(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2011 (17.11.2011)

PCT

(10) International Publication Number
WO 2011/141728 A1

(51) **International Patent Classification**:
C07D 471/10 (2006.01) ***A61P 29/00*** (2006.01)
A61K 31/438 (2006.01)

(21) **International Application Number**:
PCT/GB2011/050890

(22) **International Filing Date**:
10 May 2011 (10.05.2011)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1007789.9 10 May 2010 (10.05.2010) GB

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2011/141728 A1

(54) **Title**: SPIROCYCLIC DERIVATIVES WITH AFFINITY FOR CALCIUM CHANNELS

(57) **Abstract**: The invention relates to novel spirocyclic derivatives with affinity for Cav2.2 calcium channels and which are capable of interfering with Cav2.2 calcium channels; to processes for their preparation; to pharmaceutical compositions containing them; and to the use of such compounds in therapy for the treatment of pain.

SPIROCYCLIC DERIVATIVES WITH AFFINITY FOR CALCIUM CHANNELS

The invention relates to novel spirocyclic derivatives with affinity for $Ca_v2.2$ calcium channels and which are capable of interfering with $Ca_v2.2$ calcium channels; to processes for their preparation; to pharmaceutical compositions containing them; and to the use of such compounds in therapy.

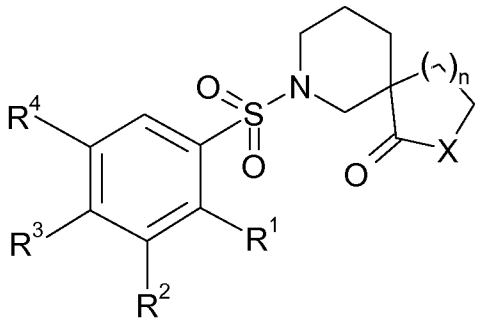
Presynaptic $Ca_v2.2$ (N-type) voltage-gated calcium channels in the dorsal horn of the spinal cord modulate the release of key pro-nociceptive neurotransmitters such as glutamate, substance P (SP) and calcitonin-gene-related peptide (CGRP), indicating the potential therapeutic use of $Ca_v2.2$ calcium channel blockers as analgesics.

Peptidic ω-conotoxins, isolated from the venom of cone snails, are selective for $Ca_v2.2$ calcium channels and can block SP release in the spinal cord (Smith *et al.* (2002) Pain, 96: 119-127). Moreover, they are antinociceptive in animal models of chronic pain following intrathecal administration (Bowersox *et al.* (1996) Journal of Pharmacology and Experimental Therapeutics, 279: 1243-1249; Smith *et al.* (2002) *supra*), and are effective analgesics in clinical use, particularly in the treatment of neuropathic pain (Brose *et al.* (1997) Clinical Journal of Pain, 13: 256-259).

However, $Ca_v2.2$ calcium channels are also important for normal neuronal function. Therefore, the aim is to identify novel molecules that preferentially block $Ca_v2.2$ under conditions of increased neuronal excitability, so-called use-dependent blockers, as is the case in chronic pain syndromes (Winquist *et al.* (2005) Biochemical Pharmacology, 70: 489-499).

WO 2007/084314 (Incyte Corporation) discloses a series of cyclic compounds as modulators of 11-β hydroxyl steroid dehydrogenase type 1 which are claimed to be useful in disorders such as diabetes and obesity. WO 2005/047286 (Ono Pharm Co Ltd) discloses a series of heterocyclic spiro compounds as mitochondrial benzodiazepine receptor antagonists which are claimed to be useful for preventing and/or treating stress induced disorders. WO 99/65494 (Merck & Co Inc) discloses a series of spirocyclic compounds as prenyl-protein transferase inhibitors which are claimed to be useful in the treatment of cancer. WO 2006/006490 (Ono Pharm Co Ltd) discloses a series of spirocyclic compounds which are claimed to be useful in preventing and treating thrombosis, embolism, accompanying cerebrovascular diseases or venous vascular diseases.

The present invention provides compounds with affinity for $Ca_v2.2$ calcium channels and which are capable of interfering with the affects of these channels. In a first aspect there is provided a compound of formula (I), or a salt thereof:



(I)

wherein R^1, R^3 and R^4 are independently selected from hydrogen, chlorine, bromine, methyl, methoxy, ethoxy, trifluoromethyl or trifluoromethoxy;

R^2 represents hydrogen, chlorine, fluorine, bromine, methyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy;

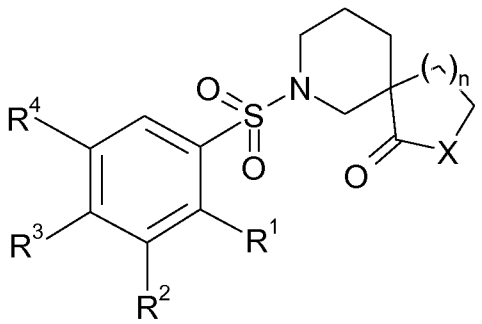
such that at least one of R^1, R^2, R^3 and R^4 represents a group other than hydrogen and such that when one of R^1, R^2, R^3 or R^4 represents methyl, at least one other of R^1, R^2, R^3 or R^4 represents a group other than hydrogen and such that when R^2 represents fluorine, R^4 represents trifluoromethyl;

n represents an integer from 1 or 2;

X represents –N-(R^5)- or –O-; and

R^5 represents hydrogen or C_{1-4} alkyl.

In one particular aspect of the invention which may be mentioned there is provided a compound of formula (I), or a salt thereof:



(I)

wherein R^1, R^3 and R^4 are independently selected from hydrogen, chlorine, bromine, methyl, trifluoromethyl or trifluoromethoxy;

R^2 represents hydrogen, chlorine, fluorine, bromine, methyl, trifluoromethyl or trifluoromethoxy;
such that at least one of R^1, R^2, R^3 and R^4 represents a group other than hydrogen and such that when one of R^1, R^2, R^3 or R^4 represents methyl, at least one other of R^1, R^2, R^3 or R^4 represents a group other than hydrogen and such that when R^2 represents fluorine, R^4 represents trifluoromethyl;
n represents an integer from 1 or 2;
X represents –N-(R^5)- or –O-; and
R^5 represents hydrogen or C_{1-4} alkyl.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_{1-4} alkyl means a straight or branched hydrocarbon chain containing at least 1 and at most 4 carbon atoms. Examples of alkyl include, but are not limited to; methyl (Me), ethyl (Et), n-propyl, i-propyl and t-butyl.

In one embodiment, n represents 1. In an alternative embodiment, n represents 2.

In one embodiment, R^2 represents hydrogen, chlorine, fluorine, methyl, trifluoromethyl or trifluoromethoxy.

In one embodiment, R^3 represents hydrogen, bromine, methyl, trifluoromethyl or trifluoromethoxy.

In one embodiment, R^4 represents hydrogen, chlorine, methyl or trifluoromethyl.

In one embodiment, one of R^1, R^2, R^3 and R^4 represents trifluoromethyl or trifluoromethoxy. In a further embodiment, one of R^1, R^2, R^3 and R^4 represents trifluoromethyl or trifluoromethoxy and the others all represent hydrogen. In a further embodiment, one of R^1, R^2, R^3 and R^4 represents trifluoromethyl and the others all represent hydrogen.

In one embodiment, R^1, R^2 and R^4 each represent hydrogen and R^3 represents methyl, ethoxy, trifluoromethyl or trifluoromethoxy.

In a further embodiment, R^1, R^2 and R^4 each represent hydrogen and R^3 represents trifluoromethyl or trifluoromethoxy. In a yet further embodiment, R^1, R^2 and R^4 each represent hydrogen and R^3 represents trifluoromethyl.

In one embodiment, R^1, R^3 and R^4 each represent hydrogen and R^2 represents difluoromethoxy, trifluoromethyl or trifluoromethoxy. In a further embodiment, R^1, R^3 and R^4 each represent hydrogen and R^2 represents trifluoromethoxy.

In one embodiment, R^2 and R^4 each represent hydrogen, R^3 represents methyl or trifluoromethyl and R^1 represents chlorine, bromine, methyl, trifluoromethyl or trifluoromethoxy. In a further embodiment, R^2 and R^4 each represent hydrogen, R^3 represents trifluoromethyl and R^1 represents chlorine, bromine or methyl.

In one embodiment, R^2 and R^3 each represent hydrogen, R^1 represents methyl, methoxy or trifluoromethyl and R^4 represents trifluoromethyl.

In one embodiment, R^1 and R^3 each represent hydrogen, R^2 represents chlorine or trifluoromethyl and R^4 represents chlorine, fluorine, methyl or trifluoromethyl. In a further embodiment, R^1 and R^3 each represent hydrogen, R^2 represents trifluoromethyl and R^4 represents methyl.

In one embodiment, R^1 and R^4 each represent hydrogen, R^2 represents chlorine or trifluoromethyl and R^3 represents methyl or trifluoromethoxy. In a further embodiment, R^1 and R^4 each represent hydrogen, R^2 represents chlorine and R^3 represents trifluoromethoxy.

In one embodiment, X represents –N(H)-, -N(Me)- or –O-. In a further embodiment, X represents –N(H)- or -N(Me)-. In a yet further embodiment, X represents –N(H)-.

In one embodiment, X represents –N-(R^5)-. In an alternative embodiment, X represents –O-.

In one embodiment, R^5 represents hydrogen or methyl. In a further embodiment, R^5 represents hydrogen. In an alternative embodiment, R^5 represents methyl.

Particular compounds according to the invention include one or more compounds selected from:

7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E1);
2-Methyl-7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E2);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E3);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-methyl-2,7-diazaspiro[4.5]decan-1-one (E4);
2-Methyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E5);
7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E6);
7-[(2,4-Dimethylphenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E7);
7-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E8);
7-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E9);
8-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E10);
8-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E11);
8-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E12);
8-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E13);
7-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E14);
7-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E15);
7-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E16);
8-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E17);
8-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E18);
7-[(3,5-Dichlorophenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E19);
7-({3-Chloro-4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E20);
7-{[2-Bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E21);
7-{[2-Methyl-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E22);
7-{[4-Methyl-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E23);
7-({4-Methyl-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E24);
7-{[3-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E25);
7-{[2-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E26);
8-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E27);
7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2-oxa-7-azaspiro[4.5]decan-1-one (E28);
7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2-oxa-7-azaspiro[4.5]decan-1-one (E29);
7-{[4-Methyl-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E30);
8-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E31);

7-{[2-(Methyloxy)-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E32);
7-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E33);
8-{[4-(Ethyloxy)phenyl]sulfonyl}-2-methyl-2,8-diazaspiro[5.5]undecan-1-one (E34);
and
8-[(4-Methylphenyl)sulfonyl]-2,8-diazaspiro[5.5]undecan-1-one (E35).

In one embodiment, the compound of formula (I) is selected from:
2-Methyl-7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E2);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E3);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-methyl-2,7-diazaspiro[4.5]decan-1-one (E4);
2-Methyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E5);
8-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E10);
8-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E11);
7-({3-Chloro-4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E20);
7-{[2-Bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E21);
7-{[2-Methyl-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E22);
7-{[3-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E25);
and
7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2-oxa-7-azaspiro[4.5]decan-1-one (E28).

In one embodiment, the compound of formula (I) is selected from:
7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E1); and
7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E6).

Because of the potential use of compounds of formula (I) in medicine, salts of compounds of formula (I) are preferably pharmaceutically acceptable.

Certain compounds of formula (I) may in some circumstances form acid addition salts thereof. It will be appreciated that for use in medicine compounds of formula (I) may be used as salts, in which case the salts should be pharmaceutically acceptable. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse , J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" includes salts prepared from pharmaceutically acceptable acids, including

inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

Examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, hydrochloric, sulfuric, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated by those skilled in the art that certain protected derivatives of the compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All protected derivatives and prodrugs of compounds are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in “Design of Prodrugs” by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as “pro-moieties”, for example as described by H. Bundgaard in “Design of Prodrugs” (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compounds of formula (I). Therefore, in a further aspect, the invention provides a prodrug of a compound of formula (I).

It will be appreciated that certain compounds of formula (I), or their salts, may exist as solvates, such as hydrates. Where solvates exist, this invention includes within its scope stoichiometric and non-stoichiometric solvates.

It will be appreciated that certain compounds of formula (I), or their salts, may exist in more than one polymorphic form. The invention extends to all such forms whether in

a pure polymorphic form or when admixed with any other material, such as another polymorphic form.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

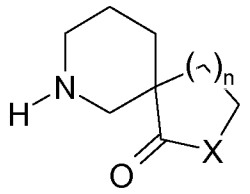
The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, fluorine such as ^{3}H, ^{11}C, ^{14}C and ^{18}F.

Compounds of formula (I) and salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography). PET is useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can 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. Isotopically labeled compounds of formula (I) and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. In one embodiment, the compounds of formula (I) or salts thereof are not isotopically labelled.

Compounds of formula (I) may be prepared as set forth in the following Schemes and in the supporting compounds. The following processes form another aspect of the present invention.

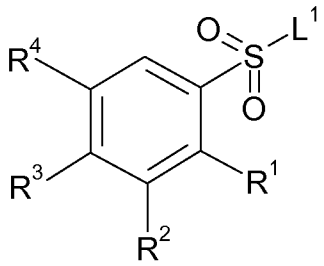
The present invention also provides a process for the preparation of a compound of formula (I) or a salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

or a protected derivative thereof, wherein X and n are as defined above, with a compound of formula (III)



(III)

wherein R^1, R^2, R^3 and R^4 are as defined above and L^1 represents a suitable leaving group such as a halogen atom (e.g. chlorine);

(b) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(c) interconversion to other compounds of formula (I).

