0.032
304	0.074		0.024
305	0.31		1.4
306	1.3		4.6
307	1.3		5.2
308	0.02		0.18
309	0.006		0.079
310	0.084		0.01
311	0.03		0.053
312	0.004		0.003
313	0.007		0.012
314	0.025		0.077
315	0.019		0.019
316	0.26		0.3
317	0.08		0.18
318	0.004		0.062
319	0.029		0.30
320	0.017		0.14
321	0.2		0.26

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
322	0.081		0.20
323	0.37		2.3
324	0.46		4.3
325	0.27		2.5
326	0.19		1.5
327	0.003		0.012
328	0.024		0.07
329	0.004		0.02
330	0.025		0.091
331	0.45		0.71
332	0.004		0.027
333	0.02		0.1
334	0.011		0.043
335	0.010		0.056
336	0.11		0.27
337	0.043		0.14
338	0.98		4.4
339	0.31		3.3
340	0.27		0.28
341			
342	0.021		0.018
343	0.023		0.029
344	0.021		0.019
345	0.008		0.009
346	0.015		0.034
347	0.014		0.067
348	0.009		0.026

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
349	0.004		0.065
350	0.73		0.61
351	0.004		0.024
352	0.044		0.12
353	0.13		0.24
354	0.024		0.17
355	0.022		0.11
356	0.074		0.52
357	0.016		0.12
358	0.012		0.062
359	0.007		0.12
360	0.004		0.061
361	0.006		0.053
362	0.0063		0.22
363	0.023		0.067
364	0.004		0.30
365	0.021		0.024
366	0.01		0.094
367	0.13		1.3
368	0.36		0.7
369	0.192		0.075
370	0.05		0.09
371	0.22		0.48
372	0.007		0.011
373	0.004		0.002
374	0.39		0.3
375	0.009		0.007

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
376	0.02		0.03
377	0.008		0.084
378	0.005		0.34
379	0.004		0.14
380	0.004		0.08
381	0.036		0.021
382	0.022		0.035
383	0.012		0.35
384	0.005		0.082
385	0.034		0.6
386			
387	0.02		1.2
388	0.007		0.28
389	0.003		0.004
390	0.003		0.019
391	0.009		0.002
392	0.005		0.003
393	0.028		0.89
394	0.011		0.52
395	0.06		0.39
396	0.025		0.074
397	0.032		0.20
398	0.006		1.3
399	0.006		0.
400	0.020		0.097
401	0.022		0.043
402	0.022		0.30

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
403	0.09		0.91
404	0.023		0.057
405	0.066		0.93
406	0.027		0.42
407			
408			
409			
410			
411			
412	0.003		0.023
413	0.004		0.003
414	0.008		0.028
415	0.006		0.01
416	0.005		0.009
417	0.10		0.19
418	0.005		0.012
419	0.004		0.058
420	0.006		0.087
421	0.004		0.032
422	0.004		0.033
423	1.4		3.6
424	0.011		0.047
425	0.004		0.059
426	0.002		0.051
427	0.003		0.13
428	0.004		0.012
429	0.008		0.10

	NaV1.7 395 Memb Binding (IC50) (micromolar)	EP_PX 293 hNav1.5 (IC50) (micromolar)	EP_PX 293 hNav1.7 (IC50) (micromolar)
430	0.003		0.01
431	0.013		0.01
432	0.022		0.032
433	0.004		
434	0.011		
435	0.003		
436	0.009		
437			
438			
439	0.028		
440	0.011	2.54	0.014
441	0.01		
442	0.006 or 0.004		
443	0.006 or 0.004		
444	0.010	0.326	
445	0.0093	0.743	0.0036
446	0.0016	0.16	0.0031
447	0.0042		
448	0.018	0.94	0.0078
449	0.004		
450	1.2		
451	0.27		
452	7.1		
453	0.95		
454	0.018		
455			

[02379] EXAMPLE 428

[02380] Analgesia Induced by sodium channel Blockers

[02381] Heat Induced Tail Flick Latency Test

[02382] In this test, the analgesia effect produced by administering a compound of the invention can be observed through heat-induced tail-flick in mice. The test includes a heat source consisting of a projector lamp with a light beam focused and directed to a point on the tail of a mouse being tested. The tail-flick latencies, which are assessed prior to drug treatment, and in response to a noxious heat stimulus, i.e., the response time from applying radiant heat on the dorsal surface of the tail to the occurrence of tail flick, are measured and recorded at 40, 80, 120, and 160 minutes.

[02383] For the first part of this study, 65 animals undergo assessment of baseline tail flick latency once a day over two consecutive days. These animals are then randomly assigned to one of the 11 different treatment groups including a vehicle control, a morphine control, and 9 compounds at 30 mg/Kg are administered intramuscularly. Following dose administration, the animals are closely monitored for signs of toxicity including tremor or seizure, hyperactivity, shallow, rapid or depressed breathing and failure to groom. The optimal incubation time for each compound is determined via regression analysis. The analgesic activity of the test compounds is expressed as a percentage of the maximum possible effect (%MPE) and is calculated using the following formula:

$$\%\ \text{MPE} \quad \frac{\text{Postdrug latency - Predrug latency}}{\text{Cut-off time (10 s) - Predrug latency}} \times 100\%$$

where:

[02384] Postdrug latency = the latency time for each individual animal taken before the tail is removed (flicked) from the heat source after receiving drug.

[02385] Predrug latency = the latency time for each individual animal taken before the tail is flicked from the heat source prior to receiving drug.

[02386] Cut-off time (10 s) = is the maximum exposure to the heat source.

[02387] Acute Pain (Formalin Test)

[02388] The formalin test is used as an animal model of acute pain. In the formalin test, animals are briefly habituated to the plexiglass test chamber on the day prior to experimental day for 20 minutes. On the test day, animals are randomly injected with the test articles. At 30 minutes after drug administration, 50 µL of 10% formalin is injected subcutaneously into the plantar surface of the left hind paw of the rats. Video data acquisition begins immediately after formalin administration, for duration of 90 minutes.

[02389] The images are captured using the Actimetrix Limelight software which stores files under the *.llii extension, and then converts it into the MPEG-4 coding. The videos are then analyzed using behaviour analysis software "The Observer 5.1", (Version 5.0, Noldus Information Technology, Wageningen, The Netherlands). The video analysis is conducted by watching the animal behaviour and scoring each according to type, and defining the length of the behaviour (Dubuisson and Dennis, 1977). Scored behaviours include: (1) normal behaviour, (2) putting no weight on the paw, (3) raising the paw, (4)

licking/biting or scratching the paw. Elevation, favoring, or excessive licking, biting and scratching of the injected paw indicate a pain response. Analgesic response or protection from compounds is indicated if both paws are resting on the floor with no obvious favoring, excessive licking, biting or scratching of the injected paw.

