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(71) **Applicant** (for all designated States except US): **TAKE-DA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and

(75) **Inventors/Applicants** (for US only): **POONI, Parminder, Kaur** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB). **MER-CHANT, Kevin, John** [GB/GB]; Takeda Cambridge Ltd, 418 Cambridge Science Park, Cambridge CB4 0PA (GB).

(74) **Agent:** **JONES, Nicholas, Andrew**; Withers & Rogers LLP, Goldings House, 2 Hays Lane, London SE1 2HW (GB).

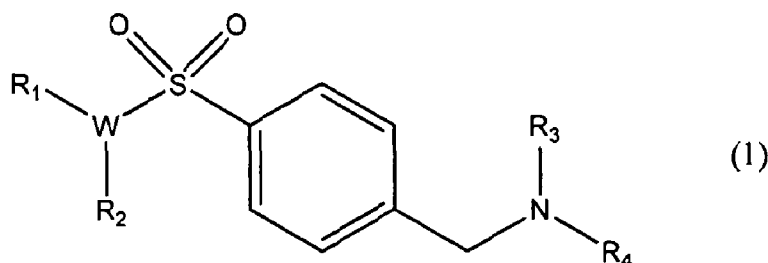
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(54) **Title:** PHENYL SULFONYL DERIVATIVES AND THEIR USE AS HISTAMINE H3 ANTAGONISTS



(57) **Abstract:** A compound having the formula (1) wherein W represents N or CH; R₁ represents H or C₁₋₃ alkyl; R₂ represents a N-containing heterocyclyl ring or a -C₁₋₃ alkylene-N-containing heterocyclyl group; in which any N-containing heterocyclyl comprising or present on R₂ may be optionally substituted; or, when W represents N, R₁ and R₂ and the N atom to which they are attached may join to form an optionally substituted azacyclic ring, wherein the azacyclic ring may be optionally substituted; R₃ represents H or C₁₋₃ alkyl; R₄ represents optionally substituted C₃₋₆ cycloalkyl, heteroaryl or heterocyclyl; or R₃ and R₄ and the N atom to which they are attached may join to form an optionally substituted heterocyclyl ring; or a pharmaceutically acceptable salt thereof. The compounds of the invention have been found to modulate the histamine H3 receptor.

Phenyl Sulfonyl Derivatives and their use as Histamine H3 Antagonists

The present invention relates to compounds and their uses, and in particular to
5 compounds having a phenyl sulfonyl scaffold and their therapeutic use in the treatment or prevention of conditions having an association with the histamine H3 receptor.

The H3 receptor was first identified pharmacologically in 1983 as an autoreceptor that regulates the production of histamine (1). The receptor was later cloned in 1999 (2). It is a constitutively active G protein-coupled receptor that is expressed predominantly in the
10 central nervous system (CNS) and modulates a variety of CNS functions both centrally and peripherally. It is expressed on the presynaptic terminals of CNS neurones and acts as a negative modulator of release of neurotransmitters such as histamine, acetylcholine, norepinephrine, serotonin and dopamine (3). Consequently, the ability of the H3 receptor to regulate the release of a wide range of neurotransmitters has fuelled research into the
15 development of antagonists / inverse agonists which have potential in behavioural and physiological conditions, for example CNS disorders such as narcolepsy, disorders of wakefulness, cognition or attention, pain and in suppression of food intake.

Histaminergic neurones are located in the tuberomammillary nucleus of the posterior hypothalamus and project their axons into brain regions including the hypothalamus, thalamus, cerebral cortex, amygdala, and septum. Activity of histaminergic neurons is
20 closely linked with the sleep / wake cycle and numerous reports in the literature have established that the H3 receptor plays a role in cognition and sleep / wake related processes, based on studies with known H3 receptor antagonists and their effects in animal models (4, 5, 6). H3 antagonist compound A-349821 is currently in preclinical
25 development and has been shown to demonstrate cognition-enhancing effects in the rat (7).

The histaminergic system is one of the targets of leptin signalling in the hypothalamus. Known H3 antagonist clobenpropit increases histamine release in the hypothalamus of mice and has the effect of reducing energy intake in both lean and obese mice (8). The
30 role of the H3 receptor in obesity has been further substantiated through studies with antagonists thioperamide and ciproxifan and more recently with non-imidazole compounds (10).

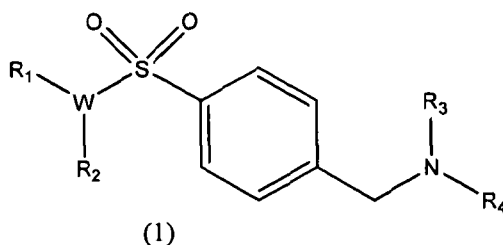
The non-selective antagonist thioperamide has an antinociceptive effect in a number of acute pain models (11). H3 antagonists have been suggested for the treatment of neuropathic pain (12). In addition GSK207040 and GSK334429 are selective non-imidazole H3 antagonist compounds that display high affinity for both rat and human H3
5 receptors. Both compounds reduced tactile allodynia in the rat, suggesting H3 antagonists have therapeutic potential in the treatment of neuropathic pain (13).

In an attempt to identify compounds with improved drug-like properties, non-imidazole compounds have been at the forefront of research, for example A-349821 (7) and GSK207040 / GSK334429 (13). ABT-239 is currently being investigated for use in
10 attention deficit hyperactivity disorder, Alzheimer's Disease and schizophrenia (14).

The specific compounds N-[[4-(1-piperidinylsulfonyl)phenyl]methyl]-2-pyrimidinamine, 1-[[4-(1-pyrrolidinylsulfonyl)phenyl]methyl]-piperazine and N-cyclopropyl-4-[(4-methyl-1-piperazinyl)sulfonyl]-benzenemethanamine are known compounds, but no literature reference is ascribed to these compounds. International
15 Patent Application WO93/013079 discloses a number of phenylsulfonamide derivatives as intermediates towards the synthesis of a class of quinazoline derivatives for use in inhibiting folate metabolic pathways. International Patent Applications WO 2008/048609, WO 2008/005338 and WO 2007/075688 claim phenylsulfonyl and phenylsulfonamide derivatives as modulators of H3. International Patent Application WO2010/026365
20 discloses a class of N-heterocyclic sulfonamide derivatives as N-myristoyl transferase inhibitors, in which the substituent "A" is an optionally substituted nitrogen-containing heteroaryl group. International Patent Application WO2008/109154 discloses a number of bicyclic sulphonamide derivatives as chemokine receptor modulators.

There exists a clinical need to generate further classes of H3 antagonist and/or inverse
25 agonist compounds that demonstrate improved drug-like properties (9).

In accordance with a first aspect of the present invention, there is provided a compound having the Formula (1):



wherein:

W represents N or CH;

R₁ represents H or C₁₋₃ alkyl;

R₂ represents a N-containing heterocyclyl ring or a -C₁₋₃ alkylene-N-containing
5 heterocyclyl group, in which any N-containing heterocyclyl comprising or present on R₂
may be optionally substituted with one or more substituents independently selected from
C₁₋₃ alkyl, C₃₋₆ cycloalkyl and -C₁₋₃ alkylene-C₃₋₆ cycloalkyl;

or, when W represents N, R₁ and R₂ and the N atom to which they are attached
may join to form an optionally substituted azacyclic ring, wherein the azacyclic ring may
10 be optionally substituted with one or more substituents independently selected from C₁₋₃
alkyl and C₃₋₆ cycloalkyl;

R₃ represents H or C₁₋₃ alkyl;

R₄ represents optionally substituted C₃₋₆ cycloalkyl, heteroaryl or heterocyclyl;

or R₃ and R₄ and the N atom to which they are attached may join to form an
15 optionally substituted heterocyclyl ring;

wherein R₄ or the heterocyclyl ring -NR₃R₄ may be optionally substituted with one
or more C₁₋₃ alkyl groups; or a pharmaceutically acceptable salt thereof,

with the proviso that the compound of formula (1) is not:

N-[[4-(1-piperidinylsulfonyl)phenyl]methyl]-2-pyrimidinamine;

20 1-[[4-(1-pyrrolidinylsulfonyl)phenyl]methyl]-piperazine; or

N-cyclopropyl-4-[(4-methyl-1-piperazinyl)sulfonyl]-benzenemethanamine.

The compounds of the invention have been found to modulate the histamine H₃ receptor.
In particular, the compounds possess antagonist or inverse agonist properties at this
receptor. Based on the high affinity for the receptor, the compounds may have the
25 potential to display useful selectivity for the H₃ receptor.

Where any group in the compound of formula (1) above is referred to as being optionally
substituted, this group may be unsubstituted or substituted by one or more substituents.
Typically any such group will be unsubstituted, or substituted by one or two substituents,
generally one substituent.

30 In the compounds of the invention as represented by formula (1) and the more detailed
description hereinafter certain of the general terms used in relation to groups or
substituents thereon are to be understood to include the following atoms or groups unless
otherwise specified.

The term 'C_{x-y} alkyl' as used herein refers to a linear or branched saturated hydrocarbon group containing from x to y carbon atoms. For example, C₁₋₃ alkyl refers to a linear or branched saturated hydrocarbon group containing from 1 to 3 carbon atoms. Examples of C₁₋₃ alkyl groups include methyl, ethyl, n-propyl and isopropyl.

- 5 The term 'C₁₋₃ alkylene' as used herein refers to a divalent hydrocarbon group obtained by removing one hydrogen atom from 'C_{x-y} alkyl' above. Examples of C₁₋₃ alkylene groups include methylene, ethylene and methylenemethylene.

- 10 The term 'C_{x-y} cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of x to y carbon atoms. For example, C₃₋₆ cycloalkyl refers to a saturated monocyclic hydrocarbon ring of 3 to 6 carbon atoms. Examples of C₃₋₆ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

- 15 The term '-C₁₋₃ alkylene-C₃₋₆ cycloalkyl' refers to a C₁₋₃ alkyl group as defined herein in which one of the H atoms is replaced with a C₃₋₆ cycloalkyl ring as defined herein. Examples include -methyl-cyclopropyl, -ethyl-cyclopropyl, -methyl-cyclobutyl, -ethyl-cyclobutyl, -methyl-cyclopentyl and -ethyl-cyclopentyl.

- 20 The term 'heterocyclyl' refers to a 4-7 membered, non-aromatic monocyclic group which may be saturated or partially unsaturated, which contains 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur. Examples of such monocyclic groups include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl and azepanyl.

- 25 The term 'N-containing heterocyclyl' refers to a 4-7 membered saturated monocyclic ring containing at least one, typically one or two, nitrogen atoms and optionally 1 to 4 other heteroatoms selected from oxygen and sulphur. Examples of such rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

- 30 It will be appreciated that any heterocyclyl ring may be attached to the rest of the molecule through any available C or N atom.