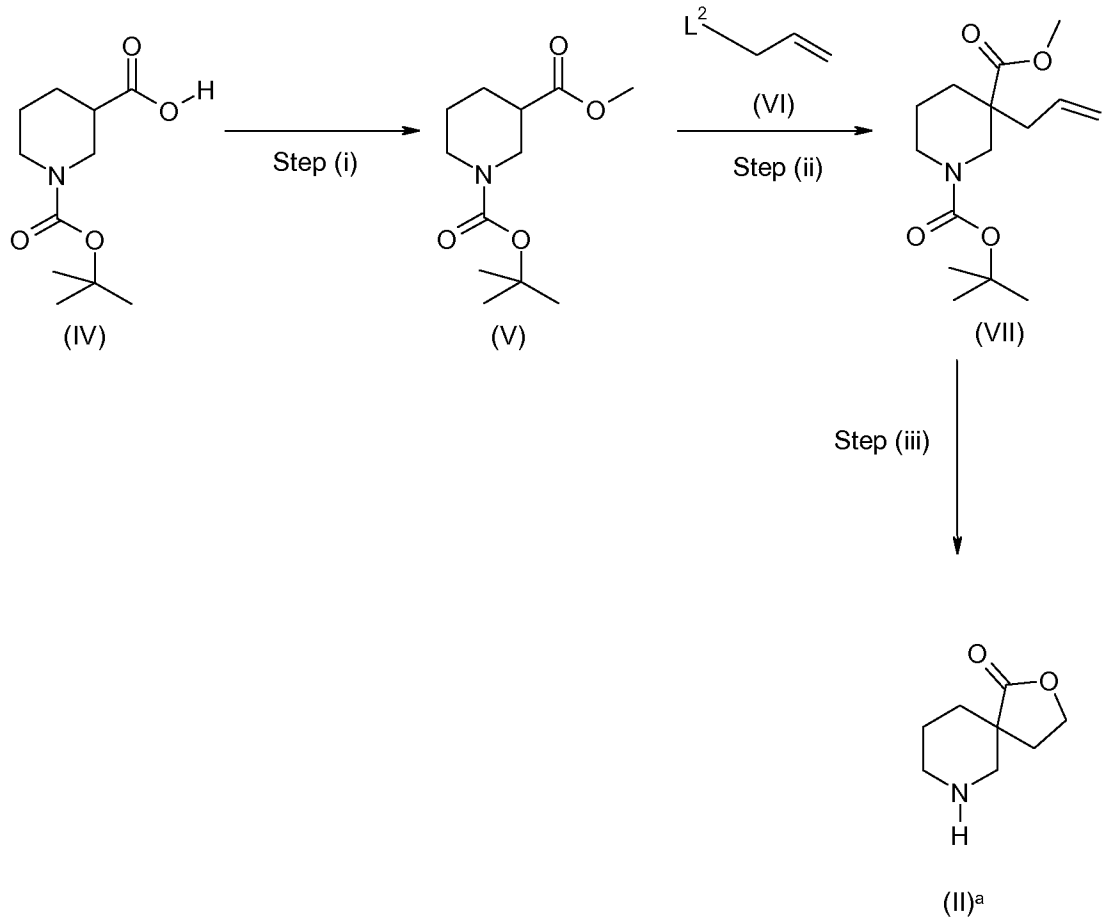
Process (a) typically comprises reaction of a compound of formula (II) with a compound of formula (III) in a suitable solvent, such as dichloromethane, in the presence of a base (for example triethylamine), at 0°C to ambient temperature (for example ambient temperature).

In process (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include sulfonyl (e.g. tosyl), acyl (e.g.

acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution or amide bond formation. One such example of interconversion may be interconversion for a compound of formula (I) wherein R^3 represents bromine to a compound of formula (I) wherein R^3 represents cyano. Such interconversion may be carried out by treating the bromine compound with a cyanide salt (for example copper (I) cyanide) in a suitable solvent (such as N,N-dimethylformamide) at elevated temperatures (such as 200°C using microwave irradiation). Alternatively the interconversion may be carried out using a cyanide salt (for example zinc cyanide) in the presence of a source of a palladium catalyst (for example tris(dibenzylideneacetone)dipalladium(0) and ligand (for example 1,1'-bis(diphenylphosphino)ferrocene) in a suitable solvent (such as N,N-dimethylformamide) at elevated temperatures (such as 120°C). One example of an interconversion reaction includes reaction of a compound of formula (I) wherein one of R^1, R^2, R^3 or R^4 represents bromine to a compound of formula (I) wherein one of R^1, R^2, R^3 or R^4 represents methyl. Such interconversion comprises reaction in the presence of trimethylboroxine in the presence of a suitable base (such as potassium carbonate) and a suitable catalyst (such as $Pd(PPh_3)_4$) at elevated temperature (e.g. 100°C).

Compounds of formula (II) wherein X represents –O- and n represents 1 may be prepared in accordance with the following Scheme:



(IV) (V) (VII)

(II)[a]

wherein L^2 represents a suitable leaving group such as bromine.

Step (i) typically comprises reacting 1-boc-piperidine-3-carboxylic acid (IV) with a (trimethylsilyl)diazomethane solution (for example 2.0 M (trimethylsilyl)diazomethane solution in hexane) in a suitable solvent (such as a mixture of methanol and diethyl ether) at ambient temperature.

Step (ii) typically comprises reacting a compound of formula (V) with an alkylating agent of formula (VI) (for example allyl bromide) in a suitable solvent (such as tetrahydrofuran) in the presence of a suitable base (such as LiHMDS) at a temperature between -78 °C and ambient temperature (for example -78 °C).

Step (iii) typically comprises reacting a compound of formula (VII) with ozone in a suitable solvent (such as a mixture of methanol and dichloromethane) at -78 °C with a reductive work up (for example sodium borohydride). This is typically followed by a treatment with a suitable acid (such as TFA or ethereal HCl) in a suitable solvent (such as dichloromethane or diethyl ether) at ambient temperature.

Compounds of formula (II) wherein X represents –N-(R^5)- and compounds of formula (III), (IV) and (VI) are either commercially available, or may be prepared by known methods.

Compounds with affinity for $Ca_v2.2$ calcium channels may be useful in the treatment or prophylaxis of pain, including acute pain, chronic pain, chronic articular pain, musculoskeletal pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer, pain associated with migraine, tension headache and cluster headaches, pain associated with functional bowel disorders, lower back and neck pain, pain associated with sprains and strains, sympathetically maintained pain; myositis, pain associated with influenza or other viral infections such as the common cold, pain associated with rheumatic fever, pain associated with myocardial ischemia, post operative pain, cancer chemotherapy, headache, toothache and dysmenorrhea.

'Chronic articular pain' conditions include rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

'Pain associated with functional bowel disorders' includes non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome.

'Neuropathic pain' syndromes include: diabetic neuropathy, sciatica, non-specific lower back pain, trigeminal neuralgia, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, post-herpetic neuralgia, trigeminal neuralgia, and pain resulting from physical trauma, amputation, phantom limb syndrome, spinal surgery, cancer, toxins or chronic inflammatory conditions. In addition, neuropathic pain conditions include pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static, thermal or cold allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

Other conditions which could potentially be treated by compounds of the present invention include neurodegenerative diseases and neurodegeneration, neurodegeneration following trauma, tinnitus, dependence on a dependence-inducing agent such as opiods (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

Neurodegenerative diseases include dementia, particularly degenerative dementia (including senile dementia, dementia with Lewy bodies, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection, meningitis and shingles); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) may also be useful for neuroprotection and in the treatment or prophylaxis of neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

Another condition which could potentially be treated by compounds of formula (I) is spasticity or muscular hypertonicity.

Thus, according to one aspect of the invention, there is provided a compound of formula (I) as defined herein for use in therapy.

In one embodiment, the therapy is to the treatment or prophylaxis of any of the disorders described herein, in particular pain. In one particular embodiment, the therapy is to the treatment of any of the disorders described herein, in particular pain.

According to a further aspect, there is provided a use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of any of the disorders herein, in particular pain. More particularly, there is provided a use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of any of the disorders herein.

According to another aspect, there is provided a method of treatment of any of the disorders herein, in particular pain in humans, which method comprises the administration to the human in need of such treatment, an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In the context of the present invention, treatment refers to symptomatic treatment.

In order to use a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, adapted for use in human or veterinary medicine.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

When used in the treatment or prophylaxis of pain, the compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in combination with other medicaments indicated to be useful in the treatment or prophylaxis of pain of neuropathic origin including neuralgias, neuritis and back pain, and inflammatory pain including osteoarthritis, rheumatoid arthritis, acute inflammatory pain, back pain and migraine. Such therapeutic agents include for example COX-2 (cyclooxygenase-2) inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib, COX-189 or 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (WO99/012930); 5-lipoxygenase inhibitors; NSAIDs (non-steroidal anti-inflammatory drugs) such as diclofenac, indomethacin, nabumetone or ibuprofen; bisphosphonates, leukotriene receptor antagonists; DMARDs (disease modifying anti-rheumatic drugs) such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA (N-methyl-D-aspartate) receptor modulators, such as glycine receptor antagonists or memantine; ligands for the $\alpha_2\delta$-subunit of voltage gated calcium channels, such as gabapentin and pregabalin; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; cholinesterase inhibitors such as galantamine; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor modulators, for example modulators of the NR2B subtype; EP_4

receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 agonists and EP_2 agonists; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabinoid receptor ligands; bradykinin receptor ligands; vanilloid receptor or Transient Receptor Potential (TRP) ligands; and purinergic receptor ligands, including antagonists at $P2X_3$, $P2X_{2/3}$, $P2X_4$, $P2X_7$ or $P2X_{4/7}$. Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995, US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

When used in the treatment or prophylaxis of Alzheimer's disease, the compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in combination with other medicaments indicated to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease.

Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as $5\text{-}HT_{1A}$ antagonists, (e.g. lecozotan), 5-HT6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonist, acetylcholinesterase inhibitors (e.g tetrahydroaminoacridine, donepezil or rivastigmine), or allosteric modulators, nicotinic receptor agonists or allosteric modulators, symptomatic agents such as 5-HT6 receptor antagonists, e.g. SB742457, H3 receptor antagonists e.g. GSK189254 and GSK239512, 5-HT4 receptor agonist, PPAR agonists, also NMDA receptor antagonists or modulators, also disease modifying agents such as α, β or γ-secretase inhibitors (e.g. R-flurbiprofen), also AMPA positive modulators and Glycine Transporter Reuptake inhibitors.

When a compound of formula (I) or a pharmaceutically acceptable salt thereof is used in combination with another therapeutic agent, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a further therapeutic agent or agents.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable

powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10% to 60% by weight, of the active material, depending on the method of administration. The dose of the compound of formula (I) as defined in the first and second aspect or a pharmaceutically acceptable salt thereof used in the treatment or prophylaxis of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and

such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks, months, years or even life.

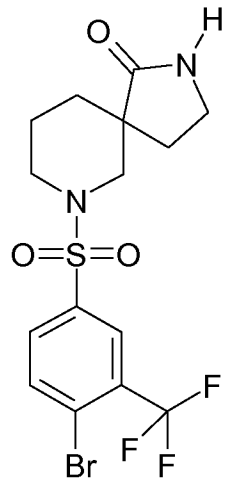
A further aspect to the invention is a pharmaceutical composition comprising 0.05 to 1000mg of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and 0 to 3 g more suitably 0 to 2g of at least one pharmaceutically acceptable carrier.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Supporting Compounds

The preparation of a number of supporting compounds of formula (I) are described below.

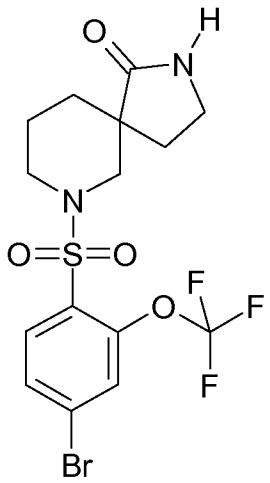
Intermediate 1 : 7-{[4-Bromo-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (D1)



To a solution of 2,7-diazaspiro[4.5]decan-1-one hydrochloride (0.572 g, 3 mmol) and triethylamine (0.836 mL, 6.00 mmol) in dichloromethane (15 mL), cooled in an ice-water bath, was added 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (0.971 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction was diluted with dichloromethane (35 mL), washed with water (30 mL), passed through a hydrophobic frit and reduced *in vacuo*. The residue was purified by silica chromatography (Biotage SP4) eluting with 60% EtOAc in *iso*-hexanes (3 column volumes), a gradient from 60 - 100% EtOAc (over 9 column

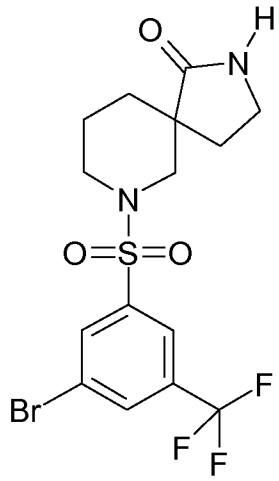
volumes) then EtOAc (3 column volumes) to yield 7-{[4-bromo-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (1.022 g, 2.316 mmol, 77% yield) as a white solid. 1H NMR (250 MHz, CHLOROFORM-*d*) δ ppm 1.59 - 1.86 (m, 4 H) 2.00 - 2.14 (m, 1 H) 2.24 - 2.51 (m, 3 H) 3.31 - 3.51 (m, 2 H) 3.52 - 3.60 (m, 1 H) 3.86 (dd, *J*=10.39, 1.96 Hz, 1 H) 5.67 (br. s., 1 H) 7.72 (dd, *J*=8.30, 1.92 Hz, 1 H) 7.90 (d, *J*=8.37 Hz, 1 H) 8.02 (d, *J*=2.13 Hz, 1 H). MS ES+ve m/z 443 (M+H).

