

ARYLSULPHONYLSTILBENE DERIVATIVES FOR TREATMENT OF
INSOMNIA AND RELATED CONDITIONS

The present invention relates to a class of sulfonyl derivatives which act on
5 serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More
particularly, the invention concerns arylsulfonylstilbenes and derivatives thereof.
These compounds are potent and selective antagonists of the human 5-HT_{2A} receptor
and are therefore useful as pharmaceutical agents, especially in the treatment and/or
prevention of adverse conditions of the central nervous system, including sleep
10 disorders such as insomnia, psychotic disorders such as schizophrenia and psychiatric
disorders such as anxiety.

Compounds of the invention typically display more effective binding to the
human 5-HT_{2A} receptor than to other human receptors such as D₂, 5HT_{2C} and IKr
receptors. They can therefore be expected to manifest fewer side-effects than
15 compounds which do not discriminate in their binding affinity between such receptors.
In particular these compounds have lower effects on the IKr receptors and there is a
separation of the desired effect from side effects such as cardiac effects.

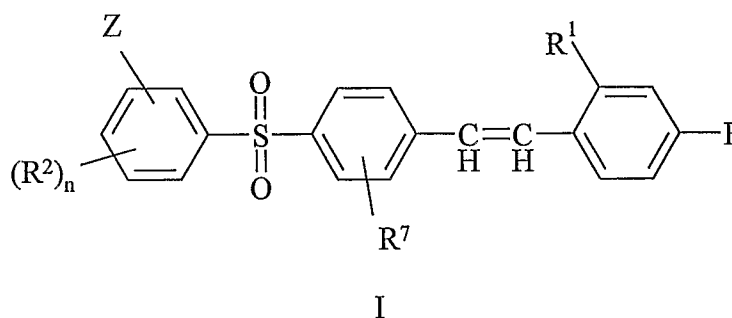
By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the
compounds of the present invention are effective in the treatment of neurological
20 conditions including sleep disorders such as insomnia, psychotic disorders such as
schizophrenia, and also depression, anxiety, panic disorder, obsessive-compulsive
disorder, pain, eating disorders such as anorexia nervosa, and dependency or acute
toxicity associated with narcotic agents such as LSD or MDMA; and moreover are
beneficial in controlling the extrapyramidal symptoms associated with the
25 administration of neuroleptic agents. They may further be effective in the lowering of
intraocular pressure, and may also be effective in treating menopausal symptoms, in
particular hot flushes (see Waldinger et al, *Maturitas*, 2000, **36**, 165-8).

Various classes of compounds containing *inter alia* a sulfonyl moiety are
described in WO 01/74797, WO 2004/101518, WO 2005/047246, WO 00/43362, WO
30 96/35666, EP-A-0261688, EP-0304888, and US Patents 4,218,455 and 4,128,552,
DE-A-3901735 and Fletcher *et al*, *J. Med. Chem.*, 2002, **45**, 492-503. None of these

publications, however, discloses or suggests the particular class of compounds provided by the present invention.

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists, suitably having a human 5-HT_{2A} receptor binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D₂ receptor and/or the human Ikr and/or 5-HT_{2c} receptors. Preferred compounds show selectivities of at least 100-fold relative to the human 5-HT_{2c} receptor.

The present invention provides a compound of formula I:



or a pharmaceutically acceptable salt or hydrate thereof; wherein:

- n is 0 or 1;
- R¹ represents H or F;
- R² represents halogen, CN, CONH₂, C₁₋₄alkyl or C₁₋₄alkoxy;
- R⁷ represents H or C₁₋₄alkyl; and
- Z represents hydroxyC₁₋₆alkyl, or C₁₋₆alkoxycarbonyl, or a 5- or 6-membered heteroaromatic ring which optionally bears a methyl substituent.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "hydroxyC₁₋₆alkyl", and "C₁₋₆alkoxy" are to be construed in an analogous manner.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred and fluorine particularly preferred.