The term 'azacyclic ring' refers to a 4 to 7 membered, non-aromatic monocyclic or bridged saturated or partially unsaturated ring containing at least one nitrogen atom,

typically one or two nitrogen atoms. Examples of such rings include pyrrolidinyl, azetidiny, piperidinyl, azepanyl, piperazinyl and 2,5-diazabicyclo[2.2.1]heptanyl.

The term '-C₁₋₃ alkylene-N-containing heterocyclyl' refers to a C₁₋₃ alkyl group as defined herein in which one of the H atoms is replaced with a N-containing heterocyclyl ring as
5 defined herein. Examples include -methyl-pyrrolidinyl, -ethyl-pyrrolidinyl, -methyl-piperidinyl, -ethyl-piperidinyl, -methyl-morpholinyl and -ethyl-morpholinyl.

The term 'heteroaryl' as used herein refers to a 5-6 membered monocyclic aromatic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of such monocyclic aromatic groups include thienyl, furyl, furazanyl, pyrrolyl, triazolyl,
10 tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like.

It will be appreciated that any heteroaryl ring may be attached to the rest of the molecule through any available C or N atom.

15 When the 'heteroaryl' contains a nitrogen atom as its ring-constituting atom, the nitrogen atom may be oxidized. For instance, pyridyl as the 'heteroaryl' may be its N-oxide.

'Pharmaceutically acceptable salts' of compounds of Formula (1) of the present invention include salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Salts with acids may,
20 in particular, be employed in some instances. In particular, 'pharmaceutically acceptable salts' of compounds of Formula (1) of the present invention include but are not limited to acid addition salts (for example, phosphates, nitrates, sulphates, borates acetates, maleates, citrates, fumarates, succinates, methanesulfonates, benzoates, salicylates and hydrohalides), and salts of amino acids (such as glycine, alanine, valine, leucine,
25 isoleucine, cysteine, methionine, proline). Further pharmaceutically acceptable salts include quaternary ammonium salts of the compounds of formula (1).

Compounds of formula (1) and their salts may be in the form of a solvate, which is included in the scope of the invention. Such solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or
30 isopropanol.

The compound of Formula (1) of the present invention may be in either hydrate or non-hydrate form.

General methods for the preparation of salts are well known to the person skilled in the art. Pharmaceutical acceptability of salts will depend on a variety of factors, including formulation processing characteristics and *in vivo* behaviour, and the skilled person would readily be able to assess such factors having regard to the present disclosure.

- 5 Where compounds of the invention exist in different enantiomeric and/or diastereoisomeric forms (including geometric isomerism about a double bond), these compounds may be prepared as isomeric mixtures or racemates, although the invention relates to all such enantiomers or isomers, whether present in an optically pure form or as mixtures with other isomers. Individual enantiomers or isomers may be obtained by
- 10 methods known in the art, such as optical resolution of products or intermediates (for example chiral chromatographic separation (e.g. chiral HPLC)), or an enantiomeric synthesis approach. Similarly, where compounds of the invention may exist as alternative tautomeric forms (e.g. keto/enol, amide/imidic acid), the invention relates to the individual tautomers in isolation, and to mixtures of the tautomers in all proportions.
- 15 In certain embodiments, the compounds of the invention bear one or more radiolabels. Such radiolabels may be introduced by using radiolabel-containing reagents in the synthesis of the compounds of formula (1), or may be introduced by coupling the compounds of formula (1) to chelating moieties capable of binding to a radioactive metal atom. Such radiolabeled versions of the compounds may be used, for example, in
- 20 diagnostic imaging studies.

In some embodiments W represents N. In other embodiments W represents CH. W preferably represents N.

In some embodiments R_1 represents H. In other embodiments R_1 represents C_{1-3} alkyl, typically methyl. Suitably R_1 represents H or methyl.

- 25 Typically any N-containing heterocyclyl comprising or present on R_2 may suitably be unsubstituted or mono- or di-substituted, typically unsubstituted or monosubstituted.

- Generally any N-containing heterocyclyl comprising or present on R_2 is linked to the rest of the compound of formula (1) through a C atom. In such instances when the R_2 N-containing heterocyclyl is asymmetric the point of attachment to the rest of the compound
- 30 of formula (1) may represent a chiral centre. In one such instance the chiral centre is racemic. In another such instance the chiral centre is the (R) enantiomer. In a further such instance the chiral centre is the (S) enantiomer.

Typical examples of R₂ include optionally substituted pyrrolidinyl, piperidinyl, -methylpyrrolidinyl or -methyl-morpholinyl, wherein the pyrrolidinyl, piperidinyl and morpholinyl are linked to the rest of the compound of formula (1) through a C atom.

- 5 Sutable substituents that may be present on any N-containing heterocyclyl comprising or present on R₂ include methyl, ethyl, isopropyl, cyclobutyl and -methyl-cyclopropyl.

Specific examples of R₂ include 1-methylpiperidin-4-yl, 1-ethylpiperidin-4-yl, 1-ethylpiperidin-3-yl, 1-ethylpyrrolidin-3-yl, 1-isopropylpyrrolidin-3-yl, 1-cyclobutylpyrrolidin-3-yl, 1-(cyclopropylmethyl)pyrrolidin-3-yl, (1-methylpyrrolidin-3-yl)methyl and (4-ethylmorpholin-2-yl)methyl.

- 10 In particular embodiments R₂ represents an optionally substituted N-containing heterocyclyl ring linked to the rest of the compound of formula (1) through a C atom.

In certain preferred embodiments R₂ represents optionally substituted C-linked pyrrolidinyl, preferably optionally substituted pyrrolidin-3-yl. In further preferred embodiments R₂ represents 1-ethylpyrrolidin-3-yl.

- 15 In some embodiments when W represents N, R₁ and R₂ and the N atom to which they are attached are joined to form an optionally substituted piperazinyl or C₁₋₃ alkylene bridged piperazinyl ring; in which the piperazinyl ring may be optionally substituted with one or more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl. Sutable examples of -NR₁R₂ rings include optionally substituted piperazinyl or 2,5-diazabicyclo[2.2.1]heptan-2-yl. Sutable optional substituents include ethyl and
20 cyclopentyl. Specific examples of -NR₁R₂ rings include 4-cyclopentylpiperazin-1-yl and 5-ethyl-2,5-diazabicyclo[2.2.1]heptan-2-yl.

In some embodiments R₃ represents H. In other embodiments R₃ represents C₁₋₃ alkyl, typically methyl. Suitably R₃ represents H or methyl.

- 25 Typical examples of R₄ include optionally substituted cyclopentyl, tetrahydrofuranyl, tetrahydropyranyl or pyridinyl. R₄ is typically unsubstituted. When R₄ is substituted, a preferred substituent is methyl.

In particular embodiments R₃ represents H or C₁₋₃ alkyl and R₄ represents optionally substituted C₃₋₆ cycloalkyl or heterocyclyl.

- 30 In further preferred embodiments R₄ represents cyclopentyl, tetrahydrofuranyl or tetrahydropyranyl.

In certain particular embodiments R_4 represents cyclopentyl. In other particular embodiments R_4 represents tetrahydrofuranyl. In further particular embodiments R_4 represents tetrahydropyranyl.

5 In certain other embodiments R_3 and R_4 and the N atom to which they are attached are joined to form an optionally substituted pyrrolidinyl ring, typically 2-methylpyrrolidin-1-yl.

In one particular subgroup of compounds according to the invention, W represents N or CH; R_1 represents H or C_{1-3} alkyl; R_2 represents N-containing heterocyclyl or $-C_{1-3}$ alkylene-N-containing heterocyclyl; in which any N-containing heterocyclyl comprising
10 or present on R_2 may be optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{3-6} cycloalkyl and $-C_{1-3}$ alkylene- C_{3-6} cycloalkyl; or when W represents N, R_1 and R_2 and the N atom to which they are attached may join to form an optionally substituted piperazinyl or C_{1-3} alkylene bridged piperazinyl ring; in which the piperazinyl ring may be optionally substituted with one or more substituents
15 independently selected from C_{1-3} alkyl and C_{3-6} cycloalkyl; R_3 represents H or C_{1-3} alkyl; R_4 represents optionally substituted C_{3-6} cycloalkyl, heteroaryl or heterocyclyl; or R_3 and R_4 and the N atom to which they are attached are joined to form an optionally substituted heterocyclyl ring; in which R_4 or the heterocyclyl ring $-NR_3R_4$ may be optionally substituted with C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof.

20 In another particular subgroup of compounds according to the invention, W represents N or CH; R_1 represents H or C_{1-3} alkyl; R_2 represents N-containing heterocyclyl or $-C_{1-3}$ alkylene-N-containing heterocyclyl; in which any N-containing heterocyclyl comprising or present on R_2 may be optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{3-6} cycloalkyl and $-C_{1-3}$ alkylene- C_{3-6} cycloalkyl;
25 R_3 represents H or C_{1-3} alkyl; R_4 represents optionally substituted C_{3-6} cycloalkyl, heteroaryl or heterocyclyl; or R_3 and R_4 and the N atom to which they are attached are joined to form an optionally substituted heterocyclyl ring; in which R_4 or the heterocyclyl ring $-NR_3R_4$ may be optionally substituted with C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof.

30 Particularly useful compounds in accordance with the invention include each of the compounds described in the accompanying examples, and pharmaceutically acceptable salts thereof.

In accordance with a second aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the first aspect of the invention, together with one or more pharmaceutically acceptable excipients, wherein the provisos to the first aspect do not apply. In an embodiment, the said provisos do apply.

5 Pharmaceutical compositions of this invention comprise any of the compounds of the first aspect of the present invention, or pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention are those conventionally employed in the field of pharmaceutical
10 formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulphate, disodium hydrogen phosphate, potassium hydrogen
15 phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene- polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally,
20 parenterally, by inhalation spray, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral administration is preferred. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal,
25 intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile
30 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition,

sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive
5 oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as that described in Ph. Helv, or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, powders,
10 granules, and aqueous suspensions and solutions. These dosage forms are prepared according to techniques well-known in the art of pharmaceutical formulation. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch.
15 When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavouring and/or colouring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing
20 a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol
25 or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilising or dispersing agents known in the art.

30 The compounds of the present invention may be administered in a dose of around 1 to around 20,000 $\mu\text{g/kg}$ per dose, depending on the condition to be treated or prevented, and the characteristics of the subject being administered with the compound. In many instances, the dose may be around 1 to around 1500 $\mu\text{g/kg}$ per dose. The dosing regimen

for a given compound could readily be determined by the skilled person having access to this disclosure.

In one particular embodiment, the pharmaceutical composition of the invention additionally comprises one or more additional active pharmaceutical ingredients. These
5 additional active ingredients may be agents known to the skilled person to be useful in the treatment or prevention of the diseases mentioned in the present disclosure, or co-morbidities thereof.

In a third aspect, the present invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in therapy,
10 wherein the provisos to the first aspect do not apply. In an embodiment, the said provisos do apply.