[02390] Analysis of the formalin test data is done according to two factors: (1) Percent Maximal Potential Inhibitory Effect (%MPIE) and (2) pain score. The %MPIEs is calculated by a series of steps, where the first is to sum the length of non-normal behaviours (behaviours 1,2,3) of each animal. A single value for the vehicle group is obtained by averaging all scores within the vehicle treatment group. The following calculation yields the MPIE value for each animal:

$$\text{MPIE (\%)} = 100 - [\text{ (treatment sum/average vehicle value) X 100\% }]$$

[02391] The pain score is calculated from a weighted scale as described above. The duration of the behaviour is multiplied by the weight (rating of the severity of the response), and divided by the total length of observation to determine a pain rating for each animal. The calculation is represented by the following formula:

$$\text{Pain rating} = [\ 0(To) + 1(T1) + 2(T2) + 3(T3)\ ] / (\ To + T1 + T2 + T3\ )$$

[02392] CFA Induced Chronic Inflammatory Pain

[02393] In this test, tactile allodynia is assessed with calibrated von Frey filaments. Following a full week of acclimatization to the vivarium facility, 150 μL of the "Complete Freund's Adjuvant" (CFA) emulsion (CFA suspended in an oil/saline (1:1) emulsion at a concentration of 0.5 mg/mL) is injected subcutaneously into the plantar surface of the left hind paw of rats under light isoflurane anaesthesia. Animals are allowed to recover from the anaesthesia and the baseline thermal and mechanical nociceptive thresholds of all animals are assessed one week after the administration of CFA. All animals are habituated to the experimental equipment for 20 minutes on the day prior to the start of the experiment. The test and control articles are administrated to the animals, and the nociceptive thresholds measured at defined time points after drug administration to determine the analgesic responses to each of the six available treatments. The time points used are previously determined to show the highest analgesic effect for each test compound.

[02394] Thermal nociceptive thresholds of the animals are assessed using the Hargreaves test. Animals are placed in a Plexiglas enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 30 °C for all test trials. Animals are allowed to accommodate for 20 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) is used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the idle intensity and active intensity of the heat source are set at 1 and 45 respectively, and a cut off time of 20 seconds is employed to prevent tissue damage.

[02395] The response thresholds of animals to tactile stimuli are measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA) following the Hargreaves test. Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represent approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

[02396] Postoperative Models of Nociception

[02397] In this model, the hypealgesia caused by an intra-planar incision in the paw is measured by applying increased tactile stimuli to the paw until the animal withdraws its paw from the applied stimuli. While animals are anaesthetized under 3.5% isofluorane, which is delivered via a nose cone, a 1 cm longitudinal incision is made using a number 10 scalpel blade in the plantar aspect of the left hind paw through the skin and fascia, starting 0.5 cm from the proximal edge of the heel and extending towards the toes. Following the incision, the skin is apposed using 2, 3-0 sterilized silk sutures. The injured site is covered with Polysporin and Betadine. Animals are returned to their home cage for overnight recovery.

[02398] The withdrawal thresholds of animals to tactile stimuli for both operated (ipsilateral) and unoperated (contralateral) paws can be measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After at least 10 minutes of acclimatization, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 10 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represent approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

[02399] Neuropathic pain model; Chronic Constriction Injury

[02400] Briefly, an approximately 3 cm incision is made through the skin and the fascia at the mid thigh level of the animals' left hind leg using a no. 10 scalpel blade. The left sciatic nerve is exposed via blunt dissection through the biceps femoris with care to minimize haemorrhagia. Four loose ligatures are tied along the sciatic nerve using 4-0 non-degradable sterilized silk sutures at intervals of 1 to 2 mm apart. The tension of the loose ligatures is tight enough to induce slight constriction of the sciatic nerve when viewed under a dissection microscope at a magnification of 4 fold. In the sham-operated animal, the left sciatic nerve is exposed without further manipulation. Antibacterial ointment is applied directly into the wound,

and the muscle is closed using sterilized sutures. Betadine is applied onto the muscle and its surroundings, followed by skin closure with surgical clips.

[02401] The response thresholds of animals to tactile stimuli are measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represents approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

[02402] Thermal nociceptive thresholds of the animals are assessed using the Hargreaves test. Following the measurement of tactile thresholds, animals are placed in a Plexiglass enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 24 to 26 oC for all test trials. Animals are allowed to accommodate for 10 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) is used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the idle intensity and active intensity of the heat source are set at 1 and 55 respectively, and a cut off time of 20 seconds is used to prevent tissue damage.

[02403] Neuropathic pain model: Spinal Nerve Ligation

[02404] The spinal nerve ligation (SNL) neuropathic pain model is used as an animal (i.e. rat) model of neuropathic pain. In the SNL test, the lumbar roots of spinal nerves L5 and L6 are tightly ligated to cause nerve injury, which results in the development of mechanical hyperalgesia, mechanical allodynia and thermal hypersensitivity. The surgery is performed two weeks before the test day in order for the pain state to fully develop in the animals. Several spinal nerve ligation variations are used to characterize the analgesic properties of a compound of the invention.

(1) Ligation of the L5 spinal nerve;

(2) Ligation of the L5 and L6 spinal nerves;

(3) Ligation and transection of the L5 spinal nerve;

(4) Ligation and transection of the L5 and L6 spinal nerves; or

(5) Mild irritation of the L4 spinal nerve in combination with any one of the above (1)-(4).

[02405] While the animals are anaesthetized under 3.5% isofluorane delivered via a nose cone, an approximately 2.5 cm longitudinal incision is made using a number 10 scalpel blade in the skin just lateral to the dorsal midline, using the level of the posterior iliac crests as the midpoint of the incision. Following the incision, the isoflourane is readjusted to maintenance levels (1.5% – 2.5%). At mid-sacral region, an

incision is made with the scalpel blade, sliding the blade along the side of the vertebral column (in the saggital plane) until the blade hits the sacrum. Scissors tips are introduced through the incision and the muscle and ligaments are removed from the spine to expose 2-3 cm of the vertebral column. The muscle and fascia are cleared from the spinal vertebra in order to locate the point where the nerve exits from the vertebra. A small glass hook is placed medial to the spinal nerves and the spinal nerves are gently elevated from the surrounding tissues. Once the spinal nerves have been isolated, a small length of non-degradable 6-0 sterilized silk thread is wound twice around the ball at the tip of the glass hook and passed back under the nerve. The spinal nerves are then firmly ligated by tying a knot, ensuring that the nerve bulges on both sides of the ligature. The procedure may be repeated as needed. In some animals, the L4 spinal nerve may be lightly rubbed (up to 20 times) with the small glass hook to maximize the development of neuropathic pain. Antibacterial ointment is applied directly into the incision, and the muscle is closed using sterilized sutures. Betadine is applied onto the muscle and its surroundings, followed by skin closure with surgical staples or sterile non-absorable monofilament 5-0 nylon sutures.