The term "heteroaromatic" as used herein refers to aromatic rings having the indicated number of atoms of which at least one is N, O or S, the remainder being carbon atoms. In the case of 6-membered heteroaromatic rings, one, two or three (preferably one or two) of the ring atoms are nitrogen atoms. In the case of 5-

5 membered heteroaromatic rings, one, two, three or four of the ring atoms are selected from N, O and S with the proviso that not more than one ring atom is O or S.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable

10 salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic

15 acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline

20 earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

When the compounds according to the invention have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds according

25 to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In formula I, R^1 represents H or F. In a particular embodiment, R^1 represents H.

30 In formula I, n is 0 or 1. In a particular embodiment, n is 0. When present, R^2 may be attached at any of the available ring positions, but is preferably in an *ortho*- or *meta*-position relative to the sulfone moiety, most preferably in an *ortho*-position.

Suitable identities for R^2 include halogen (especially fluorine), C_{1-4} alkyl (especially methyl), C_{1-4} alkoxy (such as methoxy), CN and $CONH_2$. In a preferred embodiment, R^2 is either absent or represents methyl.

In formula I, R^7 represents H or C_{1-4} alkyl, and when R^7 represents C_{1-4} alkyl
 5 said alkyl group may be attached at any of the available ring positions, but is most suitably attached in the *ortho*-position relative to the olefinic moiety. Preferably, R^7 represents H or methyl, most preferably H.

The olefinic double bond in formula I may be in either of the geometrical configurations, but is preferably in the *E*-configuration.

10 The group Z may be attached at any of the available ring positions, but is preferably in an *ortho*- or *meta*-position relative to the sulfone moiety, most preferably in an *ortho*-position.

In one embodiment of the invention, Z represents a hydroxy C_{1-6} alkyl group. In this embodiment, the alkyl group may be linear or branched, and preferably contains
 15 up to 4 carbon atoms. The hydroxyl group may be attached at any available position on said alkyl group, to form a primary, secondary or tertiary alkanol. Examples of suitable hydroxy C_{1-6} alkyl groups include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 2-hydroxy-2-propyl, of which 1-hydroxyethyl is particularly suitable. Said 1-hydroxyethyl group is very aptly in the *S*-configuration. Specific
 20 examples of compounds within this embodiment of the invention include:

(1*S*)-1-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol;
 (1*S*)-1-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol;
 (1*S*)-1-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]-3-methylphenyl}sulfonyl)phenyl]ethanol;
 [2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol;
 25 [2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol;
 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]propan-2-ol
 2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]propan-2-ol; and
 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol.

In a second embodiment of the invention, Z represents C_{1-6} alkoxycarbonyl, in
 30 particular C_{1-4} alkoxycarbonyl, such as CO_2Me , CO_2Et and CO_2^iPr . Specific examples of compounds within this second embodiment of the invention include:
 methyl 2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)benzoate;

methyl 2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate;
methyl 3-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate; and
methyl 2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)-3-methylbenzoate.

In a third embodiment of the invention, Z represents a 5- or 6-membered
5 heteroaromatic ring which optionally bears a methyl substituent. Where the group Z
represents an optionally substituted five-membered heteroaromatic ring, this is
preferably a nitrogen-containing ring such as a pyrrole, imidazole, pyrazole, oxazole,
thiazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-thiadiazole,
1,2,3-triazole, 1,2,4-triazole or tetrazole ring, any of which optionally is substituted by
10 methyl. Such rings may be attached via a carbon atom or (when chemically-feasible) a
nitrogen atom, but attachment via carbon is preferred. Suitable examples include
pyrazol-1-yl, imidazol-1-yl, 2-methyl-1,2,4-triazol-3-yl, oxazol-2-yl, thiazol-2-yl,
imidazol-2-yl, 1-methylimidazol-2-yl, pyrazol-3-yl, 1,2,3-triazol-4-yl and 1,3,4-
oxadiazol-2-yl, of which imidazol-2-yl and 1,3,4-oxadiazol-2-yl are particularly
15 suitable.