In a fourth aspect, the invention provides a compound according to the first aspect of the invention, or a composition according to the second aspect, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3
15 receptor activity, wherein the provisos to the first aspect do not apply. In an embodiment, the said provisos do apply.

A number of conditions whose development or symptoms are linked to histamine H3 receptor activity are known to the skilled person.

In a fifth aspect, the invention also provides a method of treatment or prevention of a
20 condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to the first aspect of the invention, or a composition according to the second aspect, wherein the provisos to the first aspect do not apply. In an embodiment, the said provisos do apply.

25 In particular, there is provided a compound according to the fourth aspect, or a method according to the fifth aspect, wherein the condition is a disorder of the central nervous system.

In certain embodiments, the condition to be treated may be selected from sleep disorders (such as narcolepsy and hypersomnia), cognitive disorders (such as dementia and
30 schizophrenia), attentional disorders (such as attention deficit hyperactivity disorder), neurodegenerative disorders (such as AD), schizophrenia, epilepsy, pain (such as neuropathic pain) and obesity.

In preferred embodiments the condition may be selected from schizophrenia, Alzheimer's Disease (AD) and dementia. In an alternative embodiment, the condition may be selected from narcolepsy, pain and obesity.

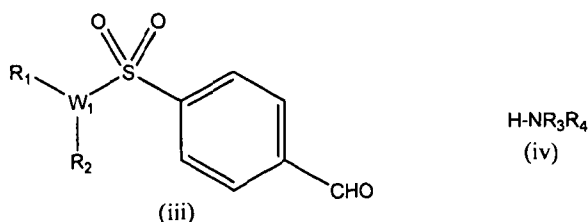
5 In particular embodiments, the condition may be selected from narcolepsy, neuropathic pain and obesity.

In a sixth aspect, the present invention provides the use of a compound according to the first aspect of the invention in the preparation of a medicament for the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, wherein the provisos to the first aspect do not apply. Such conditions
10 may be selected from those described above. In an embodiment, the said provisos do apply.

In the following process description, the symbols R_1 , R_2 , R_3 , R_4 and W when used in the formulae depicted are to be understood to represent those groups as described above in relation to formula (1) unless otherwise indicated. During any of the synthetic sequences
15 it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. The methods of addition and removal of such protecting groups are those which would conventionally be used in relation to the particular molecule-type or group being protected, for example the methods described in standard works of reference in synthetic methodology, such as Kocienski (2004) *Protecting Groups*. 4th Edn. Georg
20 Thieme Verlag. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

The following processes together with the intermediates are provided as further aspects of the invention.

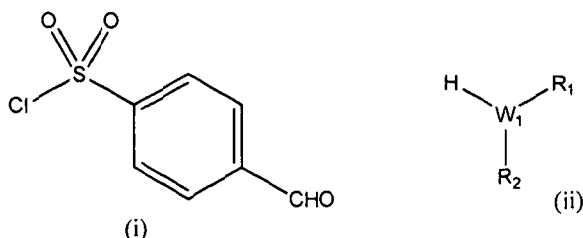
25 Thus in another aspect of the invention, the compounds of formula (1), where W represents N , may be prepared by a process which comprises reacting a compound of formula (iii) with a compound of formula (iv):



wherein R_1 , R_2 , R_3 and R_4 are as defined above and W_1 represents N .

The reaction may conveniently be effected at ambient temperature by reaction with a reducing agent, such as sodium borohydride, in a suitable solvent e.g. tetrahydrofuran.

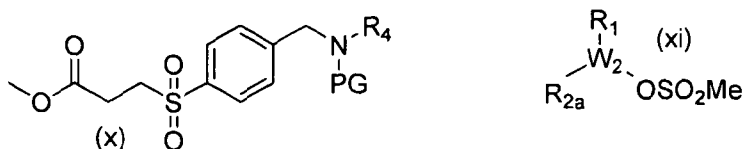
- The starting material of formula (iii) may be prepared by a process which comprises reacting commercially available 4-formylbenzene-1-sulfonyl chloride of formula (i) with
- 5 a compound of formula (ii):



The reaction may conveniently be effected at ambient temperature in a suitable solvent such as an halogenated hydrocarbon e.g. dichloromethane in the presence of an organic base such as triethylamine.

- 10 Where they are not commercially available the starting materials of formula (ii) and (iv) may be prepared using standard methodology known to the person skilled in the art.

Alternatively the compounds of formula (1), where W represents CH, may be prepared by a process which comprises reacting a compound of formula (x) with a compound of formula (xi):



15

wherein R_1 and R_4 are as herein defined, W_2 represents CH, R_{2a} represents optionally substituted heterocyclyl or C_{1-3} alkylene-heterocyclyl and PG represents a protecting group.

The protecting group is typically trifluoromethylacetyl.

- 20 The reaction may be conveniently achieved by treatment with a suitable base e.g. potassium *tert*-butoxide in a suitable solvent such as DMSO at elevated temperature under microwave conditions. The resulting material may then be deprotected using standard conditions e.g. heating in an alcoholic solvent such as ethanol in the presence of an inorganic base e.g. sodium hydroxide, to give a compound of formula (1).

The starting materials of formula (x) and (xi) may be prepared using methods known to those skilled in the art or methods analogous to those described in the Examples.

Novel intermediates form a further aspect of the invention.

The invention will now be described in more detail by way of example only.

5 1. Synthetic Methodologies

The methods used for synthesis of the compounds of the invention are illustrated by the general schemes below and the preparative examples that follow. The starting materials and reagents used in preparing these compounds are available from commercial suppliers. These general schemes are merely illustrative of methods by which the compounds of this
10 invention can be synthesised, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

Nuclear magnetic resonance (NMR) spectra were recorded at 400MHz; the chemical shifts (δ) are reported in parts per million. Spectra were recorded using a Bruker 400 Avance instrument fitted with a 5mm BBFO probe or DUL probe. Instrument control
15 was by Bruker TopSpin 2.1 software.

Purity was assessed using UPLC with UV (photodiode array) detection over a wide range of wavelengths, normally 220-450nm, using a Waters Acquity UPLC system equipped with Acquity UPLC BEH or HSS C18 columns (2.1mm id x 50mm long) operated at 50 or 60°C. Mobile phases typically consisted of acetonitrile or methanol mixed with water
20 containing either 0.05% formic acid or 0.025% ammonia. Mass spectra were recorded with a Waters SQD single quadrupole mass spectrometer using atmospheric pressure ionisation.

Compounds were purified using normal phase chromatography on silica or alumina, or by reverse phase chromatographic methods, using Biotage or Isolute KPNH Cartridge, SCX
25 cartridge and SCX-2 solid phase extraction cartridges.

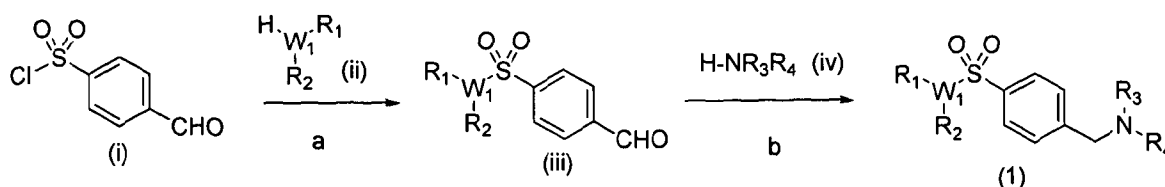
Preparative HPLC was performed using an Agilent Technologies 1100 Series system typically using Waters 19mm id x 100mm long C18 columns such as XBridge or SunFire 5 μ m materials at room temperature. Mobile phases typically consisted of acetonitrile or methanol mixed with water containing either 0.1% formic acid or 0.1% ammonia.

30 Room temperature in the following schemes means the temperature ranging from 20°C to 25°C.

Abbreviations:

- tBuOK – Potassium tert-butoxide
- CDCl₃ – Deuterated chloroform
- DCM - Dichloromethane
- 5 DMSO – Dimethyl sulfoxide
- EtOAc – Ethyl acetate
- EtOH – Ethanol
- DCM – Dichloromethane
- DMF – *N,N*-Dimethylformamide
- 10 rt – room temperature
- mCPBA - 3-Chloroperoxybenzoic acid
- MeOH – Methanol
- MeOD – Deuterated methanol
- NaBH(OAc)₃ – Sodium triacetoxyborohydride
- 15 NEt₃ - Triethylamine
- THF – tetrahydrofuran
- tlc – Thin layer chromatography

- Schemes 1.1 and 1.2 serve to illustrate the methodologies that may be employed to synthesize the exemplified compounds of formula (1) and intermediates used in the
- 20 synthesis of the exemplified compounds of formula (1).

1.1 Scheme 1

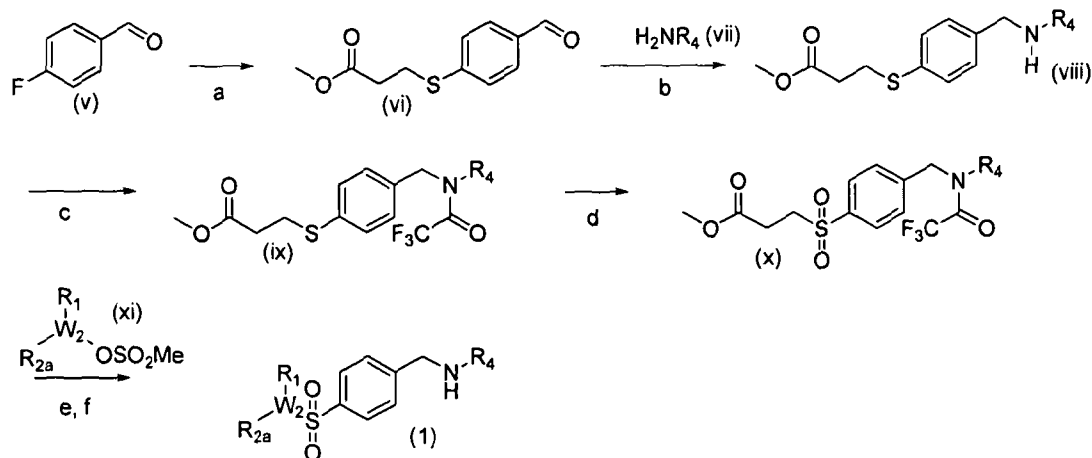
a) (ii), NEt₃, DCM, 25°C, 0.5 hr;

b) (iv), THF, 25°C, 10 min, then MeOH, NaBH₄, 25°C, 1 hr

- 25 wherein R₁, R₂, R₃ and R₄ are as defined and W₁ represents N.