[02406] The analgesic effect produced by topical administration of a compound of the invention to the animals can then be observed by measuring the paw withdrawal threshold of animals to mechanical tactile stimuli. These may be measured using either the mechanical allodynia procedure or the mechanical hyperalgesia procedure as described below. After establishment of the appropriate baseline measurements by either method, topical formulation of a compound of the invention is applied on the ipsilateral ankle and foot. The animals are then placed in plastic tunnels for 15 minutes to prevent them from licking the treated area and removing the compound. Animals are placed in the acrylic enclosure for 15 minutes before testing the ipsilateral paw by either of the methods described below, and the responses are recorded at 0.5, 1.0 and 2.0 hour post treatment.

A. Mechanical allodynia method

[02407] The pain threshold of animals to mechanical alloydnia for both operated and control animals can be measured approximately 14 days post-surgery using manual calibrated von Frey filaments as follows. Animals are placed in an elevated plexiglass enclosure set on a mire mesh surface. Animals are allowed to acclimate for 20-30 minutes. Pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of the ipsilateral paw of the animals starting from the 2.0 g hair, with sufficient force to cause slight buckling of the hair against the paw to establish the baseline measurements. Stimuli are presented in a consecutive manner, either in an ascending or descending order until the first change in response is noted, after which four additional reponses are recorded for a total of six responses. The six responses measured in grams are entered into a formula as described by Chaplan, S.R. et al., J. Neurosci. Methods, 1994 Jul;53(1):55-63, and a 50% withdrawal threshold is calculated. This constitutes the mechanical allodynia value.

B. Mechanical hyperalgesia method

[02408] The response thresholds of animals to tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglas enclosure set on a wire mesh surface. After 15 minutes of accommodation in this enclosure, a von Frey hair was applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals, with sufficient force, measured in grams, to elicit a crisp response of the paw. The response indicated a withdrawal from the painful stimulus and constituted the efficacy endpoint. The data were expressed as percent change from baseline threshold measured in grams.

[02409] EXAMPLE 427

[02410] In Vivo Assay for Treatment of Pruritis

[02411] The compounds of the invention can be evaluated for their activity as antipruritic agents by in vivo test using rodent models. One established model for peripherally elicited pruritus is through the injection of serotonin into the rostral back area (neck) in hairless rats. Prior to serotonin injections (e.g., 2 mg/mL, 50 μL), a dose of a compound of the present invention can be applied systemically through oral, intravenous or intraperitoneal routes or topically to a circular area fixed diameter (e.g. 18 mm). Following dosing, the serotonin injections are given in the area of the topical dosing. After serotonin injection the animal behaviour is monitored by video recording for 20 min-1.5 h, and the number of scratches in this time compared to vehicle treated animals. Thus, application of a compound of the current invention could suppress serotonin-induced scratching in rats.

[02412] EXAMPLE 428

[02413] Tritiated Aryl Sulfonamide Binding to membranes isolated from cells that heterologously express hNav1.7 and the β1 subunit

[02414] Preparation of membranes containing recombinantly expressed sodium channels: Frozen recombinant cell pellets were thawed on ice and diluted to 4 times the cell pellet weight with ice cold 50 mM Tris HCl, pH 7.4 buffer. The cell suspensions were homogenized on ice using a motorized glass dounce homogeniser. Homogenates were further diluted 8.4 times with ice cold 50 mM Tris HCl, pH 7.4 buffer and then centrifuged at 200 x g at 4°C for 15 min. The supernatants were collected and centrifuged at 10000 x g at 4°C for 50 min. The pellets were then re-suspended in 100 mM NaCl, 20 mM Tris HCl, pH 7.4 buffer containing 1% v/v protease inhibitors (Calbiochem) and re-homogenized on ice. The homogenized membranes were then processed through a syringe equipped with a 26 gauge needle. Protein concentrations were determined by Bradford Assay and the membranes were stored at -80°C.

[02415] Radioligand Binding Studies: Saturation experiments. A representative compound of formula (I) was tritiated. Three tritiums were incorporated in place of methyl hydrogens to generate [^{3}H]compound. Binding of this radioligand was preformed in 5 mL borosilicate glass test tubes at room temperature. Binding was initiated by adding membranes to increasing concentrations of [^{3}H]compound in 100 mM NaCl, 20 mM Tris HCl, pH 7.4 buffer containing 0.01% w/v bovine serum albumin (BSA) for 18h.

Non-specific binding was determined in the presence of 1 μM unlabelled compound. After 18h, the reactants were filtered through GF/C glass fiber filters presoaked in 0.5% w/v polyethylene imine. Filters were washed with 15 mL ice cold 100 mM NaCl, 20 mM Tris HCl, pH7.4 buffer containing 0.25% BSA to separate bound from free ligand. [^{3}H]compound bound to filters was quantified by liquid scintillation counting.

[02416] **Competitive binding experiments.** Binding reactions were preformed in 96-well polypropylene plates at room temperature for 18h. In 360 μL, membranes were incubated with 100 pM [^{3}H]compound and increasing concentrations of Test Compound. Non-specific binding was defined in the presence of 1 μM unlabelled compound. Reactions were transferred and filtered through 96-well glass fiber/C filter plates presoaked with 0.5% polyethylene imine. The filtered reactions were washed 5 times with 200 μL ice cold buffer containing 0.25% BSA. Bound radioactivity was determined by liquid scintillation counting.

[02417] Data Analysis: For saturation experiments, non-specific binding was subtracted from total binding to provide specific binding and these values were recalculated in terms of pmol ligand bound per mg protein. Saturation curves were constructed and dissociation constants were calculated using the single site ligand binding model: Beq=(Bmax*X)/(X+Kd), where Beq is the amount of ligand bound at equilibrium, Bmax is the maximum receptor density, Kd is the dissociation constant for the ligand, and X is the free ligand concentration. For competition studies percent inhibition was determined and IC_{50} values were calculated using a 4 parameter logistic model (% inhibition = (A+((B-A)/(1+((x/C)^D)))) using XLfit, where A and B are the maximal and minimum inhibition respectively, C is the IC_{50} concentration and D is the (Hill) slope.