Intermediate 2: 7-({4-Bromo-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (D2)



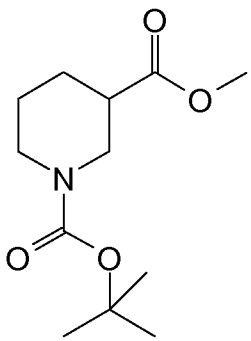
To a solution of 2,7-diazaspiro[4.5]decan-1-one hydrochloride (0.572 g, 3 mmol) and triethylamine (0.836 mL, 6.00 mmol) in dichloromethane (15 mL), cooled in an ice-water bath, was added 4-bromo-2-[(trifluoromethyl)oxy]benzenesulfonyl chloride (1.019 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction was diluted with dichloromethane (35 mL), washed with water (30 mL), passed through a hydrophobic frit and reduced *in vacuo*. The residue was purified by silica chromatography (Biotage SP4) eluting with 60% EtOAc in *iso*-hexanes (3 column volumes), a gradient from 60 - 100% EtOAc (over 9 column volumes) then EtOAc (3 column volumes) to yield 7-({4-bromo-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (0.936 g, 2.047 mmol, 68% yield) as a white solid. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.60 - 1.82 (m, 4 H) 1.99 - 2.09 (m, 1 H) 2.43 (ddd, *J*=13.17, 8.18, 4.80 Hz, 1 H) 2.55 - 2.65 (m, 1 H) 2.72 (dd, *J*=12.30, 0.96 Hz, 1 H) 3.30 - 3.46 (m, 2 H) 3.57 (dt, *J*=12.28, 1.92 Hz, 1 H) 3.89 (ddd, *J*=12.32, 3.85, 1.81 Hz, 1 H) 5.68 (br. s., 1 H) 7.51 - 7.59 (m, 2 H) 7.83 (d, *J*=8.71 Hz, 1 H). MS ES+ve m/z 459 (M+H).

Intermediate 3: 7-{[3-Bromo-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (D3)



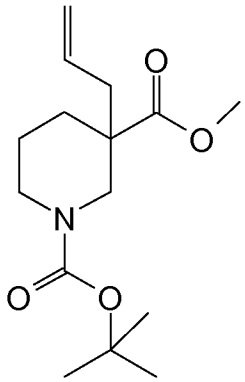
To a solution of 2,7-diazaspiro[4.5]decan-1-one hydrochloride (0.572 g, 3 mmol) and triethylamine (0.836 mL, 6.00 mmol) in dichloromethane (15 mL), cooled in an ice-water bath, was added 3-bromo-5-(trifluoromethyl)benzenesulfonyl chloride (0.971 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction was diluted with dichloromethane (35 mL), washed with water (30 mL), passed through a hydrophobic frit and reduced *in vacuo*. The residue was purified by silica chromatography (Biotage SP4) eluting with 60% EtOAc in *iso*-hexanes (3 column volumes), a gradient from 60 - 100% EtOAc (over 9 column volumes) then EtOAc (3 column volumes) to yield 7-{[3-bromo-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (798 mg, 1.808 mmol, 60% yield) as a white solid. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.61 - 1.88 (m, 4 H) 2.01 - 2.11 (m, 1 H) 2.35 (td, *J*=11.37, 3.45 Hz, 1 H) 2.43 (td, *J*=8.69, 4.11 Hz, 1 H) 2.48 (dd, *J*=11.48, 0.96 Hz, 1 H) 3.34 - 3.50 (m, 2 H) 3.57 (dt, *J*=11.51, 1.78 Hz, 1 H) 3.89 (dd, *J*=11.65, 1.56 Hz, 1 H) 5.77 (br. s., 1 H) 7.89 - 7.92 (m, 1 H) 7.99 (d, *J*=0.55 Hz, 1 H) 8.04 (t, *J*=1.45 Hz, 1 H). MS ES+ve m/z 441 (M+H).

Intermediate 4: 1-(1,1-Dimethylethyl) 3-methyl 1,3-piperidinedicarboxylate (D4)



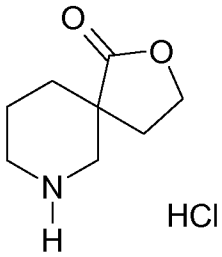
To a solution of 1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-piperidinecarboxylic acid (10 g, 43.6 mmol) in diethyl ether (100 mL) and methanol (100 mL) was cautiously added TMS-diazomethane (50 mL, 100 mmol, 2 M in hexane). The reaction was stirred at room temperature for 4 hours. The reaction was evaporated *in vacuo* and the residue partitioned between EtOAc (250 mL) and saturated $NaHCO_3$ (100 mL). The organic layer was separated, passed through a hydrophobic frit and reduced *in vacuo* to yield 1-(1,1-dimethylethyl) 3-methyl 1,3-piperidinedicarboxylate (10.8 g, 44.8 mmol, 103% yield) as a yellow oil. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.5 (s, 9 H) 1.6 (m, 2 H) 1.7 (m, 1 H) 2.0 (m, 1 H) 2.4 (m, 1 H) 2.8 (m, 1 H) 3.0 (br. s., 1 H) 3.7 (s, 3 H) 3.9 (m, 1 H) 4.1 (br. s., 1 H).

Intermediate 5: 1-(1,1-Dimethylethyl) 3-methyl 3-(2-propen-1-yl)-1,3-piperidinedicarboxylate (D5)



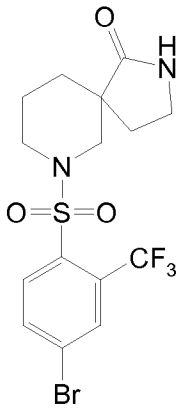
A solution of 1-(1,1-dimethylethyl) 3-methyl 1,3-piperidinedicarboxylate (D4; 10.61 g, 43.6 mmol) in tetrahydrofuran (100 mL) was cooled to -78 °C under an argon atmosphere. To the reaction was added LiHMDS (56.7 mL, 56.7 mmol, 1 M in hexane) over a period of 15 minutes. The reaction was stirred at -78 °C for one hour before the addition of allyl bromide (4.53 mL, 52.3 mmol). The cooling bath was removed and the reaction stirred for a further 5 hours. To the reaction was added saturated aqueous ammonium chloride (200 mL) and water (100 mL). The mixture was then extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with 10% aqueous citric acid (2 x 200 mL), saturated aqueous $NaHCO_3$ (200 mL), brine (200 mL), passed through a hydrophobic frit and reduced *in vacuo* to yield 1-(1,1-dimethylethyl) 3-methyl 3-(2-propen-1-yl)-1,3-piperidine-dicarboxylate (11.6 g, 40.9 mmol, 94% yield) as an orange oil. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.5 (m, 9 H) 1.6 (m, 3 H) 2.0 (m, 1 H) 2.2 (dd, *J*=13.8, 7.9 Hz, 1 H) 2.4 (dd, *J*=13.8, 7.0 Hz, 1 H) 3.2 (m, 2 H) 3.5 (m, 1 H) 3.7 (m, 3 H) 3.9 (m, 1 H) 5.0 (d, *J*=6.1 Hz, 1 H) 5.1 (m, 1 H) 5.7 (m, 1 H).

Intermediate 6: 2-Oxa-7-azaspiro[4.5]decan-1-one hydrochloride (D6)



A solution of 1-(1,1-dimethylethyl) 3-methyl 3-(2-propen-1-yl)-1,3-piperidinedicarboxylate (D5; 11.6 g, 40.9 mmol) in methanol (200 mL) and dichloromethane (300 mL) was cooled to -78 °C under argon. Oxygen was bubbled through the solution for 10 minutes then ozone for 2 hours at which time a pale blue solution had formed. The reaction was purged with oxygen for ten minutes then argon for ten minutes before the addition of sodium borohydride (3.10 g, 82 mmol). The reaction was stirred at -78 °C for 1 hour. Sodium borohydride (3.10 g, 82 mmol) was added and the reaction stirred in an ice bath for one hour. Acetone (50 mL) was added and the reaction stirred at room temperature for 1 hour. To the reaction was added saturated NH_4Cl (200 mL). The organic solvent was then removed under vacuum. The resulting suspension was diluted with water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, washed with 10% aqueous citric acid (200 mL), saturated $NaHCO_3$ (200 mL), brine (100 mL), passed through a hydrophobic frit and reduced *in vacuo* to yield a colourless oil. A solution of the intermediate oil in dichloromethane (20 mL) was cooled in an ice-water bath before the cautious addition of TFA (39.4 mL, 511 mmol). The reaction was allowed to warm to room temperature and stirred for 4 hours. The reaction was evaporated *in vacuo*. The residue was taken up in diethyl ether and the mixture extracted with 1 M hydrochloric acid (3 x 40 mL). The combined acidic fractions were washed with diethyl ether (40 mL) then adjusted to pH 9 with potassium carbonate. The solution was extracted with dichloromethane (8 x 50 mL). The DCM extracts were combined, passed through a hydrophobic frit and evaporated *in vacuo*. The residue was dissolved in ethanol (25 mL) and 1 M HCl in diethyl ether (30 mL) added. The resulting suspension was evaporated *in vacuo* to yield 2-oxa-7-azaspiro[4.5]decan-1-one hydrochloride (2.63 g, 13.72 mmol, 34% yield) as a yellow solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.7 (m, 4 H) 2.2 (m, 1 H) 2.4 (m, 1 H) 3.0 (m, 2 H) 3.1 (m, 1 H) 3.3 (d, *J*=12.9 Hz, 1 H) 4.3 (m, 2 H) 9.1 (br s, 1 H) 9.2 (br s, 1 H).

Intermediate 7: 7-{[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (D7)

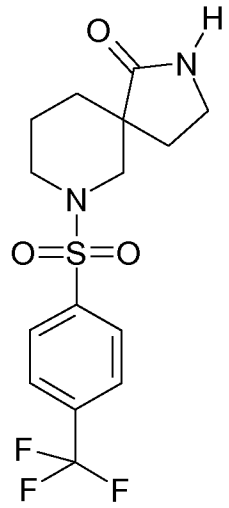


To a solution of 2,7-diazaspiro[4.5]decan-1-one hydrochloride (0.572 g, 3mmol) and triethylamine (0.836 mL, 6.00 mmol) in dichloromethane (DCM) (15mL), cooled in an ice-water bath, was added 4-bromo-2-(trifluoromethyl)benzenesulfonyl chloride (0.971 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred for 18 hours.

The reaction was diluted with DCM (35 ml), washed with water (30mL), passed through a hydrophobic frit and reduced *in vacuo*. The residue was purified by silica chromatography (Biotage SP4) eluting with 60% EtOAc in iso-hexanes (3 column volumes), a gradient from 60-100% EtOAc (over 9 column volumes) then EtOAc (3 column volumes) to yield 7-{[4-bromo-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one as a white solid (0.826g, 62%)

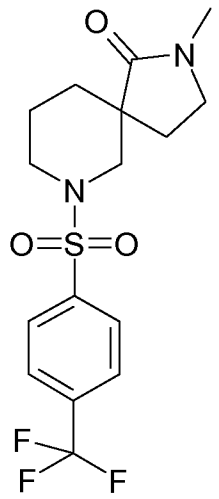
^{1}H NMR (400 MHz, Chloroform-*d*) d ppm 1.61 - 1.67 (m, 1 H) 1.69 - 1.84 (m, 3 H) 2.05 (s, 1 H) 2.43 (s, 1 H) 2.59 - 2.67 (m, 1 H) 2.85 (d, *J*=12.7 Hz, 1 H) 3.32 - 3.45 (m, 2 H) 3.67 (d, *J*=12.5 Hz, 1 H) 3.80 - 3.87 (m, 1 H) 5.72 (br. s., 1 H) 7.80 - 7.88 (m, 2 H) 8.01 (d, *J*=1.5 Hz, 1 H)

Compound 1: 7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E1)



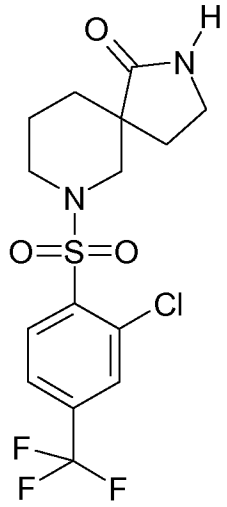
2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (2.314 g, 12.14 mmol) was dissolved in dichloromethane (50 mL), and triethylamine (8 mL, 57.4 mmol) was added. The reaction mixture was cooled to 0 °C and 4-(trifluoromethyl)benzenesulfonyl chloride (3.27 g, 13.35 mmol) was added. After 2 h, the reaction mixture was washed with aqueous 1 M HCl followed by aqueous 1 M NaOH, the organic layer was passed through a hydrophobic frit, and concentrated *in vacuo*. The resulting residue was purified by silica column chromatography on SP4 (gradient elution: 0 - 20% DCM - MeOH). The early colourless fractions led to 7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (360 mg, 0.984 mmol, 8% yield) as a white solid. The later orange fractions were combined, and concentrated *in vacuo*. The resulting residue was recrystallised from methanol to give 3 batches of white crystals: 1st batch 7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (1.506 g, 4.11 mmol, 33% yield), 2nd batch 7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (400 mg, 1.093 mmol, 9% yield), and 3rd batch 7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (324 mg, 0.885 mmol, 7% yield). 1H NMR (250 MHz, DMSO-d_6) δ ppm 1.31 - 1.76 (m, 4 H) 2.00 (qt, *J*=13.25, 6.60 Hz, 2 H) 2.18 - 2.32 (m, 2 H) 3.20 (t, *J*=6.86 Hz, 2 H) 3.34 (d, *J*=11.49 Hz, 1 H) 3.64 (d, *J*=11.59 Hz, 1 H) 7.77 (s, 1 H) 7.96 (d, *J*=8.37 Hz, 2 H) 8.04 (d, *J*=8.44 Hz, 2 H). MS ES+ve m/z 363 (M+H).