1.2 Scheme 2

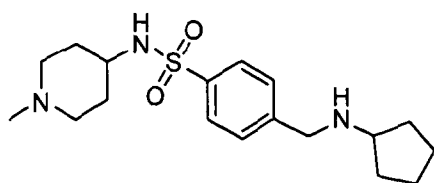
Compounds according to formula (1) where W represents CH, R₂ represents optionally substituted heterocyclyl or C₁₋₃ alkylene-heterocyclyl and R₃ represents H may be prepared according to scheme 2:



a) methyl-3-mercaptopropionate, t-BuOK, DMSO; b) NaBH(OAc)₃, H₂NR₄, DCM; c) Trifluoroacetic anhydride, pyridine, DCM; d) mCPBA, Ca(OH)₂; e) (xi), t-BuOK, DMSO; f) NaOH, EtOH, reflux, 1 hr

5

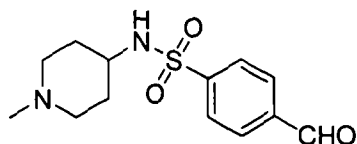
wherein W₂ represents CH, R_{2a} represents optionally substituted heterocyclyl or C₁₋₃ alkylene-heterocyclyl and R₁ and R₄ are as herein defined.

2. Example compounds**2.1 Example 1 (prepared according to scheme 1)**

4-((Cyclopentylamino)methyl)-N-(1-methylpiperidin-4-yl) benzenesulfonamide

Intermediate 1**15 4-Formyl-N-(1-methylpiperidin-4-yl)benzenesulfonamide**

Prepared according to Scheme 1 step a.



4-Formylbenzene-1-sulfonyl chloride (0.5 g, 2.44 mmol) was stirred with 1-methyl-4-aminopiperidine (CAS RN 41838-46-4) (0.28 g, 2.47 mmol) and triethylamine (0.5 mL,

3.70 mmol) in DCM (10 mL) at rt for 30 min. When the sulfonyl chloride had been used up by tlc the reaction mixture was concentrated to give an orange oil (1.1 g) and used without further purification in the next step.

5 Example 1

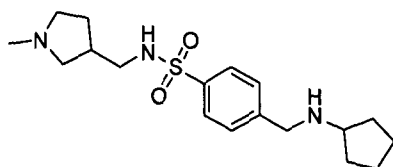
Prepared according to Scheme 1 step b.

Crude 4-formyl-N-(1-methylpiperidin-4-yl)benzenesulfonamide (**Int 1**) (1.1 g, 2.44 mmol) was mixed with cyclopentylamine (311mg, 3.66 mmol) in THF (10 mL) at rt for 10 min. The solvent was evaporated and the residue azeotroped once with toluene (20 mL). The residue was re-dissolved in MeOH (10 mL) and treated with 2 equivalents of sodium borohydride (185 mg, 4.88 mmol) with stirring for 1 hr at rt. The reaction mixture was evaporated to dryness and the residue was treated with 2 N HCl (aq) (3 mL), and then with 2N NaOH (aq) (5 mL) before extraction with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, concentrated and flash chromatographed on silica eluant (1% ammonia 5% MeOH/DCM) to give the title compound as a clear oil (627 mg, 1.78 mmol, 73% yield).

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.67 - 7.82 (m, 2 H), 7.57 - 7.66 (m, 1 H), 7.54 (m, 2 H), 3.76 (s, 2 H), 2.93 - 3.07 (m, 1 H), 2.79 - 2.92 (m, 1 H), 2.54 - 2.65 (m, 2 H), 2.07 (s, 3 H), 1.55 - 1.87 (m, 6 H), 1.19 - 1.55 (m, 8 H). MS ES⁺: 352.

The compounds of Examples 2 to 20 were prepared in a similar manner to the methodology described for Example 1 and according to Scheme 1, using either commercially available or known amines for both step a and step b. Where known amines have been used the CAS registry number is quoted.

2.2. Example 2

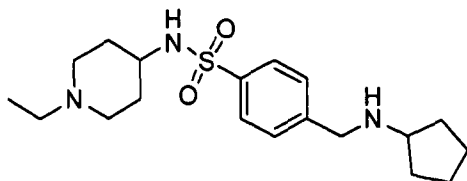


4-((Cyclopentylamino)methyl)-N-((1-methylpyrrolidin-3-yl)methyl)benzene sulfonamide

Using 1-(1-methylpyrrolidin-3-yl)methanamine (CAS RN 13005-11-3) in step a and cyclopentylamine in step b.

¹H NMR: (400 MHz, MeOD) δ 7.77 - 7.88 (m, 2 H), 7.52 - 7.64 (m, 2 H), 3.85 (s, 2 H), 3.04 - 3.18 (m, 1 H), 2.77 - 2.90 (m, 2 H), 2.62 - 2.74 (m, 1 H), 2.46 - 2.62 (m, 2 H), 2.33 (s, 5 H), 1.84 - 2.02 (m, 3 H), 1.66 - 1.82 (m, 2 H), 1.50 (m, 5 H). MS ES⁺: 352

5 2.3 Example 3



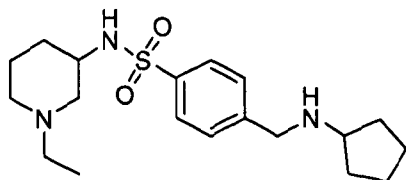
4-((Cyclopentylamino)methyl)-*N*-(1-ethylpiperidin-4-yl)benzenesulfonamide

- 10 Using 1-ethyl-4-aminopiperidine (CAS RN 50534-45-7) in step a and cyclopentylamine in step b.

¹H NMR: (400 MHz, MeOD) δ 7.80 - 7.89 (m, 2 H), 7.57 (s, 2 H), 3.85 (s, 2 H), 2.99 - 3.18 (m, 2 H), 2.77 - 2.89 (m, 2 H), 2.33 - 2.43 (m, 2 H), 1.85 - 2.05 (m, 4 H), 1.65 - 1.84 (m, 4 H), 1.36 - 1.64 (m, 6 H), 1.06 (s, 3 H). MS ES⁺: 366

15

2.4 Example 4



4-((Cyclopentylamino)methyl)-*N*-(1-ethylpiperidin-3-yl)benzenesulfonamide

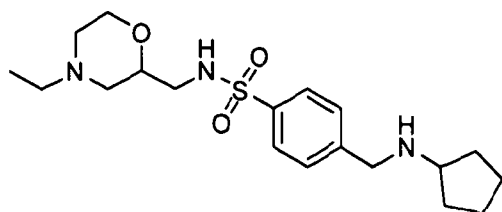
20

Using 1-ethyl-3-aminopiperidine (CAS RN 6789-94-2) in step a and cyclopentylamine in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.67 - 7.80 (m, 2 H), 7.48 - 7.57 (m, 2 H), 3.74 (s, 2 H), 2.90 - 3.04 (m, 2 H), 2.53 - 2.63 (m, 2 H), 2.10 - 2.29 (m, 2 H), 1.91 (s, 3 H), 1.19 - 1.80 (m, 12 H), 0.91 - 1.15 (m, 1 H), 0.85 (s, 3 H). MS ES⁺: 366

25

2.5 Example 5



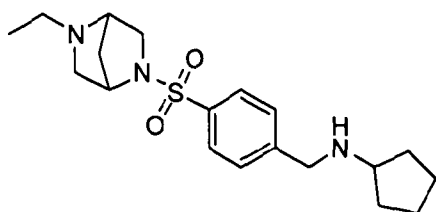
4-((Cyclopentylamino)methyl)-*N*-((4-ethylmorpholin-2-yl)methyl)benzene sulfonamide

Using 1-(4-ethylmorpholin-2-yl)methanamine (CAS RN 141814-56-4) in step a and
 5 cyclopentylamine in step b.

¹H NMR: (400 MHz, MeOD) δ 7.79 - 7.86 (m, 2 H), 7.52 - 7.60 (m, 2 H), 3.76 - 3.88 (m, 3 H), 3.45 - 3.60 (m, 2 H), 3.37 (s, 1 H), 3.02 - 3.19 (m, 1 H), 2.80 - 3.01 (m, 3 H), 2.68 - 2.78 (m, 1 H), 2.35 - 2.48 (m, 2 H), 2.00 - 2.13 (m, 1 H), 1.85 - 1.99 (m, 2 H), 1.66 - 1.83 (m, 3 H), 1.49 - 1.65 (m, 2 H), 1.35 - 1.49 (m, 2 H), 1.04 - 1.15 (m, 3 H). MS ES⁺: 382

10

2.6 Example 6

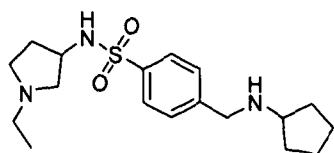


15 *N*-(4-(5-Ethyl-2,5-diazabicyclo[2.2.1]heptan-2-ylsulfonyl)benzyl)cyclopentanamine

Using 2-ethyl-2,5-diazabicyclo[2.2.1]heptane in step a and cyclopentylamine in step b.

¹H NMR: (400 MHz, MeOD) δ 7.78 - 7.99 (m, 2 H), 7.59 - 7.75 (m, 2 H), 4.34 (s, 1 H), 4.02 (s, 2 H), 3.48 - 3.59 (m, 2 H), 3.04 - 3.11 (m, 1 H), 2.85 (m, 1 H), 2.47 - 2.74 (m, 3
 20 H), 1.97 - 2.07 (m, 2 H), 1.93 (s, 2 H), 1.75 - 1.84 (m, 2 H), 1.46 - 1.72 (m, 4 H), 1.07 (m, 3 H). MS ES⁺: 364

2.7 Example 7



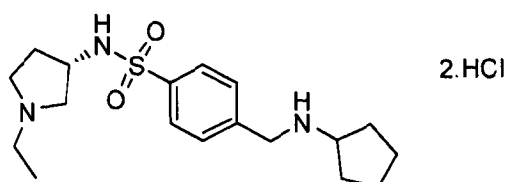
25

4-((Cyclopentylamino)methyl)-*N*-(1-ethylpyrrolidin-3-yl)benzenesulfonamide

Using 1-ethyl-3-aminopyrrolidine (CAS RN 7791-89-1) in step a and cyclopentylamine in step b.

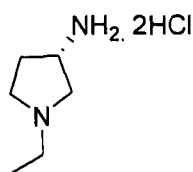
¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.73 (m, 3 H), 7.54 (m, 2 H), 3.77 (s, 2 H), 3.46 - 3.66 (m, 1 H), 2.92 - 3.04 (m, 1 H), 2.42 - 2.48 (m, 1 H), 2.18 - 2.42 (m, 4 H), 2.07 - 2.18 (m, 1 H), 1.78 - 1.92 (m, 1 H), 1.55 - 1.75 (m, 4 H), 1.18 - 1.54 (m, 5 H), 0.92 (s, 3 H). MS ES⁺: 352

2.8 Example 8



(S)-4-((cyclopentylamino)methyl)-N-(1-ethylpyrrolidin-3-yl)benzenesulfonamide dihydrochloride

Intermediate 2



(3S)-1-Ethyl-3-aminopyrrolidine dihydrochloride

Commercial (*S*)-*tert*-butyl pyrrolidine-3-ylcarbamate (5.0 g, 26.8 mmol) was dissolved in DMF (30 ml), potassium carbonate (7.40 g, 53.6 mmol) was added and the mixture was cooled to 0°C. Ethyl iodide (2.2 ml, 26.8 mmol) was added and the reaction mixture was stirred overnight. The solvent was removed under vacuum and the residue extracted with EtOAc (3 x 70 ml). The extracts were washed with saturated NaHCO₃ (50 ml) and brine (50 ml) and dried over MgSO₄. Removal of the solvent under vacuum gave (*S*)-*tert*-butyl-1-ethylpyrrolidin-3-ylcarbamate (1.31 g, 23%) as a yellow oil which was used without purification. ¹H NMR (CDCl₃, 300MHz) 4.9 (1H, m), 4.15 (1H, m), 2.8 (1H, m), 2.6 (1H, m), 2.45 (1H, m), 2.2 (2H, m), 1.6 (1H, m), 1.4 (9H, s) and 1.05 (3H, t, *J* = 7.4 Hz).