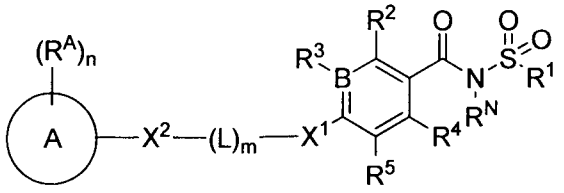
[02418] Compounds of the invention, when tested in this model, demonstrated affinities for the inactivated state of NaV1.7 membrane binding (as set forth in Table 2).

[02419] All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non patent publications referred to in this specification are incorporated herein by reference in their entireties.

[02420] Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

WE CLAIM:

1. A compound selected from a compound of Formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein in Formula I:

R^1 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 9 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-P(=O)$(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

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

B is C or N;

R^2, **R^3** and **R^4** are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

R^5 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-7} heterocycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

L is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^L substituents selected from the group consisting of =O, -OH, -OCH2.phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

the subscript m represents the integer 0 or 1;

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

the subscript n is an integer from 0 to 5;

A is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

$\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, =O, heteroaryl, -$(X^{RA})_{0-1}NR^{A1}R^{A2}$, -$(X^{RA})_{0-1}OR^{A1}$, -$(X^{RA})_{0-1}SR^{A1}$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, -$(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, -$(X^{RA})_{0-1}C(=O)OR^{A1}$, -$(X^{RA})_{0-1}OC(=O)R^{A1}$, -$P(=O)(OR^{A1})(OR^{A2})$, -$(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, -$(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, -$(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and -$(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, -NH_2, -OH, -CN, -NO_2, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)$_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy, tetrahydronaphthalene and phenyl wherein phenyl is optionally substituted with 1-3 fluoro, chloro, bromo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy , C_{1-6} alkylamino, C_{1-6} or dialkylamino;

with the proviso that a compound of Formula I is not

4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;

4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or
4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

2. The compound of claim 1 wherein:

R^1 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl, heteroaryl, or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatom selected from N, O and S as ring vertex and optionally fused thereto is a benzene or pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl;

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

B is C or N;

R^2, **R^3** and **R^4** are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

R^5 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

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

the subscript m represents the integer 0 or 1;

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

the subscript n is an integer from 0 to 5;

A is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

$\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, heteroaryl, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2N$-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2N$-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene;

with the proviso that a compound of Formula I is not

4-(cyclohexylmethoxy)-N-(methylsulfonyl)benzamide;

4-(cyclopentylmethoxy)-N-(methylsulfonyl)benzamide or

4-(cyclobutylmethoxy)-2,5-difluoro-N-(methylsulfonyl)benzamide.

3. The compound of claim 1 wherein:

$\mathbf{R^1}$ is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-12} cycloalkyl, C-linked C_{2-11} heterocycloalkyl or $-NR^{1A}R^{1B}$, wherein R^{1A} and R^{1B} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, (6-10 membered aryl)-$(X^{R1})_{0-1}$-, (5-10 membered heteroaryl)-$(X^{R1})_{0-1}$-, and wherein R^{1A} and R^{1B} are optionally combined to form a 3 to 8 membered heterocyclic ring optionally comprising 1 additional heteroatoms selected from N, O and S as ring vertex and optionally fused thereto is a benzene or

pyridine ring; X^{R1} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene, C_{2-4} alkynylene; and wherein the aliphatic and aromatic portions of R^1 are optionally substituted with from 1 to 5 R^{R1} substituents selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, $-(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, $-(X^{1R})_{0-1}OR^{R1a}$, $-(X^{1R})_{0-1}SR^{R1a}$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)OR^{R1c}$, $-(X^{1R})_{0-1}OC(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}C(=O)N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})C(=O)R^{R1b}$, $-(X^{1R})_{0-1}C(=O)OR^{R1a}$, $-(X^{1R})_{0-1}OC(=O)R^{R1a}$, $-(X^{1R})_{0-1}$-$P(=O)(OR^{R1a})(OR^{R1b})$, $-(X^{1R})_{0-1}S(O)_{1-2}R^{R1c}$, $-(X^{1R})_{0-1}S(O)_{1-2}N(R^{R1a})(R^{R1b})$, $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}N(R^{R1a})(R^{R1b})$ and $-(X^{1R})_{0-1}N(R^{R1a})S(O)_{1-2}(R^{R1c})$, wherein X^{1R} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{R1c} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl;

$\mathbf{R^N}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

B is C or N;

$\mathbf{R^2}$, $\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy, and R^3 is absent when B is nitrogen;

$\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-7} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl is further optionally substituted with from 1 to 3 R^5 substituents selected from F, Cl, Br, I, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

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

the subscript m represents the integer 0 or 1;

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

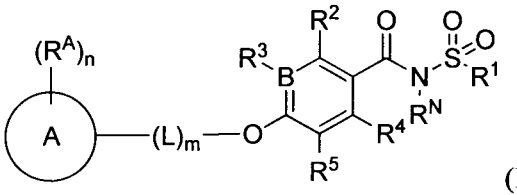
the subscript n is an integer from 0 to 5;

A is selected from the group consisting of hydrogen, C_{3-12} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto or a 5 to 6 membered heteroaryl having a 3-8 membered carbocyclic or heterocyclic ring comprising 1 to 3 heteroatoms selected from N, O and S fused thereto, and wherein if A is hydrogen then the subscript n is 0; and

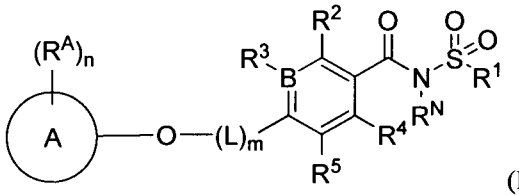
$\mathbf{R^A}$ is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$,

$-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, C_{5-6} heteroaryl and C_{2-7} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, $((halo)alkyl)_2N$-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, $((halo)alkyl)_2N$-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy and tetrahydronaphthalene.