Compound 2: 2-Methyl-7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E2)



2-Methyl-2,7-diazaspiro[4.5]decan-1-one hydrogen chloride (150 mg, 0.733 mmol) was dissolved in dichloromethane (3 mL). Triethylamine (0.306 mL, 2.195 mmol) was added followed by 4-(trifluoromethyl)benzenesulfonyl chloride (197 mg, 0.806 mmol). After stirring for 65 hours the mixture was concentrated *in vacuo* and purified by MDAP to give 2-methyl-7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]-decan-1-one (185.5 mg, 0.483 mmol, 66% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 (dd, *J*=9.84, 3.81 Hz, 2 H) 1.53 - 1.64 (m, 1 H) 1.65 - 1.73 (m, 1 H) 1.85 - 1.93 (m, 1 H) 1.98 - 2.06 (m, 1 H) 2.19 - 2.34 (m, 2 H) 2.72 (s, 3 H) 3.24 - 3.41 (m, 3 H) 3.64 (d, *J*=11.29 Hz, 1 H) 7.95 (d, *J*=8.17 Hz, 2 H) 8.03 (d, *J*=8.28 Hz, 2 H). MS ES+ve m/z 377 (M+H).

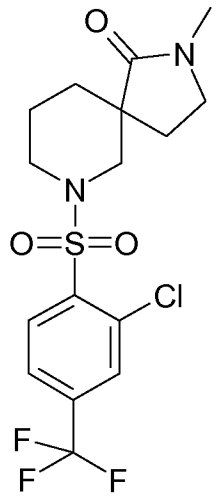
Compound 3: 7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E3)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (150 mg, 0.787 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.219 mL, 1.573 mmol), and 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride (241 mg, 0.865 mmol) was

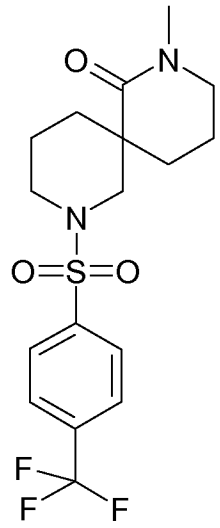
added. After stirring for 18 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by MDAP to give 7-{[2-chloro-4-(trifluoromethyl)-phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (38.2 mg, 0.094 mmol, 12% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 - 1.64 (m, 3 H) 1.65 - 1.75 (m, 1 H) 1.84 - 2.02 (m, 2 H) 2.72 - 2.83 (m, 2 H) 3.09 - 3.18 (m, *J*=7.78, 7.51 Hz, 2 H) 3.40 (d, *J*=12.11 Hz, 1 H) 3.72 (d, *J*=12.93 Hz, 1 H) 7.74 (s, 1 H) 7.93 (d, *J*=9.54 Hz, 1 H) 8.18 (d, *J*=7.45 Hz, 2 H). MS ES+ve m/z 397 (M+H).

Compound 4: 7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-methyl-2,7-diazaspiro[4.5]decan-1-one (E4)



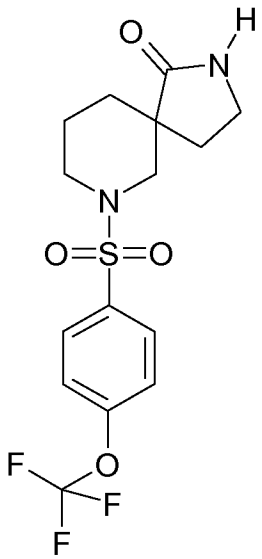
2-Methyl-2,7-diazaspiro[4.5]decan-1-one hydrogen chloride (161 mg, 0.787 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.219 mL, 1.573 mmol), and 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride (241 mg, 0.865 mmol) was added. After stirring for 18 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by MDAP to give 7-{[2-chloro-4-(trifluoromethyl)-phenyl]sulfonyl}-2-methyl-2,7-diazaspiro[4.5]decan-1-one (191.5 mg, 0.457 mmol, 58% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 - 1.74 (m, 4 H) 1.81 - 1.97 (m, 2 H) 2.71 (s, 3 H) 2.74 - 2.83 (m, 2 H) 3.22 - 3.29 (m, 2 H) 3.41 (d, *J*=12.33 Hz, 1 H) 3.72 (d, *J*=12.06 Hz, 1 H) 7.90 - 7.95 (m, 1 H) 8.14 - 8.19 (m, 2 H). MS ES+ve m/z 411 (M+H).

Compound 5: 2-Methyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E5)



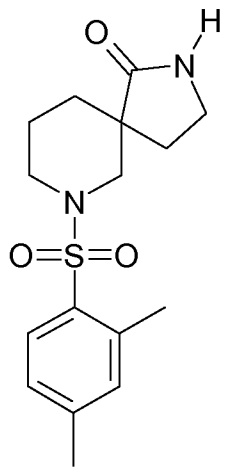
2-Methyl-2,8-diazaspiro[5.5]undecan-1-one hydrogen chloride (137 mg, 0.624 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.174 mL, 1.248 mmol), and DMAP (1 mg, 8.19 µmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (168 mg, 0.687 mmol) were added. After stirring for 2 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified using MDAP to give 2-methyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (163.7 mg, 0.411 mmol, 65% yield) as a white solid. 1H NMR (250 MHz, DMSO-d_6) δ ppm 1.44 - 1.81 (m, 6 H) 1.86 - 1.97 (m, 1 H) 2.16 - 2.32 (m, 1 H) 2.43 (d, *J*=11.53 Hz, 1 H) 2.77 (s, 3 H) 3.16 (d, *J*=4.49 Hz, 1 H) 3.26 (t, *J*=5.66 Hz, 1 H) 3.47 (d, *J*=11.46 Hz, 1 H) 3.67 (d, *J*=11.32 Hz, 1 H) 7.93 (d, *J*=8.27 Hz, 2 H) 8.03 (d, *J*=8.37 Hz, 2 H). MS ES+ve m/z 391 (M+H).

Compound 6: 7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E6)



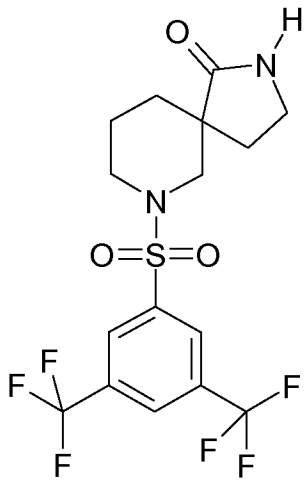
2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (80 mg, 0.420 mmol) was dissolved in dichloromethane (4 mL). Then, triethylamine (0.117 mL, 0.839 mmol) was added followed by 4-[(trifluoromethyl)oxy]benzenesulfonyl chloride (0.078 mL, 0.462 mmol). After stirring for 20 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-({4-[(trifluoromethyl)oxy]-phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (93 mg, 0.241 mmol, 57% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.47 (m, 2 H) 1.51 - 1.64 (m, 1 H) 1.66 - 1.73 (m, 1 H) 1.90 - 1.99 (m, 1 H) 2.00 - 2.08 (m, 1 H) 2.18 - 2.26 (m, 2 H) 3.19 (t, *J*=6.91 Hz, 2 H) 3.30 (s, 1 H) 3.62 (d, *J*=11.35 Hz, 1 H) 7.64 (dd, *J*=8.85, 0.90 Hz, 2 H) 7.76 (s, 1 H) 7.86 - 7.90 (m, 2 H). MS ES+ve m/z 379 (M+H).

Compound 7: 7-[(2,4-Dimethylphenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E7)



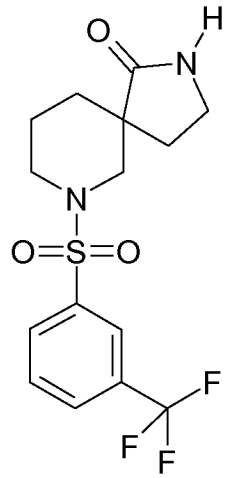
2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (80 mg, 0.420 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.117 mL, 0.839 mmol) before the addition of 2,4-dimethylbenzenesulfonyl chloride (94 mg, 0.462 mmol). After stirring for 20 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-[(2,4-dimethylphenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (64.4 mg, 0.190 mmol, 45% yield) as a white solid. 1H NMR (500 MHz, *DMSO-d6*) δ ppm 7.71 (s, 1 H) 7.66 (d, *J*=8.0 Hz, 1 H) 7.26 (s, 1 H) 7.22 (d, *J*=8.1 Hz, 1 H) 3.59 (d, *J*=12.0 Hz, 1 H) 3.23 (d, *J*=11.7 Hz, 1 H) 3.15 (m, 1 H) 3.09 (m, 1 H) 2.50 (s, 3 H) 2.48 (m, 2 H) 2.35 (s, 3 H) 1.91 (t, *J*=6.9 Hz, 2 H) 1.69 (dt, *J*=12.8, 2.8 Hz, 1 H) 1.54 (m, 1 H) 1.48 (m, 2 H). MS ES+ve m/z 323 (M+H).

Compound 8: 7-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E8)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (80 mg, 0.420 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.117 mL, 0.839 mmol) before the addition of 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (144 mg, 0.462 mmol). After stirring for 20 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-{[3,5-bis(trifluoromethyl)phenyl]-sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (14 mg, 0.032 mmol, 8% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 - 1.63 (m, 3 H) 1.66 - 1.76 (m, 1 H) 1.87 - 1.97 (m, 1 H) 2.00 - 2.08 (m, 1 H) 2.35 - 2.47 (m, 2 H) 3.15 - 3.24 (m, 2 H) 3.47 (d, *J*=11.45 Hz, 1 H) 3.71 (d, *J*=11.67 Hz, 1 H) 7.75 (s, 1 H) 8.32 (s, 2 H) 8.55 (s, 1 H). MS ES+ve m/z 431 (M+H).

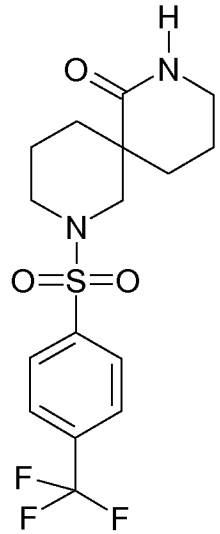
Compound 9: 7-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E9)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (80 mg, 0.420 mmol) was dissolved in dichloromethane (4 mL) and triethylamine (0.117 mL, 0.839 mmol) before the addition of 3-(trifluoromethyl)benzenesulfonyl chloride (113 mg, 0.462 mmol). After stirring for 20 h the reaction mixture was concentrated *in vacuo* and the

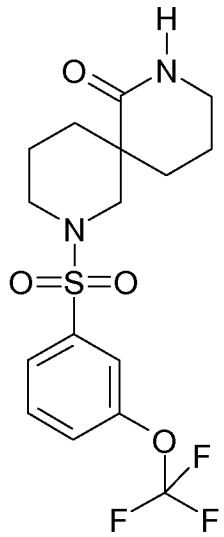
resulting residue was purified by MDAP to give 7-{[3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (60 mg, 0.162 mmol, 39% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 - 1.46 (m, 2 H) 1.51 - 1.64 (m, 1 H) 1.66 - 1.74 (m, 1 H) 1.90 - 1.98 (m, 1 H) 2.00 - 2.09 (m, 1 H) 2.20 - 2.31 (m, 2 H) 3.12 - 3.24 (m, 2 H) 3.37 (d, *J*=11.40 Hz, 1 H) 3.67 (d, *J*=11.24 Hz, 1 H) 7.76 (s, 1 H) 7.92 (t, *J*=7.87 Hz, 1 H) 7.98 (s, 1 H) 8.08 (d, *J*=7.95 Hz, 1 H) 8.14 (d, *J*=7.84 Hz, 1 H). MS ES+ve m/z 363 (M+H).

Compound 10: 8-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E10)



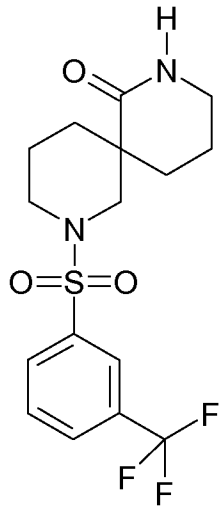
2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (300 mg, 1.466 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.409 mL, 2.93 mmol). Then DMAP (1 mg, 8.19 µmol) and 4-(trifluoromethyl)benzenesulfonyl chloride (394 mg, 1.612 mmol) were added. After stirring for 18 h the mixture was concentrated *in vacuo* and the resulting residue was purified by trituration with MeOH to give 8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (381 mg, 0.992 mmol, 68% yield) as a white solid. 1H NMR (250 MHz, DMSO-d_6) δ ppm 1.47 - 1.74 (m, 7 H) 1.81 - 1.97 (m, 1 H) 2.25 (td, *J*=10.81, 3.57 Hz, 1 H) 2.45 (d, *J*=11.60 Hz, 1 H) 3.11 (br. s., 2 H) 3.47 (d, *J*=11.56 Hz, 1 H) 3.67 (d, *J*=10.63 Hz, 1 H) 7.51 (br. s., 1 H) 7.95 (d, *J*=8.34 Hz, 2 H) 8.03 (d, *J*=8.47 Hz, 2 H). MS ES+ve m/z 377 (M+H).