Where the group Z represents an optionally substituted six-membered
heteroaromatic ring, this is suitably a pyridine, pyrazine, pyrimidine, pyridazine or
triazine ring, any of which optionally is substituted by methyl. Preferably, a 6-
membered heteroaromatic ring represented by Z contains at most 2 nitrogen atoms,
20 and most preferably is pyridyl. Specific examples of 6-membered heteroaromatic ring
represented by Z include 2-pyridyl and 3-pyridyl.

Specific examples of compounds within this third embodiment of the
invention include:

2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole;
25 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole;
2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole;
and
2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole.

The compounds of the present invention have an activity as antagonists of the
30 human 5-HT_{2A} receptor and hence find use in the treatment or prevention of disorders
mediated by 5-HT_{2A} receptor activity.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions,

and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

The present invention also provides a compound of formula I or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition mediated by 5-HT_{2A} receptor activity.

The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a condition mediated by 5-HT_{2A} receptor activity.

Also disclosed is a method of treatment of a subject suffering from or prone to a condition mediated by 5-HT_{2A} receptor activity which comprises administering to that subject an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, the condition mediated by 5-HT_{2A} receptor activity is sleep disorder, in particular insomnia. In a further aspect of the invention, the condition mediated by 5-HT_{2A} receptor activity is selected from psychotic disorders (such as schizophrenia), depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, eating disorders (such as anorexia nervosa), dependency or acute toxicity associated with narcotic agents such as LSD or MDMA, and hot flushes associated with the menopause.

In the treatment envisaged herein, for example of insomnia or schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day but preferably once per day, for example before going to bed.

If desired, the compounds according to this invention may be co-administered with another sleep inducing or anti-schizophrenic or anxiolytic medicament. Such co-administration may be desirable where a patient is already established on sleep inducing or anti-schizophrenic or anxiolytic treatment regime involving other

conventional medicaments. In particular, for the treatment of sleep disorders, the compounds of the invention may be co-administered with a GABA_A receptor agonist such as gaboxadol, or with a short term and/or rapid-onset hypnotic such as zolpidem, or a benzodiazepine, a barbiturate, a prokineticin modulator, an antihistamine, trazodone, or derivative of trazodone as disclosed in WO 03/068148.

According to a further aspect of the invention, there is provided the combination of a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol for use in treatment or prevention of sleep disorders, schizophrenia or depression.

Also according to the invention, there is provided a method of treatment or prevention of sleep disorders, schizophrenia or depression comprising administering to a subject in need thereof a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof in combination with gaboxadol.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol are administered to the subject, but places no restriction on the manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

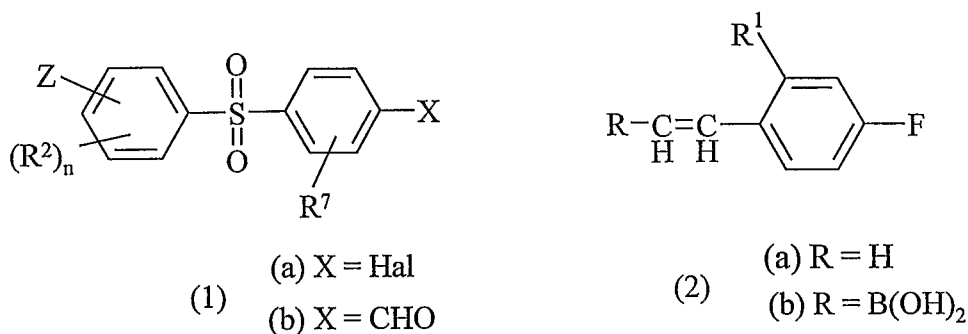
The invention further provides the use, for the manufacture of a medicament for treatment or prevention of sleep disorders, schizophrenia or depression, of a

compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

The invention further provides a kit comprising a first medicament comprising a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and a second medicament comprising gaboxadol together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from a sleep disorder, schizophrenia or depression.