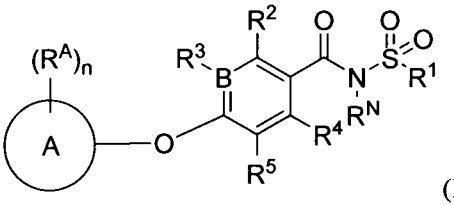
4. The compound of any one of claims 1-3 wherein the compound has the formula



(I-I),



(I-II) or



(I-III).

5. The compound of any one of claims 1-4 wherein B is N and R^3 is absent.

6. The compound of any one of claims 1-4 wherein B is C.

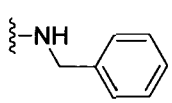
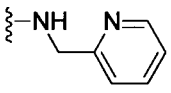
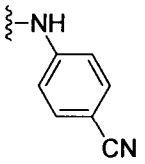
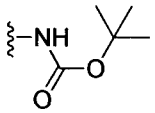
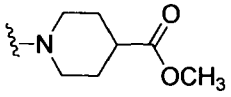
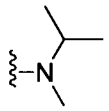
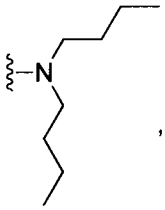
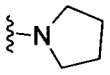
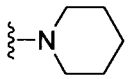
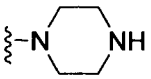
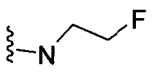
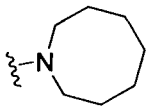
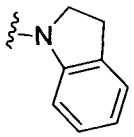
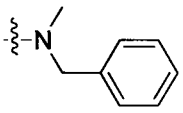
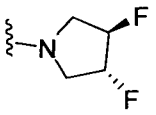
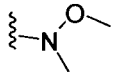
7. The compound of any one of claims 1-6 wherein R^2, R^3 and R^4 are each independently selected from H, F, or Cl.

8. The compound of any one of claims 1-6 wherein R^2 is H, F or Cl; R^3 and R^4 are each H; and R^5 is an optionally substituted group selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, and C_{1-8} alkoxy.

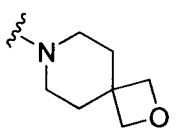
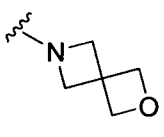
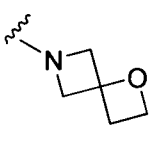
9. The compound of any one of claims 1-8 wherein R^1 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-10} cycloalkyl or $-NR^{1A}R^{1B}$.

10. The compound of claim 9, wherein R^1 is selected from the group consisting of methyl, ethyl, propyl, trifluoromethyl, difluoromethyl, monofluoromethyl, isopropyl and cyclopropyl.

11. The compound of any one of claims 1-8 wherein, R^1 is selected from the group consisting of: $-NH(CH_3)$, $-N(CH_3)_2$,
















and 

12. The compound of any one of claims 1-8 wherein R^1 is selected from the group consisting of: methyl, ethyl, *tert*-butyl, dimethylamino, methylamino, amino, morpholino, azetidino, imidazolyl, 3-hydroxyazetidino, 3-fluoroazetidino, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, N-methylimidazolyl, tetrahydorofuranyl, 2-isopropoxyethyl, 3-cyanoazetidino, 2-ethoxyethyl, 2-methoxypropyl, 2-hydroxypropyl, 4-hydroxypiperidinyl and 3-methoxypyrrolidinyl and the following formulas:



and 

13. The compound of any one of claims 1-8 wherein R^1 is selected from the group consisting of: methyl, ethyl, *tert*-butyl, dimethylamino, methylamino, amino, morpholino, azetidino, imidazolyl, 3-hydroxyazetidino, 3-fluoroazetidino, cyclopropyl, pyrrolidinyl, 3,3-difluoroazetidino, *tert*-butyl, ethyl, 2-methoxyethyl, 3-methoxyazetidino, 2-hydroxyethyl, 3-hydroxypyrrolidinyl, and N-methylimidazolyl.

14. The compound of any one of claims 1-13 wherein X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is an optionally substituted group selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene.

15. The compound of any one of claims 1-13, wherein X^1 is –O- or –N(H)-; X^2 is absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–CH_2-$, –C(=O)-, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

16. The compound of claim 15, wherein X^1 is –O-; the subscript m is 1 and –(L)- is $–CH_2-$ or $–CH_2-CH_2-$.

17. The compound of any one of claims 1-13 wherein X^1 is absent; X^2 is –O- or –N(H)-; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, –C(=O)-, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

18. The compound of any one of claims 1-13 wherein X^1 and X^2 are absent; the subscript m is 1; and –(L)- is selected from the group consisting of $–C(H)_2-$, –C(=O)-, $–C(H)(CH_3)-$, $–CH_2-CH_2-$, $–CH_2-C(H)(CH_3)-$, $–C(H)(CH_3)-C(H_2)-$, $–CH_2CH_2CH_2-$, $–CH_2-C(H)(CH_3)-CH_2-$ or $-CH_2CH_2CH_2CH_2-$.

19. The compound of any one of claims 1-13 wherein X^1 and X^2 are absent; the subscript m is 1; and –(L)- is an optionally substituted C_{1-4} heteroalkylene.

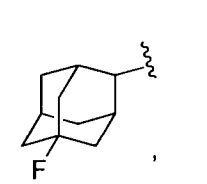
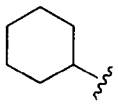
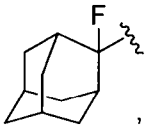
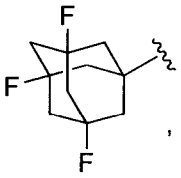
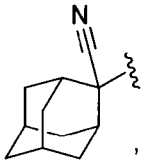
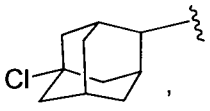
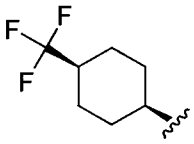
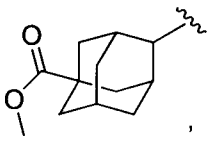
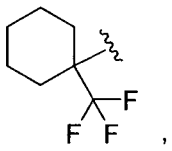
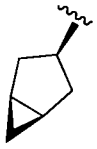
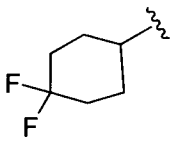
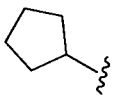
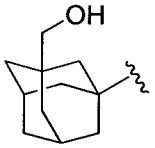
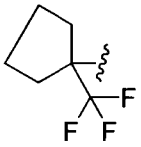
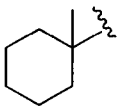
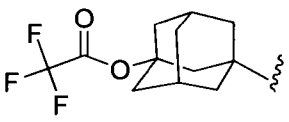
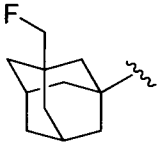
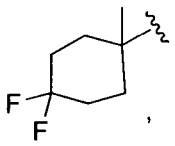
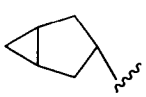
20. The compound of any one of claims 1-13 wherein m is 0; X^1 is selected from –O-, and –N(H)-; and X^2 is absent.