Compound 11: 8-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E11)



2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (107 mg, 0.524 mmol) was dissolved in dichloromethane (5 mL) and triethylamine (0.146 mL, 1.047 mmol). Then 3-[(trifluoromethyl)oxy]benzenesulfonyl chloride (0.098 mL, 0.577 mmol) was added and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 8-({3-[(trifluoromethyl)oxy]phenyl}-sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (76 mg, 0.192 mmol, 37% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.74 (m, 7 H) 1.83 - 1.92 (m, 1 H) 2.15 - 2.26 (m, 1 H) 2.41 (d, *J*=11.67 Hz, 1 H) 3.10 (br. s., 2 H) 3.47 (d, *J*=11.67 Hz, 1 H) 3.68 (d, *J*=11.07 Hz, 1 H) 7.53 (br. s., 1 H) 7.68 (br. s., 1 H) 7.74 - 7.84 (m, 3 H). MS ES+ve m/z 393 (M+H).

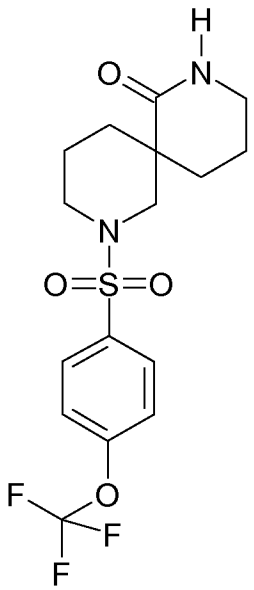
Compound 12: 8-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E12)



2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (90 mg, 0.440 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.123 mL, 0.879 mmol). 3-

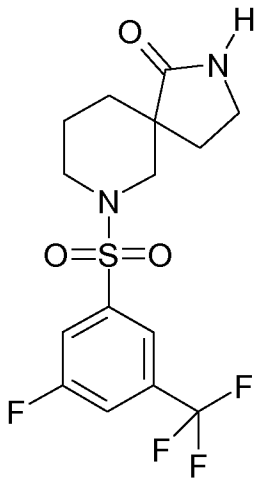
(Trifluoromethyl)benzenesulfonyl chloride (0.077 mL, 0.484 mmol) was added and stirred for 2 h. The mixture was then concentrated *in vacuo* and triturated with MeOH to give 8-{[3-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (49 mg, 0.128 mmol, 29% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 - 1.73 (m, 7 H) 1.89 (dd, *J*=10.08, 7.45 Hz, 1 H) 2.23 (td, *J*=11.35, 3.89 Hz, 1 H) 2.42 (d, *J*=11.56 Hz, 1 H) 3.07 - 3.15 (m, 2 H) 3.50 (d, *J*=11.62 Hz, 1 H) 3.70 (d, *J*=11.73 Hz, 1 H) 7.53 (br. s., 1 H) 7.91 (t, *J*=7.81 Hz, 1 H) 7.97 (s, 1 H) 8.07 (d, *J*=8.00 Hz, 1 H) 8.13 (d, *J*=7.73 Hz, 1 H). MS ES+ve m/z 377 (M+H).

Compound 13: 8-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E13)



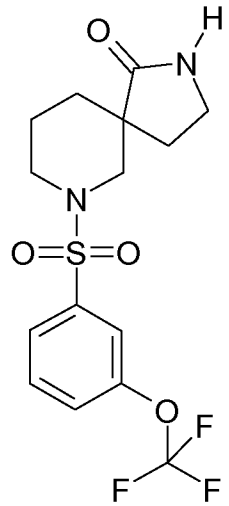
2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (90 mg, 0.440 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.123 mL, 0.879 mmol). 4-[(Trifluoromethyl)oxy]benzenesulfonyl chloride (0.082 mL, 0.484 mmol) was added and stirred for 2 h. The mixture was then concentrated *in vacuo* and purified by MDAP to give 8-({4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (118 mg, 0.298 mmol, 68% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.47 - 1.74 (m, 7 H) 1.83 - 1.94 (m, 1 H) 2.15 - 2.24 (m, 1 H) 2.40 (d, *J*=11.46 Hz, 1 H) 3.07 - 3.13 (m, 2 H) 3.44 (d, *J*=11.56 Hz, 1 H) 3.65 (d, *J*=11.02 Hz, 1 H) 7.54 (br. s., 1 H) 7.63 (dd, *J*=8.80, 0.79 Hz, 2 H) 7.87 (d, *J*=8.88 Hz, 2 H). MS ES+ve m/z 393 (M+H).

Compound 14: 7-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E14)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (100 mg, 0.524 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.219 mL, 1.573 mmol). Then, 3-fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (165 mg, 0.629 mmol) was added and stirred for 17 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (87.9 mg, 0.226 mmol, 43% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.49 (m, 2 H) 1.52 - 1.64 (m, 1 H) 1.66 - 1.75 (m, 1 H) 1.87 - 1.97 (m, 1 H) 1.99 - 2.09 (m, 1 H) 2.29 - 2.41 (m, 2 H) 3.14 - 3.24 (m, 2 H) 3.41 (d, *J*=11.73 Hz, 1 H) 3.68 (d, *J*=11.89 Hz, 1 H) 7.76 (s, 1 H) 7.84 (s, 1 H) 8.01 (d, *J*=7.84 Hz, 1 H) 8.16 (d, *J*=8.55 Hz, 1 H). MS ES+ve m/z 381 (M+H).

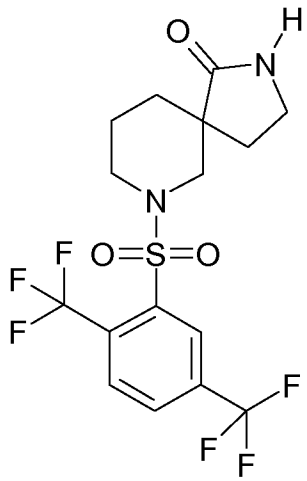
Compound 15: 7-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E15)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (100 mg, 0.524 mmol) was dissolved in dichloromethane (5 mL) and triethylamine (0.146 mL, 1.047 mmol). Then 3-[(trifluoromethyl)oxy]benzenesulfonyl chloride (0.098 mL, 0.577 mmol) was added

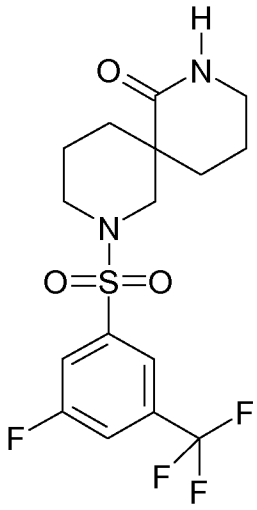
and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-({3-[(trifluoromethyl)oxy]phenyl}-sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (85 mg, 0.222 mmol, 42% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 - 1.48 (m, 2 H) 1.50 - 1.64 (m, 1 H) 1.65 - 1.75 (m, 1 H) 1.89 - 1.98 (m, 1 H) 1.99 - 2.09 (m, 1 H) 2.18 - 2.28 (m, 2 H) 3.19 (t, *J*=7.10 Hz, 2 H) 3.30 - 3.37 (m, 1 H) 3.65 (d, *J*=11.62 Hz, 1 H) 7.69 (s, 1 H) 7.73 - 7.85 (m, 4 H). MS ES+ve m/z 379 (M+H).

Compound 16: 7-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E16)



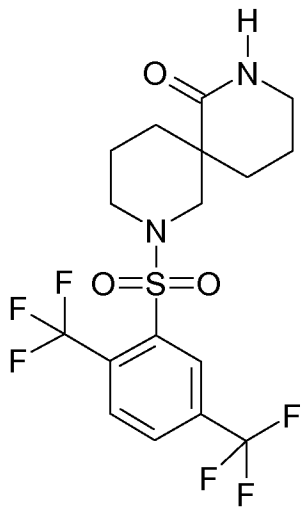
2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (100 mg, 0.524 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.219 mL, 1.573 mmol), and 2,5-bis(trifluoromethyl)benzenesulfonyl chloride (197 mg, 0.629 mmol) was added. After stirring for 17 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-{[2,5-bis(trifluoromethyl)phenyl]-sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (96 mg, 0.221 mmol, 42% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.63 (m, 3 H) 1.66 - 1.75 (m, 1 H) 1.85 - 2.03 (m, 2 H) 2.72 - 2.78 (m, 1 H) 2.80 (d, *J*=12.28 Hz, 1 H) 3.11 - 3.19 (m, 2 H) 3.47 (d, *J*=12.28 Hz, 1 H) 3.71 (d, *J*=11.78 Hz, 1 H) 7.75 (s, 1 H) 8.24 (s, 1 H) 8.26 - 8.33 (m, 2 H). MS ES+ve m/z 431 (M+H).

Compound 17: 8-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E17)



2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (107 mg, 0.524 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.219 mL, 1.573 mmol). Then 3-fluoro-5-(trifluoromethyl)benzenesulfonyl chloride (165 mg, 0.629 mmol) was added and stirred for 17 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by trituration with MeOH to give 8-{[3-fluoro-5-(trifluoromethyl)-phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (39 mg, 0.097 mmol, 18% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 - 1.82 (m, 8 H) 1.85 - 1.95 (m, 1 H) 2.34 (td, *J*=11.36, 3.75 Hz, 1 H) 3.07 - 3.14 (m, 2 H) 3.54 (d, *J*=11.73 Hz, 1 H) 3.71 (d, *J*=11.46 Hz, 1 H) 7.54 (s, 1 H) 7.83 (s, 1 H) 8.00 (d, *J*=7.78 Hz, 1 H) 8.16 (d, *J*=8.55 Hz, 1 H). MS ES+ve m/z 395 (M+H).

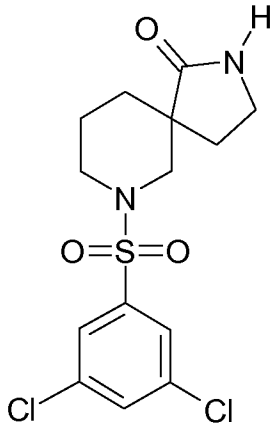
Compound 18: 8-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E18)



2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (107 mg, 0.524 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.219 mL, 1.573 mmol), and 2,5-bis(trifluoromethyl)benzenesulfonyl chloride (197 mg, 0.629 mmol) was added.

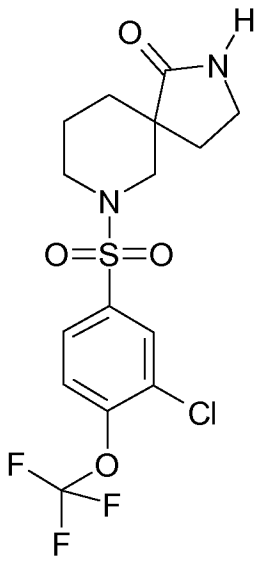
After stirring for 17 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 8-{[2,5-bis(trifluoromethyl)phenyl]-sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (14.3 mg, 0.032 mmol, 6% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.72 (m, 6 H) 1.76 - 1.93 (m, 2 H) 2.69 - 2.78 (m, 1 H) 3.01 (d, *J*=12.50 Hz, 1 H) 3.05 - 3.14 (m, 2 H) 3.59 (d, *J*=12.44 Hz, 1 H) 3.72 (d, *J*=10.74 Hz, 1 H) 7.54 (br. s., 1 H) 8.21 (s, 1 H) 8.25 - 8.34 (m, 2 H). MS ES+ve m/z 445 (M+H).

Compound 19: 7-[(3,5-Dichlorophenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E19)



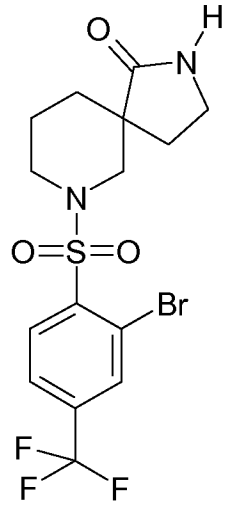
2,7-Diazaspiro[4.5]decan-1-one (90 mg, 0.584 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (0.163 mL, 1.167 mmol), and 3,5-dichlorobenzenesulfonyl chloride (158 mg, 0.642 mmol) was added. After stirring for 17 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by MDAP to give 7-[(3,5-dichlorophenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (130.5 mg, 0.352 mmol, 60% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 - 1.50 (m, 2 H) 1.50 - 1.65 (m, 1 H) 1.65 - 1.76 (m, 1 H) 1.87 - 1.98 (m, 1 H) 1.98 - 2.09 (m, 1 H) 2.30 (d, *J*=11.56 Hz, 1 H) 2.33 - 2.41 (m, 1 H) 3.12 - 3.24 (m, 2 H) 3.38 (d, *J*=11.51 Hz, 1 H) 3.65 (d, *J*=11.51 Hz, 1 H) 7.69 - 7.82 (m, 3 H) 8.04 (t, *J*=1.89 Hz, 1 H). MS ES+ve m/z 363 (M+H).