As used herein, the term "gaboxadol" is inclusive of 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol in free base or zwitterionic form and also of pharmaceutically acceptable acid addition salts thereof such as the hydrochloride salt. Most suitably, gaboxadol is in the form of a crystalline monohydrate of the zwitterionic form.

Compounds of formula I may be obtained by reacting a compound of formula (1a) with a styrene of formula (2a):



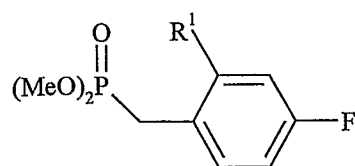
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where Hal represents Cl or Br or I and all other variables have the same meanings as before. The reaction takes place at elevated temperature (e.g. 130°C) in 1-methylpyrrolidone in the presence of palladium acetate and sodium acetate. "Hal" is preferably Br.

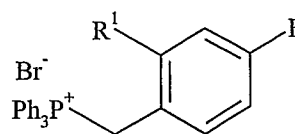
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Alternatively, the compound of formula (1a) may be reacted with a boronic acid derivative (2b), typically in THF solution in the presence of (PPh₃)₄Pd(0) and a base such as sodium carbonate with heating (e.g. to 150°C via microwave irradiation).

In a further alternative, an aldehyde of formula (1b) is coupled with a benzylphosphonate such as (3a) or a benzylphosphonium salt such as (3b):



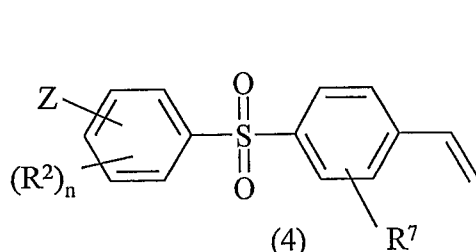
(3a)



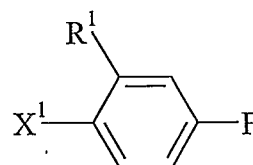
(3b)

where R^1 has the same meaning as before. The reaction may be carried out in THF in the presence of strong base such as BuLi or the combination of sodium hydride with a crown ether.

- 5 In a further alternative, a compound of formula (1a) may be treated with tributyl(vinyl)tin to provide an alkene (4) which may be coupled with a bromobenzene or iodobenzene (5):



(4)

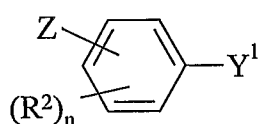


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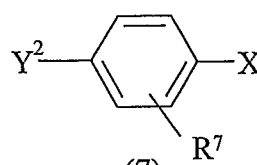
where X^1 represents Br or I and all other variables have the same meanings as before.

- 10 The coupling takes place under similar conditions to the coupling of (1a) with (2a).

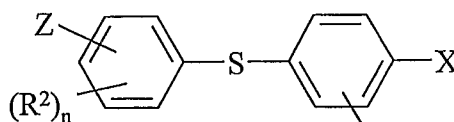
Compounds of formula (1a) and (1b) are obtainable by reaction of compounds (6) with compounds (7) followed by oxidation of the resulting thioether (8):



(6)



(7)



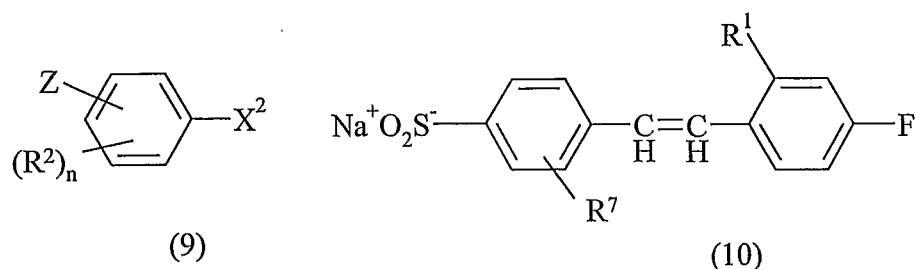
(8)