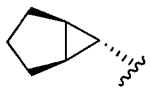
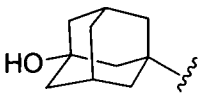
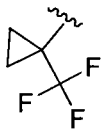
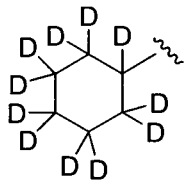
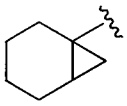
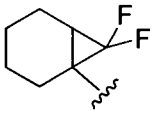
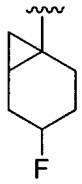
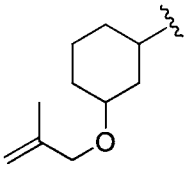
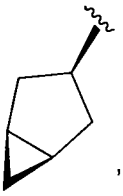
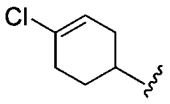
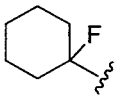
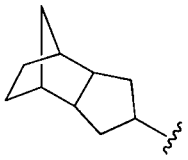
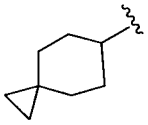
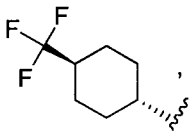
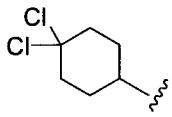
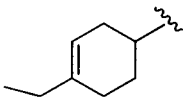
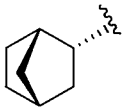
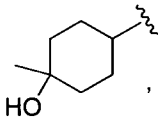
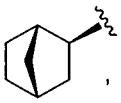
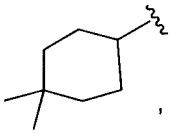
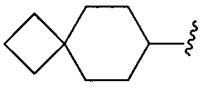
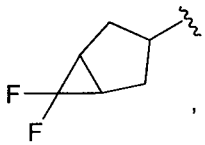
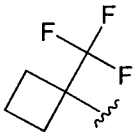
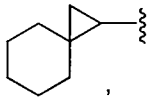
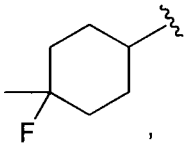
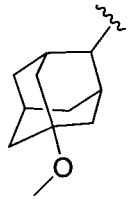
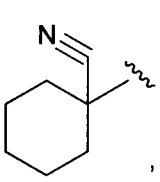
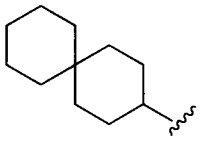
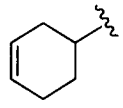
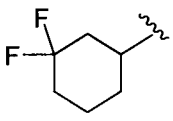
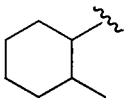
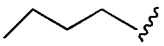
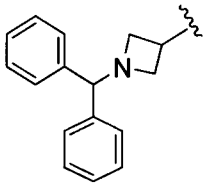
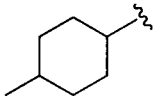
21. The compound of any one of claims 1-20 wherein A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, adamantane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, bicyclo[3.3.1]nonane and 1,2,3,4-tetrahydro-1,4-methanonaphthalene, 1,2,3,4-tetrahydroisoquinoline and chroman.

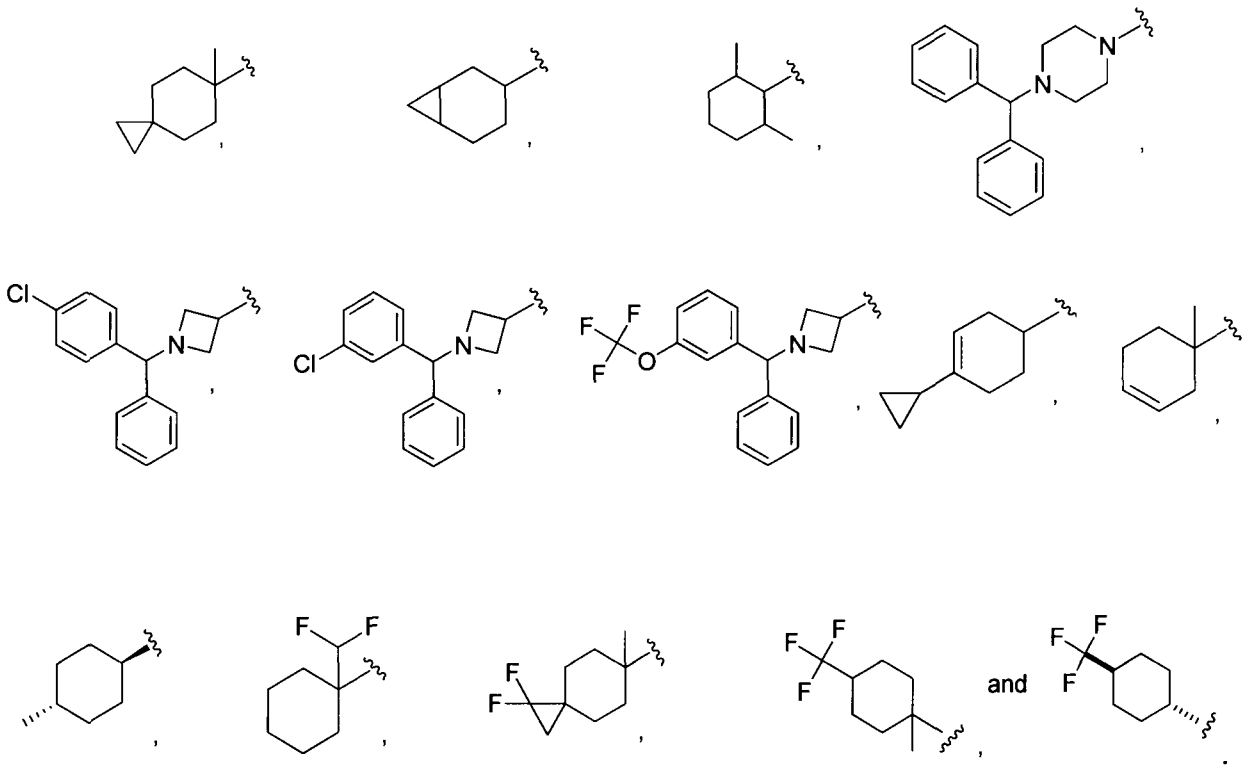
22. The compound of any one of claims 1-20, wherein ring A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane, cubane, bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, piperidinyl, tetrahydrofuranyl, tetrahydronaphthyl, spiro[2,5]octanyl, norpinanyl, spiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, norbornanyl, spiro[4.5]decanyl, bicyclo[4.1.0]heptane and spiro[5.5]undecanyl.