Compound 20: 7-({3-Chloro-4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E20)



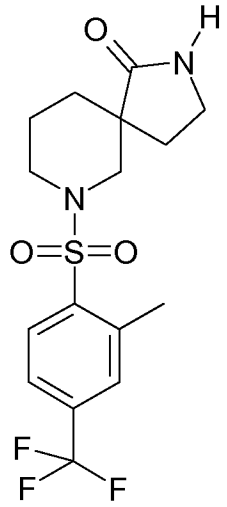
2,7-Diazaspiro[4.5]decan-1-one (150 mg, 0.973 mmol) was dissolved in a mixture of triethylamine (0.542 mL, 3.89 mmol) and dichloromethane (10 mL), and 3-chloro-4-[(trifluoromethyl)oxy]benzenesulfonyl chloride (344 mg, 1.167 mmol) was added. After 16 h the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica column chromatography on SP4 (gradient elution: 0 - 20% MeOH - DCM) to give 7-({3-chloro-4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (350 mg, 0.839 mmol, 86% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 - 1.49 (m, 2 H) 1.49 - 1.65 (m, 1 H) 1.65 - 1.76 (m, 1 H) 1.88 - 2.08 (m, 2 H) 2.27 - 2.40 (m, 2 H) 3.19 (t, *J*=6.63 Hz, 2 H) 3.36 (d, *J*=11.51 Hz, 1 H) 3.64 (d, *J*=11.62 Hz, 1 H) 7.77 (s, 1 H) 7.80 - 7.87 (m, 2 H) 8.06 (dd, *J*=1.59, 0.82 Hz, 1 H). MS ES+ve m/z 413 (M+H).

Compound 21: 7-{[2-Bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E21)



2,7-Diazaspiro[4.5]decan-1-one hydrogen chloride (430 mg, 2.255 mmol) was dissolved in dichloromethane (4 mL), and triethylamine (0.628 mL, 4.53 mmol) was added followed by 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride (804 mg, 2.484 mmol). After stirring for 20 h the reaction mixture was concentrated *in vacuo.* The resulting residue was redissolved in EtOAc, washed with aqueous 1 M HCl followed by washing by saturated aqueous Na_2CO_3. The organic layer was passed through a hydrophobic frit, concentrated *in vacuo* and recrystallised from methanol to give 7-{[2-bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (395 mg, 0.877 mmol, 38% yield). The mother liquor was concentrated *in vacuo* to give the following impure material: 7-{[2-bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (419 mg, 0.548 mmol, 57.7% purity by mass, 24% yield), a mixture of desired product and 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride (1:1 by molar equivalence). 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.63 (m, 3 H) 1.65 - 1.74 (m, 1 H) 1.87 - 1.99 (m, 2 H) 2.74 - 2.80 (m, 1 H) 2.83 (d, *J*=12.50 Hz, 1 H) 3.05 - 3.20 (m, 2 H) 3.43 (d, *J*=12.39 Hz, 1 H) 3.72 (d, *J*=11.40 Hz, 1 H) 7.74 (s, 1 H) 7.97 (dd, *J*=8.28, 1.21 Hz, 1 H) 8.18 (d, *J*=8.00 Hz, 1 H) 8.29 (d, *J*=1.15 Hz, 1 H). MS ES+ve m/z 441 (M+H).

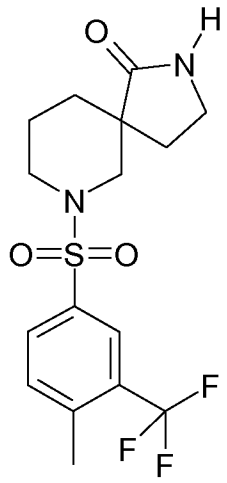
Compound 22: 7-{[2-Methyl-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E22)



The mixture of 7-{[2-bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]-decan-1-one (419 mg, 0.548 mmol, 57.7% purity by mass) and 2-bromo-4-(trifluoromethyl)benzenesulfonyl chloride (1:1 by molar equivalence) formed in the previous experiment was added to potassium carbonate (197 mg, 1.425 mmol) and stirred in anhydrous 1,4-dioxane (10 mL) for 5 minutes before the addition of trimethylboroxine (0.198 mL, 1.426 mmol) and $Pd(PPh_3)_4$ (110 mg, 0.095 mmol). The

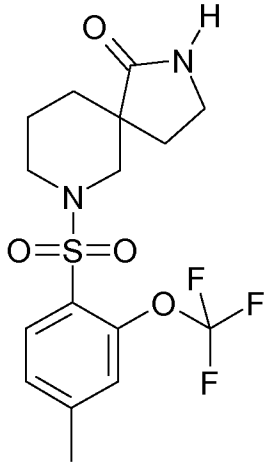
reaction was heated to 100 °C and stirred for 4 hours. It was allowed to cool to room temperature then diluted with ethyl acetate (25 mL), washed with water (25 mL), the organic layer was passed through a hydrophobic frit and concentrated *in vacuo*. The crude product was purified by MDAP. It was then further purified by silica column chromatography on SP4 (gradient elution: 0 - 10% MeOH - DCM) to give 7-{[2-methyl-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (98.1 mg, 0.248 mmol, 45% yield) as a white solid. 1H NMR (500 MHz, *DMSO-d*6) δ ppm 7.99 (d, *J*=8.2 Hz, 1 H) 7.88 (s, 1 H) 7.78 (d, *J*=8.3 Hz, 1 H) 7.74 (s, 1 H) 3.64 (d, *J*=11.7 Hz, 1 H) 3.33 (d, *J*=11.9 Hz, 1 H) 3.15 (m, 2 H) 2.69 (d, *J*=12.0 Hz, 1 H) 2.66 (m, 1 H) 2.64 (s, 3 H) 1.94 (m, 2 H) 1.71 (m, 1 H) 1.59 (m, 1 H) 1.53 (m, 2 H). MS ES+ve m/z 377 (M+H).

Compound 23: 7-{[4-Methyl-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E23)



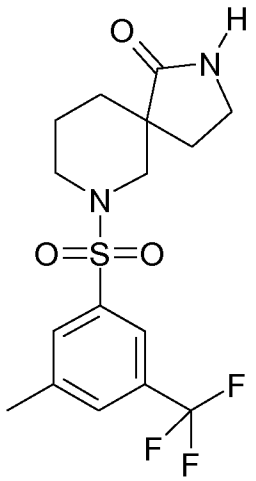
7-{[4-Bromo-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (D1; 214 mg, 0.484 mmol) was dissolved 1,4-dioxane (4 mL). Potassium carbonate (100 mg, 0.727 mmol) was added followed by trimethylboroxine (0.101 mL, 0.726 mmol) and $Pd(PPh_3)_4$ (56.0 mg, 0.048 mmol). The reaction were heated to 100 °C and stirred for 70 hours. The solution was removed from the reaction mixture using a pipette and concentrated *in vacuo.* The resulting residue was dissolved in DMSO and purified using MDAP to give 7-{[4-methyl-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (99 mg, 0.258 mmol, 53% yield) as a white solid. 1H NMR (250 MHz, DMSO-d_6) δ ppm 1.33 - 1.77 (m, 4 H) 1.86 - 2.11 (m, 2 H) 2.15 - 2.31 (m, 2 H) 2.55 (d, *J*=1.44 Hz, 3 H) 3.19 (t, *J*=6.93 Hz, 2 H) 3.30 - 3.37 (m, 1 H) 3.64 (d, *J*=11.29 Hz, 1 H) 7.71 - 7.79 (m, 2 H) 7.86 (s, 1 H) 7.91 - 7.98 (m, 1 H). MS ES+ve m/z 377 (M+H).

Compound 24: 7-({4-Methyl-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E24)



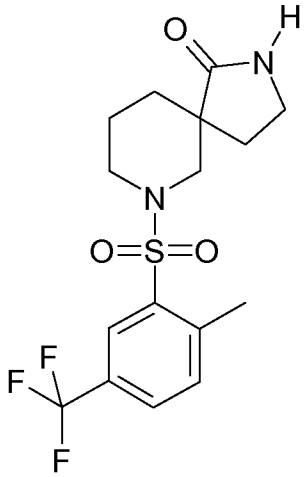
7-({4-Bromo-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (D2; 222 mg, 0.484 mmol) was dissolved 1,4-dioxane (4 mL). Potassium carbonate (100 mg, 0.727 mmol) was added followed by trimethylboroxine (0.101 mL, 0.726 mmol) and $Pd(PPh_3)_4$ (56.0 mg, 0.048 mmol). The reaction were heated to 100 °C and stirred for 70 hours. The solution was removed from the reaction mixture using a pipette and concentrated *in vacuo.* The resulting residue was dissolved in DMSO and purified using MDAP to give 7-({4-methyl-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (7 mg, 0.017 mmol, 4% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.39 - 1.63 (m, 3 H) 1.63 - 1.74 (m, 1 H) 1.87 - 2.04 (m, 2 H) 2.40 - 2.48 (m, 2 H) 2.45 (s, 3 H) 3.10 - 3.22 (m, 2 H) 3.28 - 3.31 (m, 1 H) 3.63 (d, *J*=11.73 Hz, 1 H) 7.41 (d, *J*=8.77 Hz, 1 H) 7.45 (s, 1 H) 7.74 (s, 1 H) 7.80 (d, *J*=8.06 Hz, 1 H). MS ES+ve m/z 393 (M+H).

Compound 25: 7-{[3-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E25)



7-{[3-Bromo-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (D3; 214 mg, 0.484 mmol) from the previous experiment was dissolved 1,4-dioxane (4 mL). Potassium carbonate (100 mg, 0.727 mmol) was added followed by trimethylboroxine (0.101 mL, 0.726 mmol) and $Pd(PPh_3)_4$ (56.0 mg, 0.048 mmol). The reaction were heated to 100 °C and stirred for 70 hours. The solution was removed from the reaction mixture using a pipette and concentrated *in vacuo.* The resulting residue was dissolved in DMSO and purified using MDAP to give 7-{[3-methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (54 mg, 0.141 mmol, 29% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.48 (m, 2 H) 1.48 - 1.66 (m, 1 H) 1.66 - 1.76 (m, 1 H) 1.88 - 1.98 (m, 1 H) 1.98 - 2.08 (m, 1 H) 2.19 - 2.31 (m, 2 H) 2.51 (br. s., 3 H) 3.13 - 3.23 (m, 2 H) 3.35 - 3.39 (m, 1 H) 3.67 (d, *J*=11.24 Hz, 1 H) 7.76 (s, 2 H) 7.89 (s, 1 H) 7.96 (s, 1 H). MS ES+ve m/z 377 (M+H).

Compound 26: 7-{[2-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E26)

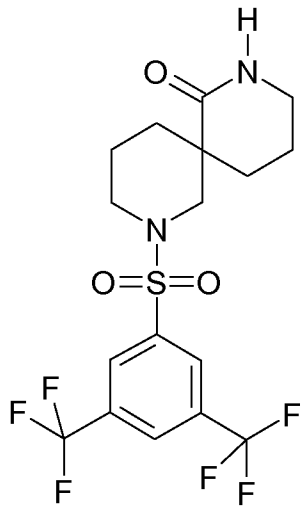


2,7-Diazaspiro[4.5]decan-1-one (200 mg, 1.297 mmol) was dissolved in a mixture of triethylamine (0.542 mL, 3.89 mmol) and dichloromethane (10 mL), and 2-bromo-5-(trifluoromethyl)benzenesulfonyl chloride (503 mg, 1.556 mmol) was added. The reaction mixture was stirred for 16 h and the reaction mixture was concentrated *in vacuo*. The resulting yellow solid 7-{[2-bromo-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (829 mg, impure) was used in the next reaction without further purification. MS ES+ve m/z 443 (M+H).

7-{[2-Bromo-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (829 mg, impure) and potassium carbonate (269 mg, 1.946 mmol) was suspended in 1,4-dioxane (20 mL). Trimethylboroxine (0.271 mL, 1.946 mmol) and $Pd(PPh_3)_4$ (150 mg, 0.130 mmol) were then added and the reaction mixture was heated to 100 °C. After

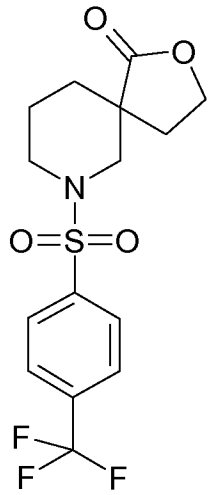
20 h, the reaction was cooled, filtered through a hydrophobic frit, and concentrated *in vacuo*. The resulting residue was purified by silica column chromatography on SP4 (gradient elution: 0 - 20% MeOH - DCM). The resulting brown residue was further purified on MDAP to give 7-{[2-methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (152 mg, 0.400 mmol, 31% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (s, 3 H) 1.63 - 1.76 (m, 1 H) 1.91 (t, *J*=6.88 Hz, 2 H) 2.56 - 2.72 (m, 5 H) 3.04 - 3.20 (m, 2 H) 3.34 - 3.37 (m, 1 H) 3.62 (d, *J*=11.62 Hz, 1 H) 7.69 - 7.76 (m, 2 H) 7.98 (d, *J*=8.00 Hz, 1 H) 8.01 (s, 1 H). MS ES+ve m/z 377 (M+H).

Compound 27: 8-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E27)



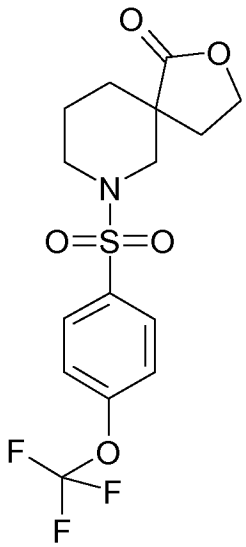
2,8-Diazaspiro[5.5]undecan-1-one hydrogen chloride (100 mg, 0.489 mmol) was dissolved in a mixture of dichloromethane (10 ml) and triethylamine (0.204 ml, 1.466 mmol), and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (183 mg, 0.586 mmol) was added. The reaction mixture was stirred for 16 h and concentrated *in vacuo*. The resulting residue was purified by MDAP to give 8-{[3,5-bis(trifluoromethyl)phenyl]-sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (74 mg, 0.165 mmol, 34% yield) as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 - 1.80 (m, 7 H) 1.84 - 1.95 (m, 1 H) 2.40 (td, *J*=11.25, 4.03 Hz, 1 H) 2.54 (d, *J*=11.67 Hz, 1 H) 3.03 - 3.17 (m, 2 H) 3.60 (d, *J*=11.56 Hz, 1 H) 3.76 (d, *J*=12.06 Hz, 1 H) 7.53 (s, 1 H) 8.31 (s, 2 H) 8.55 (s, 1 H). MS ES+ve m/z 445 (M+H).