- 15 where either Y^1 is I and Y^2 is SH or Y^1 is SH and Y^2 is I, and all other variables have the same meanings as before. Formation of thioethers (8) takes place in the presence of CuI and ethylene glycol and a base such as potassium carbonate in a solvent such as

isopropanol. Oxidation of thioethers (8) with two or more equivalents of oxidant (e.g. m-chloroperoxybenzoic acid or oxone) provides sulfones (1a).

Alternatively, the sulfones (1a) may be obtained directly by the reaction between a compound of formula (6) and a compound of formula (7) wherein one of Y^1 and Y^2 is I or Br (preferably I) and the other is SO_2Na^+ . This reaction may be carried out in a polar aprotic solvent such as DMSO at elevated temperature (e.g. at about 110°C) in the presence of a Cu(I) salt such as the iodide or triflate. Preferably, about 3 molar equivalents of the Cu(I) salt are used.

It will be readily apparent that it is possible to vary the order in which the reaction steps outlined above are carried out. For example, it is possible to couple a compound of formula (2a), (2b), (3a) or (3b) with a compound of formula (7) ($X=Hal$ or CHO as appropriate) and to react the product with a compound of formula (6) under similar conditions to those outlined above. Thus, a preferred synthesis of the compounds of formula I comprises reaction of a bromo- or iodobenzene derivative (9) with a stilbenesulfinic acid salt (10):



where X^2 represents Br or I and all other variables have the same meanings as before. Preferably, X^2 represents I and the reaction is carried out in DMSO at about 110°C in the presence of CuI. The stilbene derivatives (10) may be prepared by coupling of compounds (2a), (2b), (3a) or (3b) with compounds of formula (7) wherein Y^2 represents SO_2Na^+ and X represents Hal or CHO as appropriate. During said coupling, the SO_2Na^+ group is preferably protected as the adduct with acrylonitrile. This may be achieved by reacting the relevant compound of formula (7) ($Y^2 = SO_2Na^+$) with 2 equivalents of acrylonitrile in a mixture of acetic acid and water at 100°C to form the corresponding arylsulfonylpropanenitrile. After coupling, the SO_2Na^+ functionality may be regenerated by treatment with alkoxide, e.g. sodium

methoxide, at ambient temperature in an alcohol solvent, e.g. a methanol/THF mixture.

Where they are not themselves commercially available, the starting materials and reagents described above may be obtained from commercially available precursors by means of well known synthetic procedures. Suitable methods are disclosed in the Examples section herein. Thus, compounds of formula (6) or formula (9) in which Z represents hydroxyC₁₋₆alkyl may be prepared (if necessary) by reduction of the corresponding compounds in which Z represents the appropriate aldehyde or ketone with sodium borohydride or by reaction of the appropriate aldehyde or ketone with the appropriate alkyl Grignard reagent. Compounds of formula (6) or formula (9) in which Z represents a 5-membered heteroaromatic ring bonded through N may be prepared (if necessary) by reaction of the corresponding compounds in which Z represents F with the appropriate N-heterocycle (e.g. by heating in DMSO solution). Compounds of formula (6) or formula (9) in which Z represents a 5- or 6-membered heteroaromatic ring bonded through C may be prepared (if necessary) by reaction of the corresponding compounds in which Z represents Br or I with the appropriate heteroarylzinc or heteroaryltributylstannane derivative, typically with heating in an aprotic solvent such as DMF in the presence of a catalyst such as (Ph₃P)₄Pd(0). Alternatively, a 5- or 6-membered heteroaromatic ring represented by Z may be constructed using conventional techniques of heterocyclic synthesis. For example, a methoxycarbonyl or ethoxycarbonyl group represented by Z may be converted to a 1,3,4-oxadiazol-2-yl group by sequential treatment with hydrazine hydrate and triethylorthoformate. Similarly, compounds in which Z represents 1,2,3-triazol-4-yl may be obtained by treatment of corresponding compounds in which Z is ethynyl with azidotrimethylsilane (e.g. in a sealed tube at 150°C overnight). Similarly, compounds in which Z represents 1,2,4-triazol-3-yl may be obtained by treatment of corresponding compounds in which Z is CN with 4*H*-1,2,4-triazol-4-amine and sodium ethoxide in refluxing ethanol, followed by reaction of the resulting N'-4*H*-1,2,4-triazol-4-yl carboximidamide with ethyl chloroformate (e.g. in refluxing acetonitrile). Similarly, compounds in which Z represents thiazol-2-yl may be obtained by treatment of corresponding compounds in which Z is C(S)NH₂ with bromoacetaldehyde or its diethyl acetal (e.g. in refluxing ethanol). Similarly,