23. The compound of any one of claims 1-20 wherein ring A is an optionally substituted ring selected from the group consisting of azetidine, pyrrolidine, piperidine, homopiperidine, (1R,5S)-8-azabicyclo[3.2.1]octane, 3-oxa-9-azabicyclo[3.3.1]nonane, (1s,4s)-7-azabicyclo[2.2.1]heptane, (1R,4S)-5-azabicyclo[2.1.1]hexane, 7-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and quinuclidine

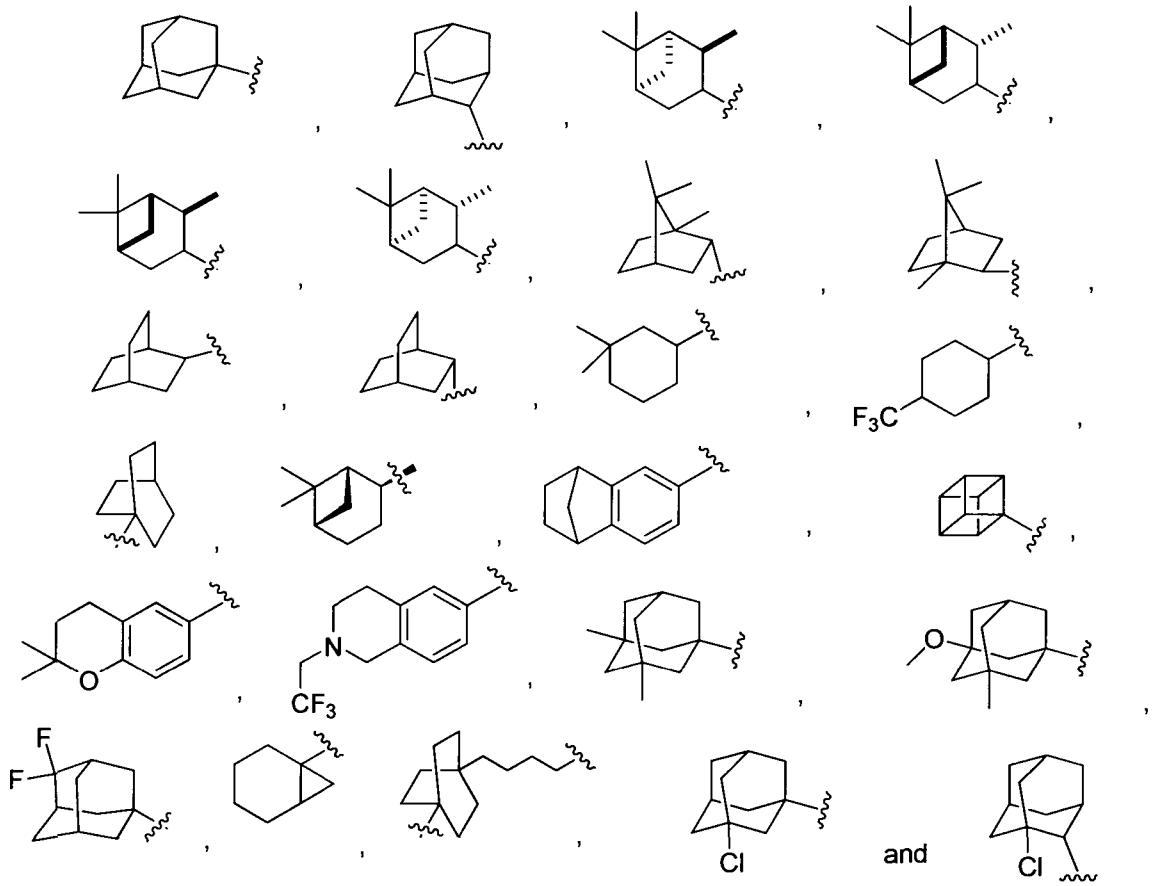
24. The compound of any one of claims 1-20 wherein ring A-$(R^A)_n$ is selected from the group consisting of

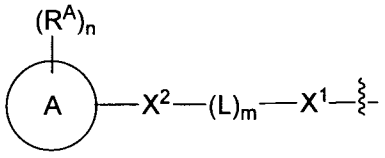

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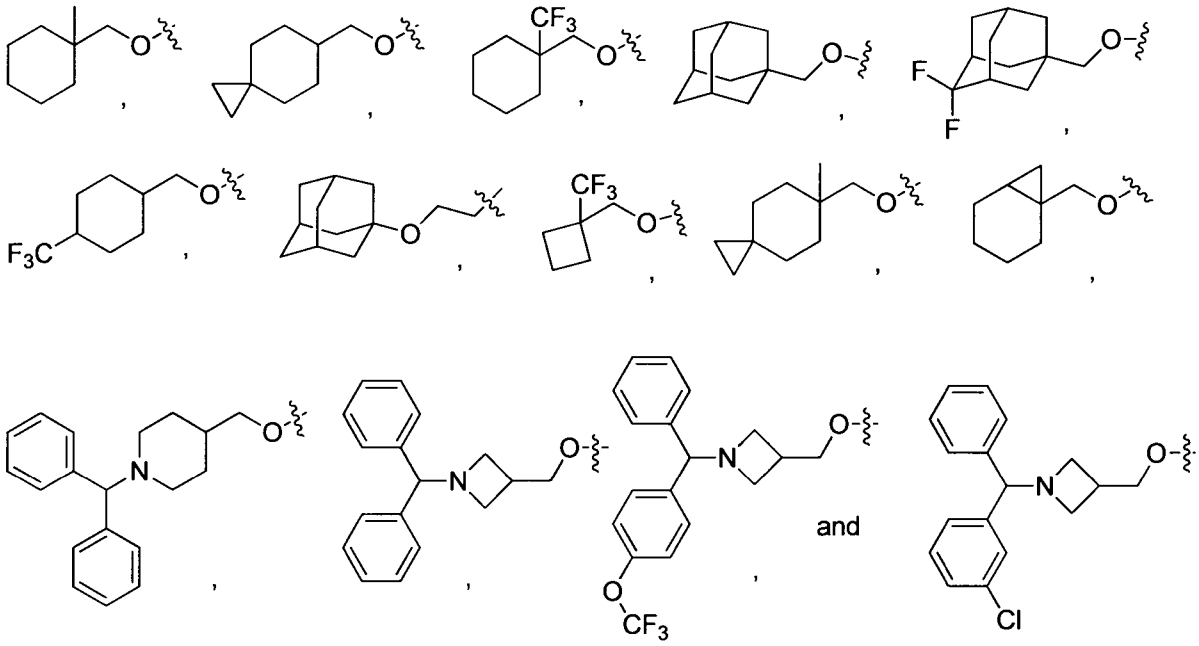
25. The compound of any one of claims 1-20 wherein ring A-$(R^A)_n$ is selected from the group consisting of