Compound 28: 7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2-oxa-7-azaspiro[4.5]decan-1-one (E28)



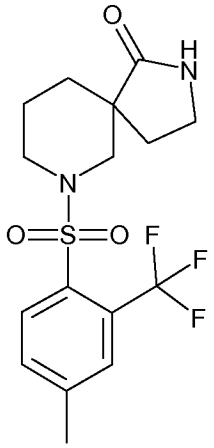
To a solution of 2-oxa-7-azaspiro[4.5]decan-1-one hydrochloride (D6; 200 mg, 1.044 mmol) and triethylamine (0.305 mL, 2.191 mmol) in dichloromethane (5 mL) was added 4-(trifluoromethyl)benzenesulfonyl chloride (281 mg, 1.148 mmol). The reaction was stirred at 21 °C overnight. The reaction was diluted with dichloromethane (10 mL) and water (5 mL). The organic layer was collected *via* a hydrophobic frit and then evaporated under a stream of argon. The residue was purified by MDAP to yield 7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2-oxa-7-azaspiro[4.5]decan-1-one (0.149 g, 0.410 mmol, 39% yield) as a white solid. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.8 (m, 4 H) 2.2 (m, 1 H) 2.3 (td, *J*=11.6, 2.9 Hz, 1 H) 2.5 (dd, *J*=11.6, 0.9 Hz, 1 H) 2.6 (m, 1 H) 3.7 (dt, *J*=11.6, 1.8 Hz, 1 H) 3.9 (m, 1 H) 4.4 (m, 2 H) 7.8 (d, *J*=8.6 Hz, 2 H) 7.9 (d, *J*=8.6 Hz, 2 H). MS ES+ve m/z 364 (M+H).

Compound 29: 7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2-oxa-7-azaspiro[4.5]decan-1-one (E29)



To a solution of 2-oxa-7-azaspiro[4.5]decan-1-one hydrochloride (D6; 200 mg, 1.044 mmol) and triethylamine (0.305 mL, 2.191 mmol) in dichloromethane (5 mL) was added 4-[(trifluoromethyl)oxy]benzenesulfonyl chloride (0.195 mL, 1.148 mmol). The reaction was stirred at 21 °C overnight. The reaction was diluted with dichloromethane (10 mL) and water (5 mL). The organic layer was collected *via* a hydrophobic frit and then evaporated under a stream of argon. The residue was sonicated in DMSO:acetonitrile (1:1, 1.8 mL), filtered, and the solid collected washed with a minimum of cold diethyl ether. The solid was dried at 40 °C under vacuum to yield 7-({4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2-oxa-7-azaspiro[4.5]decan-1-one (0.112 g, 0.295 mmol, 28% yield) as a white solid. The DMSO:acetonitrile filtrate was subjected to MDAP purification. Fractions containing the desired product were combined and the solvent removed to yield a second batch of 7-({4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2-oxa-7-azaspiro[4.5]decan-1-one (95 mg, 0.250 mmol, 24% yield). 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.8 (m, 4 H) 2.2 (m, 1 H) 2.3 (td, *J*=11.4, 3.1 Hz, 1 H) 2.5 (dd, *J*=11.6, 0.9 Hz, 1 H) 2.6 (m, 1 H) 3.6 (dt, *J*=11.6, 1.8 Hz, 1 H) 3.9 (m, 1 H) 4.4 (m, 2 H) 7.4 (m, 2 H) 7.8 (m, 2 H). MS ES+ve m/z 380 (M+H).

Compound 30: 7-{[4-Methyl-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E30)



7-{[4-Bromo-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (214 mg, 0.484 mmol) (D7) was dissolved 1,4-Dioxane (4 ml). Potassium carbonate (100 mg, 0.727 mmol) was added followed by trimethylboroxin (0.101 ml, 0.726 mmol) and $Pd(Ph_3P)_4$ (56.0 mg, 0.048 mmol). The reaction was heated to 100°C and stirred for 70 hours. The solution was removed from the reaction mixture using a pipette and

concentrated *in vacuo.* The resulting residue was dissolved in DMSO and purified using MDAP. The isolated compound was further purified by preparative HPLC (High Performance Liquid Chromatography) using the following conditions:

Column: Zorbax Stablebond C8 (250 mm x 21.2 mm internal diameter column; 7 micron particle size)

Eluent: A= [Water + 0.1% v/v Trifluoroacetic Acid]
B = [Methanol + 0.1% v/v Trifluoroacetic Acid]
A:B =35:65 v/v; pump-mixed
ISOCRATIC for 15 minutes

Flow-rate: 17 mLmin-1 throughout run

Max. pressure: 150 bar

Run-time: 15 minutes

Temperature: Ambient throughout run

Inj. Volume: Via auto-sampler = 200 uL of a solution of the crude product at an assumed concentration of approx.100 mgmL-1 in dimethylformamide at room temperature

Detection: (a) U.V. absorbance at 215 nm (band-width = 10 nm)
and 270 nm (band-width = 10 nm)
(b) M.S. by E.S.+ (mass range = 200 a.m.u. > 600 a.m.u.;
maximum settings)

Fractionation: Using U.V. absorbance with peak threshold of 20 mA.U.

Isolated fractions were combined and the organic solvent was removed *via* rotary evaporation. The remaining mainly aqueous residue was loaded onto a water conditioned isolute ENV+ cartridge (500mg). The cartridge was eluted with water (2 x 25mL) then acetonitrile (3 x 25mL). The acetonitrile fractions were combined and the solvent removed. The compound was dried at 40°C overnight under vacuum to

yield 7-{[4-methyl-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (94 mg, 50 % yield) as a white solid.

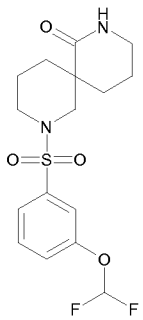
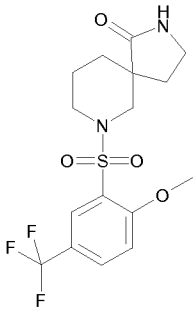
ES+ve m/z 377 (M+H)

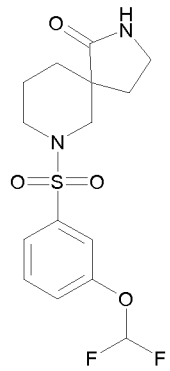
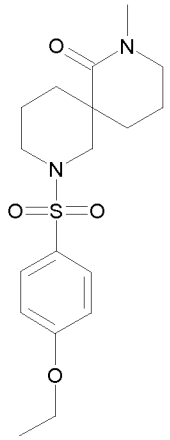
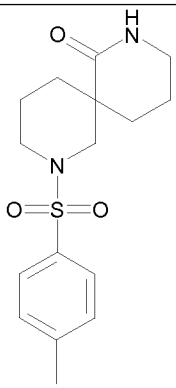
^{1}H NMR (400 MHz, DMSO-D6) d ppm 1.47-1.57 (m, 4 H) 1.7 (m, 1 H) 1.9 (m, 1 H) 2.0 (m, 1 H) 2.5 (s, 3 H) 2.7 (m, 1 H) 3.1 (m, 1 H) 3.2 (m, 1 H) 3.4 (m, 1 H) 3.7 (m, 1 H) 7.7 (m, 1 H) 7.7 (br.s., 1 H) 7.8 (m, 1 H) 7.9 (d, *J*=8.1 Hz, 1 H)

Compounds 31-35:

The compounds of Table 1 were prepared by a similar procedure to that described for compound 2 using the appropriate amine and sulphonyl chloride.

Table 1

Compound no.	Compound name	Structure	m/z $[M+H]^+$	Retention Time (min)
31	8-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one		375	0.93
32	7-{[2-(Methyloxy)-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one		393	0.91

33	7-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one		361	0.89
34	8-{[4-(Ethyloxy)phenyl]sulfonyl}-2-methyl-2,8-diazaspiro[5.5]undecan-1-one		367	0.97
35	8-[(4-Methylphenyl)sulfonyl]-2,8-diazaspiro[5.5]undecan-1-one		323	0.85

Abbreviations

DCM	Dichloromethane
DMF	*N,N*-dimethylformamide
MeOH	Methanol
DMSO	*N,N*-Dimethylsulfoxide
LiHMDS	Lithium hexamethyldisilazide
TMS	Trimethylsilyl
DMAP	4-(Dimethylamino)pyridine
h	Hours

EtOAc	Ethyl acetate
NMR	Nuclear magnetic resonance (spectroscopy)
ppm	Parts per million
δ	Chemical shift
DMSO-d_6	Deuterated dimethyl sulfoxide
CHLOROFORM-*d*	Deuterated chloroform
TFA	Trifluoroacetic acid
LCMS	Liquid chromatography – Mass spectroscopy
MDAP	Mass directed automated preparation

Equipment

^{1}H NMR spectra

Chemical shifts are expressed in parts per million (ppm, units). Coupling constants (*J*) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet) q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad).

ISOLUTE ENV+ – solid phase extraction cartridge

Isolute ENV+ cartridges are available from Biotage Inc. They contain a hydroxylated polystyrene-divinylbenzene copolymer as a very strong non-polar (hydrophobic phase).

Mass-directed automated HPLC/Mass-directed automated preparation (MDAP)

Where indicated in the above Compounds, purification by mass-directed automated HPLC was carried out using the following apparatus and conditions:

Hardware

Waters 2525 Binary Gradient Module
Waters 515 Makeup Pump
Waters Pump Control Module
Waters 2767 Inject Collect
Waters Column Fluidics Manager
Waters 2996 Photodiode Array Detector
Waters ZQ Mass Spectrometer

Gilson 202 fraction collector
Gilson Aspec waste collector

Software

Waters MassLynx version 4 SP2

Column

The columns used are Waters Atlantis, the dimensions of which are 19 mm x 100 mm (small scale) and 30 mm x 100 mm (large scale). The stationary phase particle size is 5 μm.

Solvents

A : Aqueous solvent = Water + 0.1% Formic Acid
B : Organic solvent = Acetonitrile + 0.1% Formic Acid
Make up solvent = Methanol : Water 80:20
Needle rinse solvent = Methanol

Methods

There are five methods used depending on the analytical retention time of the compound of interest. They have a 13.5-minute runtime, which comprises of a 10-minute gradient followed by a 3.5 minute column flush and re-equilibration step.
Large/Small Scale 1.0-1.5 = 5-30% B
Large/Small Scale 1.5-2.2 = 15-55% B
Large/Small Scale 2.2-2.9 = 30-85% B
Large/Small Scale 2.9-3.6 = 50-99% B
Large/Small Scale 3.6-5.0 = 80-99% B (in 6 minutes followed by 7.5 minutes flush and re-equilibration)

Flow rate

All of the above methods have a flow rate of either 20 mL/min (Small Scale) or 40 mL/min (Large Scale).
Shallow gradients
Large 1.5 to 2.3 min = 13-29% B
Large 1.9 to 2.3 min = 25-41% B
Large 2.3 to 2.6 min = 37-53% B
Large 2.6 to 3.1 min = 49-65% B
Large 3.1 to 3.6 min = 61-77% B

Liquid Chromatography / Mass Spectrometry

Analysis of the above Compounds by Liquid Chromatography / Mass Spectrometry (LC/MS) was carried out using the following apparatus and conditions:

Hardware

Waters Acquity Binary Solvent Manager

Waters Acquity Sample Manager

Waters Acquity PDA

Waters ZQ Mass Spectrometer

Sedere Sedex 75

Software

Waters MassLynx version 4.1

Column

The column used is a Waters Acquity BEH UPLC C18, the dimensions of which are 2.1 mm x 50 mm. The stationary phase particle size is 1.7 μm.

Solvents

A : Aqueous solvent = Water + 0.05% Formic Acid

B : Organic solvent = Acetonitrile + 0.05% Formic Acid

Weak Wash = 1:1 Methanol : Water

Strong Wash = Water

Method

The generic method used has a 2 minute runtime.

Time / min	%B
0	3
0.1	3
1.5	97
1.9	97
2.0	3

The above method has a flow rate of 1 ml/min.
The injection volume for the generic method is 0.5 µl
The column temperature is 40 deg
The UV detection range is from 220 to 330 nm

Biotage SP4®

Biotage - SP4® is an automated purification system. It uses preloaded silica gel columns. The user applies their material to the top of the column and chooses solvents, gradients, flow rates, column size, collection method and eluting volumes.

Phase Separators (Hydrophobic frit)

Phase separators are a range of ISOLUTE® columns fitted with an optimized frit material that easily separates aqueous phase from chlorinated solvents under gravity.

SCX – Strong Cation Exchange Cartridge

Where indicated in the Compounds, an SCX cartridge was used as part of the compound purification process. Typically an ISOLUTE SCX-2 cartridge was used. ISOLUTE SCX-2 is a silica-based sorbent with a chemically bonded propylsulfonic acid functional group.

ISOLUTE SCX-2 Chemical Data
Base Material: Silica, 50 µm
Functional Group: Propylsulfonic acid
Capacity: 0.6 meq/g
Counter Ion: Proton

ISOLUTE NH2 – Weak Anion Exchange Cartridge

Where indicated in the Compounds, an isolute NH2 cartridge was used as part of the compound purification process. Typically an ISOLUTE NH2 cartridge was used. ISOLUTE NH2 is a silica-based sorbent with a chemically bonded aminopropyl functional group.