(*S*)-*tert*-Butyl-1-ethylpyrrolidin-3-ylcarbamate (1.30 g, 6.07 mmol) was dissolved in 2M methanolic HCl, (5 ml) and stirred at room temperature for 18 h. The solvent was removed under vacuum to give the *title compound* (*Intermediate 2*) (1.08 g, 95%) as a brown foam. A small quantity was neutralised with 20% NH₃ in methanol and

concentrated ^1H NMR (free base) (CDCl_3 , 300MHz) 3.54 (1H, m), 2.73 (1H, m), 2.47 (3H, m), 2.31 (2H, m), 1.51 (2H, m), and 1.13 (3H, t, $J = 7.2$ Hz)

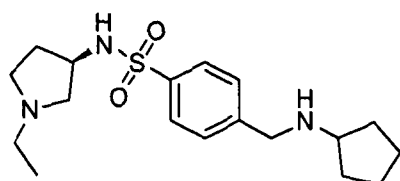
Example 8 was prepared using (3S)-1-ethyl-3-aminopyrrolidine dihydrochloride (**Int 2**)

5 in step a and cyclopentylamine in step b.

^1H NMR: (400 MHz, $\text{DMSO}-d_6$) δ 9.29 - 9.61 (m, 2 H), 8.26 - 8.58 (m, 1 H), 7.74 - 7.96 (m, 4 H), 4.24 (br. s., 2 H), 3.87 - 4.02 (m, 1 H), 3.68 - 3.84 (m, 1 H), 3.40 - 3.67 (m, 2 H), 3.03 - 3.26 (m, 3 H), 2.77 - 3.03 (m, 1 H), 1.89 - 2.21 (m, 2 H), 1.74 (br. s., 4 H), 1.43 - 1.62 (m, 2 H), 1.19 (t, 3 H). MS ES^+ : 352

10

2.9 Example 9



(R)-4-((Cyclopentylamino)methyl)-N-(1-ethylpyrrolidin-3-yl)benzenesulfonamide

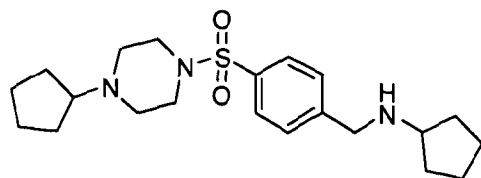
15

Using (3R)-1-ethyl-3-aminopyrrolidine (CAS RN: 216667-65-1) in step a and cyclopentylamine in step b.

^1H NMR: (400 MHz, $\text{DMSO}-d_6$) δ 7.67 - 7.83 (m, 3 H), 7.53 (d, 2 H), 3.74 (s, 2 H), 3.47 - 3.63 (m, 1 H), 2.90 - 3.03 (m, 1 H), 2.05 - 2.42 (m, 6 H), 1.75 - 1.90 (m, 1 H), 1.53 - 1.76 (m, 4 H), 1.21 - 1.54 (m, 5 H), 0.92 (t, 3 H). MS ES^+ : 352

20

2.10 Example 10

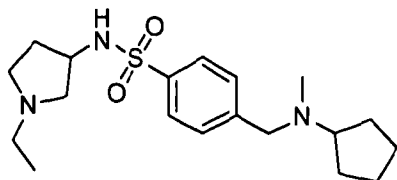


25 N-(4-(4-Cyclopentylpiperazin-1-yl)sulfonyl)benzyl)cyclopentanamine

Using 1-cyclopentylpiperazine (CAS RN 21043-40-3) in step a and cyclopentylamine in step b.

^1H NMR: (400 MHz, DMSO- d_6) δ 7.55 - 7.72 (m, 2 H), 3.69 - 3.82 (m, 2 H), 2.93 - 3.04 (m, 1 H), 2.74 - 2.92 (m, 4 H), 2.34 - 2.47 (m, 5 H), 2.08 - 2.26 (m, 1 H), 1.39 - 1.78 (m, 13 H), 1.12 - 1.39 (m, 4 H). MS ES^+ : 392

5 2.11 Example 11



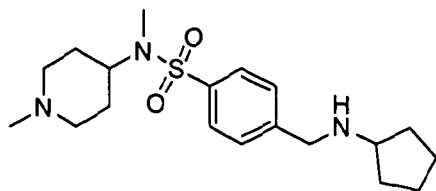
4-((Cyclopentyl(methyl)amino)methyl)-*N*-(1-ethylpyrrolidin-3-yl)benzene sulfonamide

- 10 Using 1-ethyl-3-aminopyrrolidine in step a and *N*-methylcyclopentylamine (CAS RN 2439-56-7) in step b.

^1H NMR: (400 MHz, DMSO- d_6) δ 7.75 (m, 3 H), 7.44 - 7.59 (m, 2 H), 3.55 (s, 3 H), 2.64 - 2.83 (m, 1 H), 2.42 - 2.48 (m, 1 H), 2.22 - 2.42 (m, 4 H), 2.07 - 2.20 (m, 1 H), 2.04 (s, 3 H), 1.72 - 1.92 (m, 3 H), 1.33 - 1.71 (m, 7 H), 0.91 (s, 3 H). MS ES^+ : 366

15

2.12 Example 12



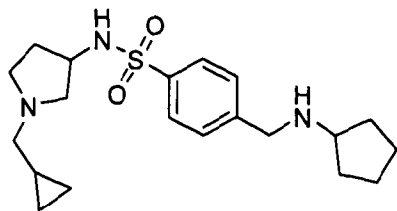
4-((Cyclopentylamino)methyl)-*N*-methyl-*N*-(1-methylpiperidin-4-yl)benzenesulfonamide

20

Using *N*,1-dimethylpiperidine-4-amine (CAS RN 73579-08-5) in step a and cyclopentylamine in step b.

- ^1H NMR: (400 MHz, DMSO- d_6) δ 7.63 - 7.80 (m, 2 H), 7.49 - 7.62 (m, 2 H), 3.73 (none, 2 H), 3.51 - 3.66 (m, 1 H), 2.89 - 3.05 (m, 1 H), 2.68 (br. s., 5 H), 1.99 - 2.28 (m, 4 H),
 25 1.78 - 1.92 (m, 2 H), 1.50 - 1.74 (m, 6 H), 1.38 - 1.50 (m, 2 H), 1.22 - 1.40 (m, 2 H), 1.07 - 1.25 (m, 2 H). MS ES^+ : 366.

2.13 Example 13

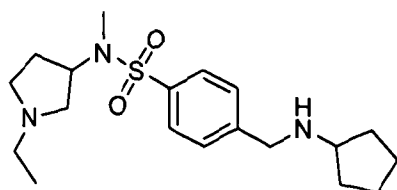


4-((Cyclopentylamino)methyl)-N-(1-(cyclopropylmethyl)pyrrolidin-3-yl)benzenesulfonamide

- 5 Using 1-(cyclopropylmethyl)pyrrolidin-3-amine (CAS RN 72135-44-5) in step a and cyclopentylamine in step b.

^1H NMR: (400 MHz, DMSO- d_6) δ 7.69 - 7.82 (m, 3 H), 7.46 - 7.60 (m, 2 H), 3.69 - 3.84 (m, 2 H), 3.47 - 3.65 (m, 1 H), 2.92 - 3.04 (m, 1 H), 2.55 - 2.61 (m, 1 H), 2.35 - 2.47 (m, 2 H), 2.05 - 2.21 (m, 3 H), 1.77 - 1.95 (m, 1 H), 1.54 - 1.76 (m, 4 H), 1.23 - 1.56 (m, 5 H),
 10 0.67 - 0.80 (m, 1 H), 0.36 (m, 2 H). MS ES⁺: 378.

2.14 Example 14

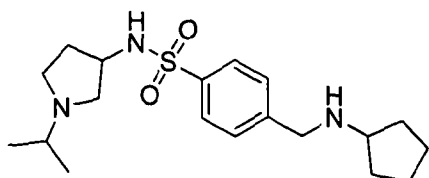


- 15 4-((Cyclopentylamino)methyl)-N-(1-ethylpyrrolidin-3-yl)-N-methylbenzenesulfonamide

Using 1-ethyl-N-methylpyrrolidin-3-amine in step a and cyclopentylamine in step b.

^1H NMR: (400 MHz, DMSO- d_6) δ 7.66 - 7.73 (m, 2 H), 7.57 (m, 2 H), 4.39 - 4.50 (m, 1 H), 3.77 (s, 2 H), 2.91 - 3.04 (m, 1 H), 2.68 (s, 3 H), 2.55 - 2.64 (m, 1 H), 2.13 - 2.38 (m,
 20 4 H), 1.98 - 2.10 (m, 1 H), 1.75 - 1.88 (m, 1 H), 1.54 - 1.75 (m, 4 H), 1.25 - 1.54 (m, 5 H), 0.92 (m, 3 H). MS ES⁺: 367.

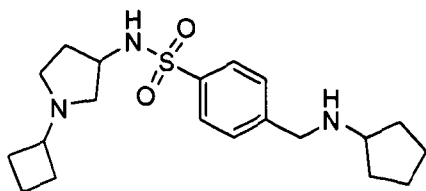
2.15 Example 15



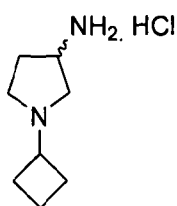
4-((Cyclopentylamino)methyl)-N-(1-isopropylpyrrolidin-3-yl)benzenesulfonamide

Using 1-(isopropan-2-yl)pyrrolidin-3-amine in step a and cyclopentylamine in step b.

- 5 ¹H NMR: (400 MHZ, DMSO-*D*₆) δ 7.68 - 7.81 (M, 3 H), 7.54 (S, 2 H), 3.75 (S, 2 H), 3.46 - 3.61 (M, 1 H), 2.88 - 3.04 (M, 1 H), 2.52 - 2.58 (M, 1 H), 2.32 - 2.47 (M, 2 H), 2.09 - 2.31 (M, 2 H), 1.76 - 1.94 (M, 1 H), 1.53 - 1.74 (M, 4 H), 1.20 - 1.53 (M, 5 H), 0.91 (M, 6 H). MS ES⁺: 366.