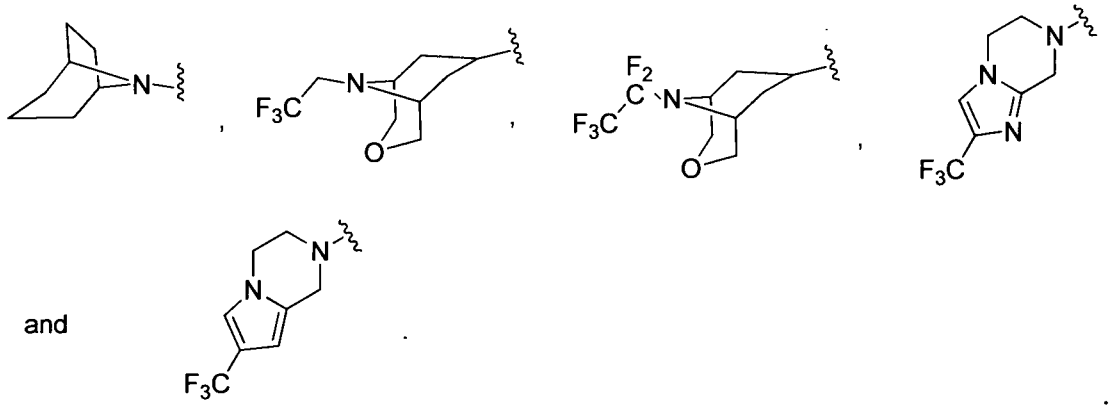
26. The compound of any one of claims 1-13 wherein the group:



is selected from the group consisting of



27. The compound of any one of claims 1-20 wherein ring A is selected from the group consisting of



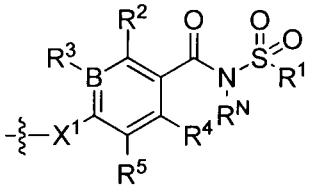
28. The compound of any one of claims 1-23 wherein R^A is selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{2-4} heterocycloalkyl, F, Cl, Br, I, -OH, $-NH_2$, -CN, $-NO_2$, C_{1-4} alkoxy, $-C(=O)-N(R^{A1})(R^{A2})$ and $-N(R^{A1})(R^{A2})$.

29. The compound of any one of claims 1-23 wherein R^A is methyl, trifluromethyl, difluoromethyl, monofluoromethyl, ethyl, pentafluoroethyl, cyclopropyl, -F, Cl, -OH, $-NH_2$ or –CN.

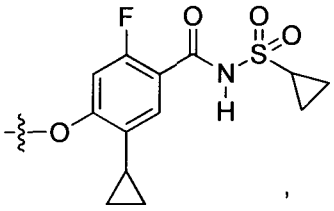
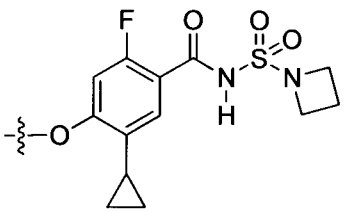
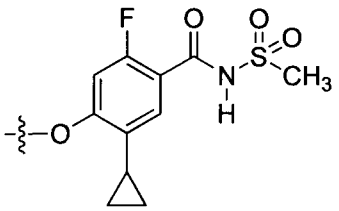
30. The compound of any one of claims 1-4 and 7-29 wherein B is C; R^3 is H, R^2 is F, Cl, Br, or I; R^4 is H; and R^5 is C_{3-8} cycloalkyl, wherein said C_{3-8} cycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy.

31. The compound of any one of claim 30 wherein R^5 is C_{3-8} cycloalkyl.

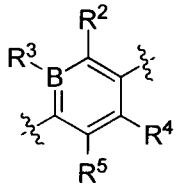
32. The compound of any one of claims 1-4, 21-25, and 27-29 wherein the group:



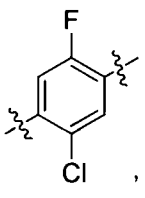
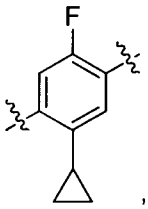
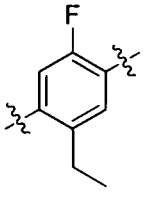
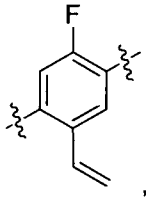
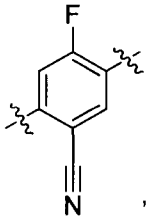
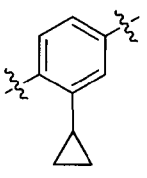
is selected from the group consisting of


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and

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33. The compound of any one of claims 1-3 and 9-29 wherein the group:



is selected from the group consisting of


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and

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34. The compound of claim 1, selected from the group consisting of compounds set forth in Table 1 and the pharmaceutically acceptable salts thereof.

35. A pharmaceutical composition comprising a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

36. A method of treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

37. The method of claim 36, wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

38. The method of claim 36, wherein said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

39. A method of treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal, wherein the method comprises administring to the mammal in need thereof a therapeutically effective amount of a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

40. A method of decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

41. A method of treating pruritus in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

42. A method of treating cancer in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

43. A method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula I as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

44. The method of claim 43, wherein the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

45. The method of claim 43, wherein the pain is associated with a disease or condition selected from the group consisting of HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

46. A method for the treatment or prophylaxis of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, which method comprises administering an

effective amount of a compound of formula (I) as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof.

47. A compound of formula (I) as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

48. The use of a compound of formula (I) as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

49. A compound of formula (I) as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease.

50. A compound of formula (I) as described in any one of claims 1-34 or a pharmaceutically acceptable salt thereof for use in medical therapy.

51. The invention as hereinbefore described.