compounds in which Z represents 2-pyridyl may be obtained by diazotisation of corresponding compounds in which Z is NH₂ and treatment of the resulting diazonium salts with excess pyridine (e.g. at 80°C).

5 It will be readily apparent that the above-described transformations of the substituent Z may be carried out as a final step in the synthesis of compounds of formula I if desired.

Similarly, the identity of R² (when present) in the compounds of formula I or their precursors may be altered using standard synthetic techniques. For example, compounds in which R² is CN may be obtained from the corresponding compounds in which R² is Br by treatment with ZnCN in the presence of (Ph₃P)₄Pd(0), and the
10 resulting nitriles may be converted to the corresponding carboxamides (R² = CONH₂) by acid hydrolysis or by treatment with potassium trimethylsilanolate (e.g. in refluxing tetrahydrofuran).

Where the above-described processes for the preparation of the compounds of
15 use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques
20 such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as di-*p*-toluoyl-D-tartaric acid and/or di-*p*-toluoyl-L-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

25 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic*
30 *Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Compounds were tested for their binding to the 5-HT_{2A} receptor and to other receptors such as 5-HT_{2C} and IKr using the methodology described in Fletcher *et al*, *J. Med. Chem.*, 2002, **45**, 492-503.

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EXAMPLES

Intermediate 1

Sodium 4-[(*E*)-2-(4-fluorophenyl)vinyl]benzenesulfinate

Step 1

- 10 To a suspension of sodium 4-bromophenylsulfinate dihydrate (130 g, 0.53 mol) in water (600 mL) was added acrylonitrile (70 mL, 1.07 mol) and acetic acid (62 mL, 1.07 mol). The reaction was stirred for 1.5 h at 100 °C then cooled to room temperature. The solid was filtered off, washed thoroughly with water and dried over P₂O₅ to give 3-[(4-bromophenyl)sulfonyl]propanenitrile (125 g). δ_H (400 MHz, CDCl₃): 7.27-7.22 (4H, m), 2.85 (2H, t, J 7.6), 2.30 (2H, t, J 7.6).
- 15

Step 2

- To a suspension of sodium acetate (54 g, 0.66 mol) and 4-fluorostyrene (90 g, 0.74 mol) in 1-methyl-2-pyrrolidinone (500 mL) was added 3-[(4-bromophenyl)sulfonyl]propanenitrile (Step 1, 90 g, 0.33 mol) and palladium (II) acetate (1.4 g, 6.2 mmol). The mixture was plunged into an oil-bath at 100 °C and heated to 135 °C for 20 minutes. The cooled reaction mixture was diluted with water and EtOAc and filtered through Hyflo[®]. The organic layer of the filtrate was washed with water (x3) then concentrated *in vacuo*. The residue was triturated with isohexane to give 3-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)propanenitrile (73 g). δ_H (360 MHz, CDCl₃): 7.88 (2H, d, J 8.0), 7.69 (2H, d, J 8.3), 7.51 (2H, dd, J 5.6, 8.3), 7.22 (1H, d, J 15.0), 7.10-7.02 (3H, m), 3.39 (2H, t, J 7.7), 2.83 (2H, t, J 7.7).
- 20
- 25