10 **2.16 Example 16**

N-(1-Cyclobutylpyrrolidin-3-yl)-4-((cyclopentylamino)methyl)benzenesulfonamide

15 **Intermediate 3**

1-Cyclobutylpyrrolidin-3-amine hydrochloride

- 20 To a solution of *tert*-butylpyrrolidine-3-ylcarbamate (0.93 g, 4.99 mmol) and cyclobutanone (0.52 g, 7.5 mmol) in DCM (10 ml) at rt was added sodium triacetoxyborohydride (1.58 g, 7.5 mmol). The reaction mixture was stirred for 1 h then quenched with 2 M NaOH (10 ml). The organic layer was separated and the aqueous extracted with DCM (20 ml) the combined organic layers were dried over MgSO₄ and
- 25 concentrated to give *tert*-butyl-1-cyclobutylpyrrolidin-3-ylcarbamate (1.04 g, 87%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) 4.83 (1H, br-s), 4.13 (1H, br-s), 2.85 (1H, m), 2.75 - 2.49 (3H, m), 2.25 (2H, m), 1.91 (4H, m), 1.71 (2H, m) and 1.42 (9H, s).
- tert*-Butyl-1-cyclobutylpyrrolidin-3-ylcarbamate (1.04 g, 4.32 mmol) was dissolved in 2M methanolic HCl, (15 ml) and stirred at rt for 18 h. The solvent was removed under
- 30 vacuum to give the *title compound* (Intermediate 3) (0.85 g, 92%) as a brown foam. ¹H

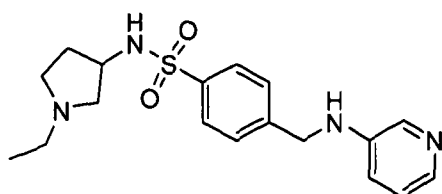
NMR (MeOD, 300 MHz) 4.01-3.29 (6H, m), 2.54 (2H, m), 2.34 (4H, m) and 1.90 (2H, m).

Example 16 was prepared using 1-cyclobutylpyrrolidin-3-amine (**Int 3**) in step a and
5 cyclopentylamine in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.69 - 7.80 (m, 3 H), 7.49 - 7.60 (m, 2 H), 3.73 - 3.81 (m, 2 H), 3.46 - 3.63 (m, 1 H), 2.91 - 3.05 (m, 1 H), 2.71 - 2.85 (m, 1 H), 2.41 - 2.47 (m, 1 H), 2.24 - 2.38 (m, 2 H), 2.00 - 2.13 (m, 1 H), 1.62 (m, 11 H), 1.39 (m, 5 H). MS ES⁺:
378.

10

2.17 Example 17



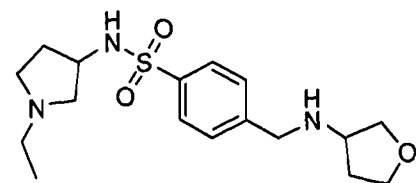
15

N-(1-Ethylpyrrolidin-3-yl)-4-((pyridin-3-ylamino)methyl)benzenesulfonamide

Using 1-ethyl-3-aminopyrrolidine in step a and 3-aminopyridine (CAS RN 462-08-8) in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.93 - 8.03 (m, 1 H), 7.72 - 7.84 (m, 3 H), 7.60 - 7.71 (m, 1 H), 7.51 - 7.61 (m, 2 H), 6.96 - 7.06 (m, 1 H), 6.81 - 6.93 (m, 1 H), 6.43 - 6.54 (m, 1 H), 4.40 (m, 2 H), 3.50 - 3.68 (m, 1 H), 3.04 - 3.18 (m, 1 H), 2.26 - 2.46 (m, 4 H), 2.10 - 2.26 (m, 1 H), 1.76 - 1.93 (m, 1 H), 1.35 - 1.55 (m, 1 H), 0.93 (s, 3 H). MS ES⁺: 361.

25

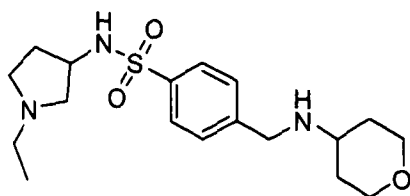


N-(1-Ethylpyrrolidin-3-yl)-4-((tetrahydrofuran-3-ylamino)methyl)benzene sulfonamide

Using 1-ethyl-3-aminopyrrolidine in step a and tetrahydrofuran-3-amine (CAS RN: 45379-55-3) in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.75 (m, 2 H), 7.58 - 7.69 (m, 1 H), 7.48 - 7.58 (m, 2 H), 3.53 - 3.84 (m, 6 H), 3.37 - 3.49 (m, 1 H), 3.25 - 3.33 (m, 1 H), 2.37 (s, 5 H), 2.12 - 2.22 (m, 1 H), 1.79 - 2.02 (m, 2 H), 1.61 - 1.75 (m, 1 H), 1.40 - 1.54 (m, 1 H), 0.93 (m, 3 H). MS ES⁺: 354.

2.19 Example 19



10

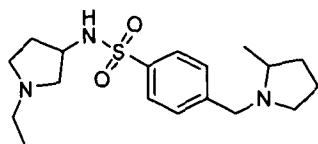
N-(1-Ethylpyrrolidin-3-yl)-4-((tetrahydro-2H-pyran-4-ylamino)methyl)benzenesulfonamide

Using 1-ethyl-3-aminopyrrolidine in step a and tetrahydro-2H-pyran-4-amine (CAS RN: 38041-19-9) in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.71 - 7.79 (m, 2 H), 7.59 - 7.66 (m, 1 H), 7.49 - 7.59 (m, 2 H), 3.82 (s, 4 H), 3.51 - 3.68 (m, 1 H), 3.28 (m, 2 H), 2.57 - 2.69 (m, 1 H), 2.23 - 2.44 (m, 4 H), 2.10 - 2.23 (m, 2 H), 1.72 - 1.91 (m, 3 H), 1.39 - 1.56 (m, 1 H), 1.22 - 1.37 (m, 2 H), 0.94 (s, 3 H). MS ES⁺: 368.

20

2.20 Example 20



25

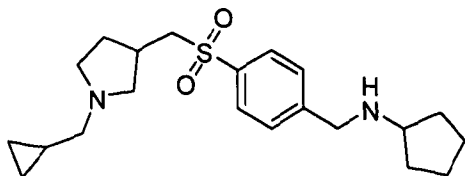
N-(1-Ethylpyrrolidin-3-yl)-4-((2-methylpyrrolidin-1-yl)methyl)benzenesulfonamide

Using 1-ethyl-3-aminopyrrolidine in step a and 2-methylpyrrolidine (CAS RN: 41720-98-3) in step b.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 7.75 (m, 2 H), 7.58 - 7.70 (m, 1 H), 7.50 (m, 2 H), 4.00 (m, 1 H), 3.49 - 3.67 (m, 1 H), 3.30 (m, 1 H), 2.72 - 2.86 (m, 1 H), 2.21 - 2.49 (m, 5

H), 2.02 - 2.20 (m, 2 H), 1.78 - 2.01 (m, 2 H), 1.55 - 1.71 (m, 2 H), 1.27 - 1.55 (m, 2 H), 1.08 (m, 3 H), 0.92 (m, 3 H). MS ES⁺: 352.

2.21 Example 21 (Prepared according to Scheme 2)



5

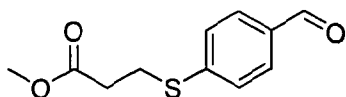
N-(4-((1-(cyclopropylmethyl)pyrrolidin-3-yl)methylsulfonyl)benzyl) cyclopentanamine

Intermediate 4

Methyl 3-(4-formylphenylthio)propanoate

10

Prepared according to Scheme 2 step a



15

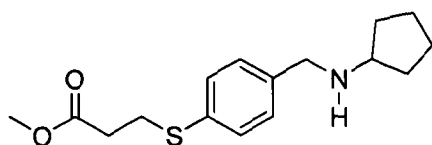
Potassium tert-butoxide (5.6 g, 50 mmol) was added to a nitrogen degassed suspension of methyl 3-mercaptopropanoate (6.0 g, 50 mmol) and 4-fluorobenzaldehyde (5.3 ml, 50.0 mmol) in DMSO (50 ml). A significant exotherm was observed. The reaction was allowed to cool to room temperature and then was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl (x3) and dried over magnesium sulphate and evaporated. The residue was purified on Biotage silica gel column, eluting with 10:1 Hexane/EtOAc to yield methyl 3-(4-formylphenylthio)propanoate (4.3 g, 19.17 mmol, 38.3 % yield).

20

Intermediate 5

Methyl 3-(4-((cyclopentylamino)methyl)phenylthio)propanoate

Prepared according to Scheme 2 step b



25

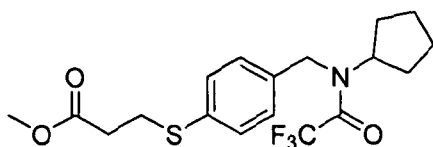
Methyl 3-(4-formylphenylthio)propanoate (**Int 4**) (4.30 g, 19.17 mmol) and cyclopentanamine (1.63 g, 19.17 mmol) were stirred with sodium triacetoxyborohydride (4.0 g, 19.17 mmol) in DCM (100 mL) at rt for 2 hrs. The solvent was removed and the residue was taken up into EtOAc and washed with saturated sodium carbonate (x2). The

organic layer was separated and dried over MgSO_4 and evaporated to yield methyl 3-(4-((cyclopentylamino)methyl)phenylthio) propanoate (5.63 g, 19.19 mmol, 100 % yield) which was used crude in the next step.