Description: Aminopropyl functionalized silica. Manufactured using trifunctional silane. pK 9.8. Non end-capped.
Average Particle Size: 50 µm
Nominal Porosity: 60 Å

Exchange Capacity: 0.6 meq/g
Comments: Weak anion exchange sorbent for extraction of strongly ionized acidic drugs, particularly for ease of elution

Pharmacological data

Compounds of the invention may be tested for *in vitro* biological activity in the $hCa_V2.2$ assay in accordance with the following studies:

Methods

Cell biology

Stable cell lines expressing the human $Ca_V2.2$ α ($α1_B$) subunit, along with the human β3 and α2δ1 auxiliary subunits were created following sequential transfection and selection of human embryonic kidney (HEK293) cells. HEK293 cells were cultured in Dulbecco's modified Eagles media/F12 media (Invitrogen, Cat # 041-95750V) containing 10% fetal bovine serum, with added L-glutamine (2 mM; Invitrogen, Cat # 25030-024) and non-essential amino acids (5%; Invitrogen, Cat # 11140-035). Initially HEK293 cells were transfected with two plasmid vectors for expression of the $hCa_V2.2$ α subunit (pCIN5- $hCa_V2.2$ which carries a neomycin resistance marker) and the hCa_V β3 subunit (pCIH-hCa_V β3 which carries a hygromycin resistance marker). Clonal cell lines were isolated following selection in media supplemented with 0.4 mg ml^{-1} Geneticin G418 (Invitrogen, Cat # 10131-027) and 0.1 mg ml^{-1} hygromycin (Invitrogen, Cat # 10687-010). These clonal cell lines were assessed for $Ca_v2.2$ α/ β3-mediated current expression using the IonWorks planar array electrophysiology technology (described below). A clonal line was identified that gave a reasonable level of functional $Ca_v2.2$ α/ β3 current expression. This cell line was transfected with a plasmid vector for expression of the human α2δ1 subunit (pCIP-α2δ1which carries a puromycin resistance marker) and clonal cell lines isolated following selection in media containing 0.62 μg ml^{-1} puromycin (Sigma, Cat # P-7255), in addition to 0.4 mg ml^{-1} Geneticin G418 and 0.1 mg ml^{-1} hygromycin. Several cell lines were identified that gave robust levels of $Ca_v2.2$ α/ β3/α2δ1-mediated current expression and one of these was selected for compound profiling. Expression of all three subunits within this cell line was continuously maintained by the inclusion of G418 (0.4 mg ml^{-1}), hygromycin (0.1 mg ml^{-1}) and puromycin (0.62 μg ml^{-1}). Cells were maintained at 37°C in a humidified environment containing 5% CO_2 in air. Cells were liberated from the T175 culture flasks for passage and harvesting using TrpLE (Invitrogen, Cat # 12604-013).

Cell preparation

Cells were grown to 30–60% confluence in T175 flasks and maintained at 30°C for 24 hrs prior to recording. Cells were lifted by removing the growth media, washing with Ca^{2+} free PBS (Invitrogen, Cat #14190-094) and incubating with 3 ml of warmed (37°C) TrpLE (Invitrogen, Cat # 12604-013) for 6 minutes. Lifted cells were suspended in 10 ml of extracellular buffer. Cell suspension was then placed into a 15 ml tube and centrifuged for 2 minutes at 700 rpm. After centrifugation, the supernatant was removed and the cell pellet was resuspended in 4.5 ml of extracellular solution.

Electrophysiology

Currents were recorded at room temperature (21–23°C) using the IonWorks planar array electrophysiology technology (Molecular Devices Corp.). Stimulation protocols and data acquisition were carried out using a microcomputer (Dell Pentium 4). In order to determine planar electrode hole resistances (Rp), a 10 mV, 160 ms potential difference was applied across each hole. These measurements were performed before cell addition. After cell addition a seal test was performed prior to antibiotic (amphotericin) circulation to achieve intracellular access. Leak subtraction was conducted in all experiments by applying a 160 ms hyperpolarizing (10 mV) prepulse 200 ms before the test pulses to measure leak conductance. Test pulses stepping from the holding potential (V_H) of -90 mV to +10 mV were applied for 20 ms and repeated 10 times at a frequency of 10 Hz. In all experiments, the test pulse protocol was performed in the absence (pre-read) and presence (post-read) of a compound. Pre- and post-reads were separated by a compound addition followed by a 3–3.5 min incubation.

Solutions and drugs

The intracellular solution contained the following (in m*M*): K-gluconate 120, KCl 20mM, $MgCl_2$ 5, EGTA 5, HEPES 10, adjusted to pH 7.3. Amphotericin was prepared as 30 mg/ml stock solution and diluted to a final working concentration of 0.2 mg ml^{-1} in intracellular buffer solution. The extracellular solution contained the following (in m*M*): Na-gluconate 120, NaCl 20, $MgCl_2$ 1, HEPES 10, $BaCl_2$ 5, adjusted to pH 7.4.

Compounds were prepared in DMSO as 10mM stock solutions and subsequent 1:3 serial dilutions performed. Finally the compounds were diluted 1:100 in external solution resulting in a final DMSO concentration of 1%.

Data analysis

The recordings were analysed and filtered using seal resistance (>40 MΩ), resistance reduction (>35%) and peak current amplitude (>200pA) in the absence of compound to eliminate unsuitable cells from further analysis. Paired comparisons between pre-compound and post-compound additions were used to determine the inhibitory effect of each compound. The concentrations of compounds required to inhibit current elicited by the 1st depolarising pulse by 50% (tonic pIC50) were determined by fitting of the Hill equation to the concentration response data. In addition the use-dependent inhibitory properties of the compounds were determined by assessing the effect of compounds on the 10th versus 1st depolarising pulse. The ratio of the 10th over 1st pulse was determined in the absence and presence of drug and the % use-dependent inhibition calculated. The data was fitted using the same equation as for the tonic pIC_{50} and the concentration producing 30% inhibition (use-dependent pUD_{30}) determined.

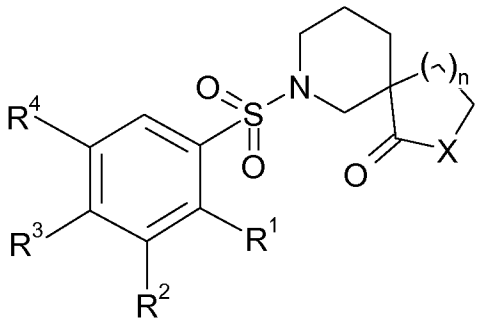
The compounds 1 to 35 were tested in the $hCa_V2.2$ assay.

The compounds 1 to 35 exhibited a pUD_{30} value of 4.5 or more than 4.5. The compounds 1 to 26, 28 to 33 exhibited a pUD_{30} value of 5.0 or more than 5.0. The compounds 2 to 5, 10, 11, 20 to 22, 25 and 28 exhibited a pUD_{30} value of 5.5 or more than 5.5.

The compounds 1 to 35 exhibited a mean pIC_{50} value of 5.0 or less than 5.0. The compounds 2, 5 to 10, 12 to 21, 23 to 35 exhibited a mean pIC_{50} value of 4.5 or less than 4.5.

Claims

1. A compound of formula (I), or a salt thereof:



(I)

wherein R^1, R^3 and R^4 are independently selected from hydrogen, chlorine, bromine, methyl, methoxy, ethoxy, trifluoromethyl or trifluoromethoxy;
R^2 represents hydrogen, chlorine, fluorine, bromine, methyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy;
such that at least one of R^1, R^2, R^3 and R^4 represents a group other than hydrogen and such that when one of R^1, R^2, R^3 or R^4 represents methyl, at least one other of R^1, R^2, R^3 or R^4 represents a group other than hydrogen and such that when R^2 represents fluorine, R^4 represents trifluoromethyl;
n represents an integer from 1 or 2;
X represents –N-(R^5)- or –O-; and
R^5 represents hydrogen or C_{1-4} alkyl.

2. A compound as defined in claim 1, wherein n represents 1.

3. A compound as defined in claim 1 or claim 2, wherein R^1, R^2 and R^4 each represent hydrogen and R^3 represents methyl, ethoxy, trifluoromethyl or trifluoromethoxy, such as trifluoromethyl or trifluoromethoxy.

4. A compound as defined in claim 1 or claim 2, wherein R^1, R^3 and R^4 each represent hydrogen and R^2 represents difluoromethoxy, trifluoromethyl or trifluoromethoxy.

5. A compound as defined in claim 1 or claim 2, wherein R^2 and R^4 each represent hydrogen, R^3 represents methyl or trifluoromethyl and R^1 represents chlorine, bromine, methyl, trifluoromethyl or trifluoromethoxy.

6. A compound as defined in claim 1 or claim 2, wherein R^2 and R^3 each represent hydrogen, R^1 represents methyl, methoxy or trifluoromethyl and R^4 represents trifluoromethyl.

7. A compound as defined in claim 1 or claim 2, wherein R^1 and R^3 each represent hydrogen, R^2 represents chlorine or trifluoromethyl and R^4 represents chlorine, fluorine, methyl or trifluoromethyl.

8. A compound as defined in claim 1 or claim 2, wherein R^1 and R^4 each represent hydrogen, R^2 represents chlorine or trifluoromethyl and R^3 represents methyl or trifluoromethoxy.

9. A compound as defined in any of claims 1 to 8, wherein X represents –N(H)-, -N(Me)- or –O-, such as -N(H)- or -N(Me)-, in particular, –N(H)-.

10. A compound or salt as defined in claim 1 which is selected from:
7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E1);
2-Methyl-7-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E2);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E3);
7-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-methyl-2,7-diazaspiro[4.5]decan-1-one (E4);
2-Methyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E5);
7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E6);
7-[(2,4-Dimethylphenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E7);
7-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E8);
7-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E9);
8-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E10);
8-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E11);
8-{[3-(Trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E12);
8-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E13);
7-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E14);
7-({3-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E15);
7-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E16);
8-{[3-Fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E17);
8-{[2,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E18);

7-[(3,5-Dichlorophenyl)sulfonyl]-2,7-diazaspiro[4.5]decan-1-one (E19);
7-({3-Chloro-4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E20);
7-{[2-Bromo-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E21);
7-{[2-Methyl-4-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E22);
7-{[4-Methyl-3-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E23);
7-({4-Methyl-2-[(trifluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E24);
7-{[3-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E25);
7-{[2-Methyl-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E26);
8-{[3,5-Bis(trifluoromethyl)phenyl]sulfonyl}-2,8-diazaspiro[5.5]undecan-1-one (E27);
7-{[4-(Trifluoromethyl)phenyl]sulfonyl}-2-oxa-7-azaspiro[4.5]decan-1-one (E28);
7-({4-[(Trifluoromethyl)oxy]phenyl}sulfonyl)-2-oxa-7-azaspiro[4.5]decan-1-one (E29);
7-{[4-Methyl-2-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E30);
8-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,8-diazaspiro[5.5]undecan-1-one (E31);
7-{[2-(Methyloxy)-5-(trifluoromethyl)phenyl]sulfonyl}-2,7-diazaspiro[4.5]decan-1-one (E32);
7-({3-[(Difluoromethyl)oxy]phenyl}sulfonyl)-2,7-diazaspiro[4.5]decan-1-one (E33);
8-{[4-(Ethyloxy)phenyl]sulfonyl}-2-methyl-2,8-diazaspiro[5.5]undecan-1-one (E34);
and
8-[(4-Methylphenyl)sulfonyl]-2,8-diazaspiro[5.5]undecan-1-one (E35).

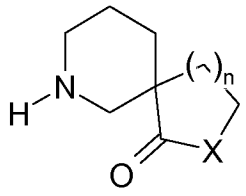
11. A pharmaceutical composition which comprises a compound of formula (I) as defined in any of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

12. A compound, or a pharmaceutically acceptable salt thereof, as defined in any of claims 1 to 10for use in therapy.

13. A compound as defined in any of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain.

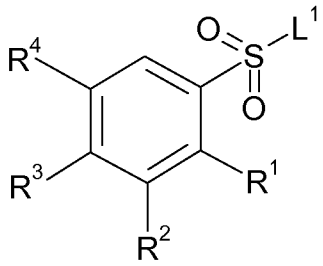
14. A process for the preparation of a compound of formula (I) or a salt thereof as defined in claim 1, which process comprises:

(a) reacting a compound of formula (II)



(II)

or a protected derivative thereof, wherein X and n are as defined in claim 1, with a compound of formula (III)



(III)

wherein R^1, R^2, R^3 and R^4 are as defined in claim 1 and L^1 represents a suitable leaving group such as a halogen atom, in particular chlorine;

(b) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(c) interconversion to other compounds of formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/050890

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/10 A61K31/438 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/028638 A1 (EURO CELTIQUE SA [LU]; CHEN ZHENGMING [US]; TAFESSE LAYKEA [US]; YAO J) 15 March 2007 (2007-03-15) the whole document	1-14
A	WO 99/36398 A1 (LILLY CO ELI [GB]; MILUTINOVIC SANDRA [GB]; SIMMONDS ROBIN GEORGE [GB]) 22 July 1999 (1999-07-22)	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2011	11/08/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/050890

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2009507800 A	26-02-2009
		US 2009118319 A1	07-05-2009
WO 9936398 A1	22-07-1999	AU 2172899 A	02-08-1999
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		EP 1047670 A1	02-11-2000
		JP 2002509135 A	26-03-2002