5 Intermediate 6

Methyl 3-(4-((N-cyclopentyl-2,2,2-trifluoroacetamido)methyl)phenylthio) propanoate

Prepared according to Scheme 2 step c

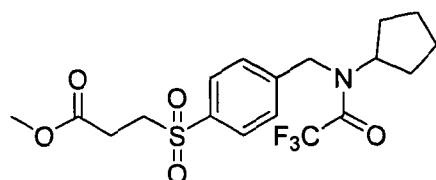


A solution of methyl 3-(4-((cyclopentylamino)methyl)phenylthio)propanoate (**Int 5**) (5.6 g, 19.17 mmol) and pyridine (4.6 mL, 57.5 mmol) in DCM (30 mL) was cooled to 0°C and trifluoroacetic anhydride (5.4 mL, 38.3 mmol) was added dropwise. The reaction was stirred for 16 hours and the solvent was evaporated and the residue was taken up into EtOAc and washed with 1M HCl, saturated NaCl, and saturated NaHCO_3 . The organic layer was dried over magnesium sulphate and evaporated. The residue was purified on Biotage silica gel column eluting 10:1 Hex:EtOAc to yield methyl 3-(4-((N-cyclopentyl-2,2,2-trifluoroacetamido)methyl)phenylthio)propanoate (6.2 g, 15.92 mmol, 83 % yield). ^1H NMR (400 MHz, CDCl_3) δ 7.24 - 7.41 (m, 2 H), 7.13 (m, 2 H), 4.54 (s, 2 H), 4.33 - 4.50 (m, 1 H), 3.69 (s, 3 H), 3.15 (s, 2 H), 2.63 (s, 2 H), 1.81 - 1.99 (m, 1 H), 1.41 - 1.77 (m, 6 H), 0.80-0.95 (m, 1H)

Intermediate 7

Methyl 3-(4-((N-cyclopentyl-2,2,2-trifluoroacetamido)methyl)phenylsulfonyl) propanoate

Prepared according to Scheme 2 step d



m-CPBA (8.2 g, 47.8 mmol) was added cautiously to methyl 3-(4-((N-cyclopentyl-2,2,2-trifluoroacetamido)methyl)phenylthio)propanoate (**Int 6**) (6.2 g, 15.92 mmol) and the mixture was stirred at room temperature for 1 hour. Calcium hydroxide (5.3 g, 71.6 mmol) was added and the reaction was stirred for 0.25 hours. The reaction mixture was filtered through celite and evaporated to yield methyl 3-(4-((N-cyclopentyl-2,2,2-

trifluoroacetamido)methyl)phenylsulfonyl)propanoate as a white solid (5.6 g, 13.29 mmol, 83 % yield) .

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 - 7.95 (m, 2 H), 7.44 (m, 2 H), 4.78 - 4.88 (m, 1 H), 4.71 (s, 1 H), 4.34 - 4.47 (m, 1 H), 3.45 - 3.64 (m, 5 H), 2.57 - 2.70 (m, 2 H), 1.79 - 1.93 (m, 1 H), 1.56 (m, 7 H).

Example 21

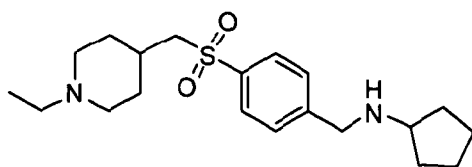
Prepared according to Scheme 2 steps e and f

Potassium tert-butoxide (0.11 g, 1 mmol) was added to methyl 3-(4-((N-cyclopentyl-2,2,2-trifluoroacetamido)methyl)phenylsulfonyl)propanoate (**Int 7**) (0.42 g, 1 mmol) and (1-(cyclopropylmethyl)pyrrolidin-3-yl)methyl methanesulfonate in DMSO and mixture was microwaved for 10 minutes at 150 °C. MS ES⁺: 473

The reaction mixture was diluted with ethanol (10 mL) and 2M NaOH (5 mL) was added and the reaction was heated to reflux for 1 hour. The reaction mixture was extracted with ethyl acetate and washed with 5% aqueous ammonia (x 3). The organic layer was dried over magnesium sulphate and evaporated. The residue was purified on Biotage silica gel column eluting 15% (10% methanol/ammonia) in DCM to yield N-(4-((1-(cyclopropylmethyl)pyrrolidin-3-yl)methylsulfonyl)benzyl)cyclopentanamine (0.04 g, 0.120 mmol, 11.95 % yield).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 2 H), 7.54 (m, 2 H), 3.87 (s, 2 H), 3.01 - 3.27 (m, 3 H), 2.87 (s, 1 H), 2.46 - 2.68 (m, 3 H), 2.21 - 2.35 (m, 3 H), 2.03 - 2.15 (m, 1 H), 1.85 (m, 2 H), 1.72 (m, 2 H), 1.31 - 1.43 (m, 2 H), 1.26 (s, 3 H), 0.78 - 0.93 (m, 2 H), 0.48 (m, 2 H), 0.08 (m, 2 H). MS ES⁺: 377

2.22 Example 22



N-(4-((1-Ethylpiperidin-4-yl)methylsulfonyl)benzyl)cyclopentanamine

The compound according to Example 22 was prepared in a similar manner to the methodology described for Example 21 and according to Scheme 2, using **Intermediate 7** and (1-ethylpiperidin-4-yl)methyl methanesulfonate in step e.

¹H NMR: (400 MHz, MeOD) δ 7.71 - 7.82 (m, 2 H), 7.46 - 7.57 (m, 2 H), 3.71 - 3.82 (m, 2 H), 3.03 - 3.16 (m, 2 H), 2.88 - 3.02 (m, 1 H), 2.73 - 2.86 (m, 2 H), 2.23 - 2.33 (m, 2 H), 1.71 - 1.92 (m, 7 H), 1.56 - 1.67 (m, 2 H), 1.37 - 1.55 (m, 2 H), 1.22 - 1.36 (m, 4 H), 0.97 (m, 3 H). MS ES⁺: 365

3. Biological efficacy of compounds of the invention

10 3.1 In Vitro H3 Binding Assay

The ability of compounds to bind to the H3 receptor was determined by measuring the reduction in tritiated N-α-methyl-histamine (³H-NαMH) binding in a competition binding assay. Changes in the levels of bound radio-label were monitored by scintillation counting with a Trilux Microbeta (Perkin Elmer).

15 Membranes were prepared from CHO-K1 cells stably expressing human H3 receptor; routinely grown as monolayers in Ham's F12 medium (Invitrogen) supplemented with 10% Foetal Clone III (Hyclone), 500 μg/mL G418 (Invitrogen), 5 μg/mL blasticidine S (Invivogen) and 50 μg/mL Gentamicin (Sigma) in 5% CO₂ at 37°C. Cells were grown to 80-95% confluency, rinsed once with 1x PBS (Invitrogen) and detached by incubating
20 with 1x PBS containing 0.02% EDTA (Sigma) for 10 min at room temperature. Cells were collected by centrifugation at 900 xg, 4°C for 10 min. Cells were rinsed once with 1x PBS and re-suspended in ice cold homogenisation buffer (50mM Tris-HCl (pH 7.4), 2.5mM EDTA, 5mM MgCl₂, 200mM Sucrose) at 1x10⁷ cells/mL and kept on ice. Cells were homogenised on ice and debris removed by centrifugation at 500 x g, 4°C for 5 min.
25 The resulting supernatant was centrifuged at 75,600 xg, 4°C for 60 min. Membranes were suspended in homogenisation buffer, protein concentration was determined (BCA Protein Assay kit (Pierce)), diluted to 2.2 mg/mL, dispensed into 1mL aliquots and stored at -80 °C.

30 Membranes were thawed on ice, sonicated with 4 cycles of 20 pulses (50% amplitude, 0.5 pulse) (UP200S Hielscher) on ice, diluted in assay buffer (50mM Tris-HCl (pH7.4), 5mM MgCl₂) to 62.5 μg/mL. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 5 μg of membrane in 80 μl of assay buffer was added per well of a

96 well polystyrene plate (Corning). 10 µl of compound was added per well. The assay was initiated by the addition of 10 µl of 20nM ³H-NαMH per well and incubated for one h at room temperature with shaking. Total binding was determined in the presence of 1% DMSO and non-specific binding was determined by the inclusion of 1 µM R-α-methyl-histamine (RαMH). Incubations were then filtered through filtermat A (Perkin Elmer) and washed three times with assay buffer. Filtermats were dried at 42°C for two h, scintillant added and the level of bound radioactivity determined.

IC50 values for compounds were determined from seven point log scale dose-response studies and represent the concentration of compound required to inhibit 50% of the specific binding of 2nM ³H-NαMH (difference between total and non-specific binding). Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of sigmoidal dose response (variable slope).

3.2 In Vitro H3 Functional Assay

The functional activity of compounds at the H3 receptor was determined by measuring changes in the level of intracellular cAMP using a cAMP response element driven luciferase reporter assay. The changes in luciferase expression were monitored by a luminescence plate reader, Analyst HT (MDS Analytical). Increases in intracellular cAMP were readily detected upon activation of protein kinase A by forskolin (Sigma) and suppression of this response observed with the application of the H3 receptor agonist RαMH (Sigma).

CHO(dhfr⁺)-cre-luc cells stably expressing human H3 receptor were routinely grown as monolayers in Minimal Essential Medium α (MEMα) (Invitrogen) supplemented with 10% dialysed FBS (Hyclone), in 5% CO₂ at 37°C. 48 h prior to assay, cells were seeded in clear-base white walled 384-well plates (Corning) at a density of 5000 cells/well. On the day of assay, growth media was removed and replaced with 15 µl of assay buffer (MEMα, 5 mg/mL fatty acid free BSA (Sigma)) per well. Cells were then incubated for 30 m at 37°C, 5% CO₂. Compound was serially diluted in DMSO before being diluted 1:10 with assay buffer. 2.5 µl of compound diluted in assay buffer was added and cells incubated for 5 m at 37°C, 5% CO₂. 2.5 µl of each reagent was then added in the following order: RαMH (10 nM), isobutylmethylxanthine (1-methyl-3-(2-methylpropyl)-7H-purine-2,6-dione; IBMX) (500 µM) (Sigma) and forskolin (1 µM). Cells were then incubated for 90 m at 37°C, 5% CO₂, followed by 30 m at room temperature. At the end

of incubation 25 μ l of Steadylite reagent (Perkin Elmer) was added, plates were sealed and placed on a shaker for 5 min. The level of light output to determine the level of luciferase expression was then measured.

- 5 IC₅₀ values for compounds were determined from ten point half log scale dose-response studies and represent the concentration of compound required to prevent 50% inhibition of forskolin stimulated cells in the presence of R α MH alone. Curves were generated using the average of duplicate wells for each data point and analyzed using nonlinear regression of four parameter dose response.

3.3 Results

Example Compound	hH3 binding IC ₅₀ /nM	hH3 functional IC ₅₀ /nM
7	7	2.3
10	145	-
11	19	-
13	3	-
14	1	1.1
17	197	-
18	12	9.7
20	22	-
22	21	24

10

- These results indicate that compounds of the invention have potent antagonist or inverse agonist activity at the H3 receptor, both in terms of binding and where tested in terms of inhibition of the functional response caused by receptor activation. The compounds tested above exhibit IC₅₀ values significantly less than 1 μ M, with the compounds showing low nanomolar affinity at the H3 receptor. Accordingly, the compounds of the invention are expected to have usefulness in the prevention or treatment of conditions, such as those discussed above, in which H3 receptor activity is implicated.
- 15

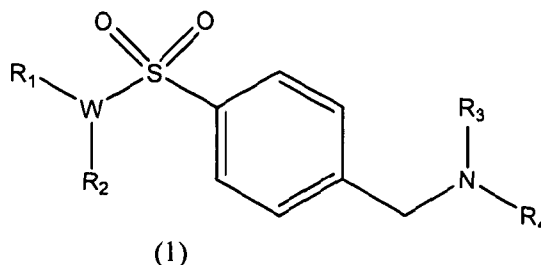
REFERENCES

- 20 1. J.-M. Arrang, M. Garbarg and J.-C. Schwartz. Nature, 1983, 302, 832
2. T. W. Lovenberg, B. L. Roland, S. J. Wilson, X. Jiang, J. Pyati, A. Huvar, M. R. Jackson and M. G. Erlander. Mol. Pharmacol., 1999, 55, 1101.

3. S. J. Hill, C. Ganellin, H. Timmermans, J. C. Schwartz, N. Shankley, J. M. Young, W. Schunack, R. Levi and H. L. Haas. *Pharmacol. Rev.*, 1997, 49, 253.
4. Passani MB, Lin J-S, Hancock A, Crochet S, Blandina P. The histamine H3 receptor as a novel therapeutic target for cognitive and sleep disorders. *Trends Pharmacol. Sci.* 2004;25:618–25.
5. Witkin JM, Nelson DL. Selective histamine H3 receptor antagonists for treatment of cognitive deficiencies and other disorders of the central nervous system. *Pharmacol. Ther.* 2004;103:1–20
6. Monti J.M et al. Effect of Selective activation or blockade of the hitamine H3 receptor on sleep and wakefulness. 1991 *Eur. J. Pharmacol.*205, 283-287.
7. Esbenshade T.A. et al. *Biochemical Pharmacology* 68 (2004) 933-945.
8. Morimoto T, Yamamoto Y, Yamatodani A. Leptin facilitates histamine release from the hypothalamus in rats. *Brain Res.* 2000; 868:367–9
9. A. A. Hancock. *Biochem. Pharmacol.*, 2006, 71, 1103.
10. A. A. Hancock and M. E. Brune. *Expert Opin. Investig. Drugs*, 2005, 14, 223
11. D. Farzin, L. Asghari and M. Nowrouzi. *Pharmacol. Biochem. Behav.*, 2002, 72, 751.
12. WO 04/089410
13. Medhurst A.D. et al. *Biochemical Pharmacology* 73 (2007) 1182-94
14. Esbenshade T.A et al. *J. Pharmacol. Exp. Ther.* 2005 313(1) 165-75

CLAIMS

1. A compound having the formula (1):



wherein:

W represents N or CH;

R₁ represents H or C₁₋₃ alkyl;

R₂ represents a N-containing heterocyclyl ring or a -C₁₋₃ alkylene-N-containing heterocyclyl group, in which any N-containing heterocyclyl comprising or present on R₂ may be optionally substituted with one or more substituents independently selected from C₁₋₃ alkyl, C₃₋₆ cycloalkyl and -C₁₋₃ alkylene-C₃₋₆ cycloalkyl;

or, when W represents N, R₁ and R₂ and the N atom to which they are attached may join to form an optionally substituted azacyclic ring, wherein the azacyclic ring may be optionally substituted with one or more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl;

R₃ represents H or C₁₋₃ alkyl;

R₄ represents optionally substituted C₃₋₆ cycloalkyl, heteroaryl or heterocyclyl;

or R₃ and R₄ and the N atom to which they are attached may join to form an optionally substituted heterocyclyl ring;

wherein R₄ or the heterocyclyl ring -NR₃R₄ may be optionally substituted with one or more C₁₋₃ alkyl groups; or a pharmaceutically acceptable salt thereof;

with the proviso that the compound of formula (1) is not:

N-[[4-(1-piperidinylsulfonyl)phenyl]methyl]-2-pyrimidinamine;

1-[[4-(1-pyrrolidinylsulfonyl)phenyl]methyl]-piperazine; or

N-cyclopropyl-4-[(4-methyl-1-piperazinyl)sulfonyl]-benzenemethanamine.

2. A compound according to claim 1 wherein W represents N or CH; R₁ represents H or C₁₋₃ alkyl; R₂ represents N-containing heterocyclyl or -C₁₋₃ alkylene-N-containing heterocyclyl; in which any N-containing heterocyclyl comprising or present on R₂ may be

optionally substituted with one or more substituents independently selected from C₁₋₃ alkyl, C₃₋₆ cycloalkyl and -C₁₋₃ alkylene-C₃₋₆ cycloalkyl; R₃ represents H or C₁₋₃ alkyl; R₄ represents optionally substituted C₃₋₆ cycloalkyl, heteroaryl or heterocyclyl; or R₃ and R₄ and the N atom to which they are attached are joined to form an optionally substituted heterocyclyl ring; in which R₄ or the heterocyclyl ring -NR₃R₄ may be optionally substituted with C₁₋₃ alkyl; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 wherein W represents N.

4. A compound according to any of claims 1 to 3 wherein R₂ represents an optionally substituted N-containing heterocyclyl ring.

10 5. A compound according to any of claims 1 to 4 wherein any N-containing heterocyclyl ring comprising or present on R₂ is linked to the rest of the compound of formula (1) through a C atom.

15 6. A compound according to any of claims 1, 2, 3 or 5 wherein R₂ represents optionally substituted pyrrolidinyl, piperidinyl, -methyl-pyrrolidinyl or -methyl-morpholinyl, wherein the pyrrolidinyl, piperidinyl and morpholinyl are linked to the rest of the compound of formula (1) through a C atom.

7. A compound according to any preceding claim wherein the optional substituents that may be present on any N-containing heterocyclyl comprising or present on R₂ include methyl, ethyl, isopropyl, cyclobutyl and -methyl-cyclopropyl.

20 8. A compound according to claim 1 wherein when W represents N, R₁ and R₂ and the N atom to which they are attached are joined to form an optionally substituted piperazinyl or C₁₋₃ alkylene bridged piperazinyl ring; in which the piperazinyl ring may be optionally substituted with one or more substituents independently selected from C₁₋₃ alkyl and C₃₋₆ cycloalkyl.

25 9. A compound according to any preceding claim wherein R₄ represents optionally substituted C₃₋₆ cycloalkyl or heterocyclyl.

10. A compound according to claim 9 wherein R₄ represents cyclopentyl, tetrahydrofuranyl or tetrahydropyranyl.

30 11. A pharmaceutical composition comprising a compound according to any preceding claim, together with one or more pharmaceutically acceptable excipients, wherein the provisos to claim 1 do not apply.

12. A compound according to any of claims 1 to 10, or a composition according to claim 11, for use in therapy, wherein the provisos to claim 1 do not apply.

13. A compound according to any of claims 1 to 10, or a composition according to claim 11, for use in the treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, wherein the provisos to claim 1 do not apply.

14. A method of treatment or prevention of a condition whose development or symptoms are linked to histamine H3 receptor activity, the method comprising the administration, to a subject in need of such treatment or prevention, of a therapeutically effective amount of a compound according to any of claims 1 to 10, wherein the provisos to claim 1 do not apply.

15. A compound for use according to claim 13, or a method according to claim 14, wherein the condition is a disorder of the central nervous system.

16. A compound for use or a method according to any of claims 13 to 15, wherein the disorder is selected from schizophrenia, neurodegenerative disorders (such as Alzheimer's Disease), cognitive disorders (such as dementia and schizophrenia), sleep disorders (such as narcolepsy and hypersomnia), pain, obesity, attentional disorders and epilepsy.

17. A composition according to claim 11, comprising one or more additional, pharmaceutically active ingredients.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/000501

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D207/08	C07D207/14
	C07D265/30	C07D401/12
	A61P25/00	A61K31/40
		A61K31/445
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 A61P A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where 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.
X	WO 2008/109154 A1 (METASTATIX INC [US]; CLARK MICHAEL P [US]; LOCKWOOD MARK A [US]; WAGNE) 12 September 2008 (2008-09-12) cited in the application page 249 - page 257; compounds ID, IE, IT-IX, IZ, JF, JO, JQ-JW, JY, KF, KN, KR-KW, LE, LG formula (ID); page 197 page 209; compound H0 -----	1-3,7,9, 11,12,17
X	US 2002/147192 A1 (BRIDGER GARY [US] ET AL) 10 October 2002 (2002-10-10) page 14; compound AMD9367 ----- -/-	1-3,5,7, 9,11,12, 17
☒ 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
27 July 2011		22/08/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Duval, Eric

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/000501

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92/05173 A1 (AGOURON PHARMA [US]) 2 April 1992 (1992-04-02) page 42; compound 11 -----	1,3,8,9, 11,12,17
X	WO 2010/026365 A1 (UNIV DUNDEE [GB]; BRAND STEPHEN [GB]; WYATT PAUL [GB]) 11 March 2010 (2010-03-11) page 100; compound DDD73226 page 111; compound DDD73510 page 113; compound DD85596 page 39 -----	1-5,7,9, 11-17
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 15 September 2009 (2009-09-15), XP002639709, retrieved from STN Database accession no. 1184647-93-5 CAS Registry Number: 1184364-45-1 -----	1,3,8,9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 February 2007 (2007-02-28), XP002639710, retrieved from STN Database accession no. 923887-86-9 the whole document -----	1,3,9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 September 2009 (2009-09-14), XP002653486, retrieved from STN Database accession no. 1184185-62-3 the whole document -----	1,3,8,9
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 September 2009 (2009-09-13), XP002653487, retrieved from STN Database accession no. 1183355-02-3 CAS Registry Numbers: 1183267-98-2, 1183197-13-8 ----- -/--	1,3,8,9

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/000501

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 3 September 2009 (2009-09-03), XP002653488, retrieved from STN Database accession no. 1179594-96-7 the whole document	1,3,8,9
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 September 2009 (2009-09-02), XP002653489, retrieved from STN Database accession no. 1179212-60-2 the whole document	1,3,8,9
X	----- DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 August 2009 (2009-08-31), XP002653490, retrieved from STN Database accession no. 1178286-59-3 the whole document	1,3,8,9
A	----- WO 2008/048609 A1 (ARENA PHARM INC [US]; SANTORA VINCENT J [US]; HART RYAN M [US]; IBARRA) 24 April 2008 (2008-04-24) cited in the application abstract; claim 1 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/000501

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008109154 A1	12-09-2008	US 2008261978 A1	23-10-2008
US 2002147192 A1	10-10-2002	US 2005026942 A1	03-02-2005
WO 9205173 A1	02-04-1992	AU 8628791 A	15-04-1992
		CA 2091690 A1	26-03-1992
		CN 1062908 A	22-07-1992
		EP 0550589 A1	14-07-1993
		JP 6503814 T	28-04-1994
		ZA 9107613 A	26-08-1992
WO 2010026365 A1	11-03-2010	EP 2323987 A1	25-05-2011
WO 2008048609 A1	24-04-2008	AR 063226 A1	14-01-2009
		AT 512948 T	15-07-2011
		AU 2007313180 A1	24-04-2008
		CA 2665204 A1	24-04-2008
		CL 29772007 A1	06-06-2008
		EA 200970386 A1	30-10-2009
		EP 2074086 A1	01-07-2009
		JP 2010506918 A	04-03-2010
		KR 20090069333 A	30-06-2009
		PA 8750901 A1	31-03-2009
		PE 14622008 A1	18-10-2008
		US 2010240653 A1	23-09-2010