Step 3

- To a mixture of 3-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)propanenitrile (Step 2, 75 g, 0.24 mol) in THF (1 L) and MeOH (500 mL) was added sodium methoxide (13 g, 0.24 mol). The mixture was stirred for 1 h at room temperature then diluted with isohexane and Et₂O. The solid was filtered off, triturated with isohexane and dried under vacuum to give sodium 4-[(*E*)-2-(4-
- 30

fluorophenyl)vinyl]benzenesulfinate (66 g). δ_H (500 MHz, d^6 DMSO): 7.65 (2H, t, J 6.8), 7.53 (2H, d, J 7.8), 7.45 (2H, d, J 7.7), 7.26-7.18 (4H, m). m/z (ES⁺) 261 [(M-Na)⁺].

5 Intermediate 2

Sodium 4-[(*E*)-2-(2,4-difluorophenyl)vinyl]benzenesulfinate

Prepared in the same manner as Intermediate 1 using 2,4-difluorostyrene in place of 4-fluorostyrene in Step 2. δ_H (400 MHz, d^6 DMSO): 7.84 (1H, q, J 8.1), 7.55 (2H, d, J 8.0), 7.47 (2H, d, J 8.0), 7.32-7.20 (3H, m), 7.15-7.11 (1H, m). m/z (ES⁺) 279 [(M-Na)⁺].

Example 1

(1*S*)-1-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol

Step 1

15 To each of three identical Emrys microwave reaction vessels was added (*S*)-1-(2-bromophenyl)ethanol (1.67g, 8.3 mmol), CuI (189mg, 1.0 mmol), 1,4-dioxane (12.4 ml), *N,N'*-dimethylethylenediamine (0.18 ml, 1.7 mmol) and sodium iodide dihydrate (3.1 g, 16.6 mmol). Each vessel was sealed and heated in an Emrys microwave reactor to 150 °C for 2 h. On cooling, the mixtures were combined and partitioned
20 between water (20 ml) and EtOAc (20 ml). The organic phase was washed with brine (20 ml), dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was taken up in isohexane (50 ml) and the solution held at -15 °C for 16 h to afford (*S*)-1-(2-iodophenyl)ethanol as a white crystalline solid (4.95 g).

Step 2

25 A suspension of (*S*)-1-(2-iodophenyl)ethanol (Step 1; 4.4 g, 17.7 mmol), Intermediate 1 (5.54 g, 19.5 mmol), CuI (10.1 g, 53.0 mmol) and DMSO (80 ml) was degassed by repeated evacuation and release to N₂, then heated in an oil bath at 110 °C for 75 minutes. The cooled mixture was partitioned between concentrated ammonium hydroxide solution (100 ml) and EtOAc (100 ml), and the aqueous phase extracted
30 with further EtOAc (50 ml). The combined organics were washed with water (2x100 ml) and brine (100 ml), dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica (eluant 25 to 35 to 45 %

EtOAc/isohexane) and then again with 5% Et₂O/CH₂Cl₂. The resulting foam was stirred with pentane for 1 h to afford the pure product as a white amorphous solid (3.97 g). The material was recrystallised from a *circa* 90% MeOH/water mixture to afford colourless crystals; m.p. 75 °C. δ_{H} (500 MHz, d⁶ DMSO): 8.02 (1H, d, J 7.3), 7.81-7.78 (5H, m), 7.73-7.67 (3H, m), 7.52 (1H, t, J 7.2), 7.43 (1H, d, J 16.5), 7.29 (1H, d, J 16.4), 7.22 (2H, t, J 8.8), 5.44-5.40 (1H, m), 5.28 (1H, d, J 4.0), 1.09 (3H, d, J 6.2); m/z (ES⁺) 365 [(M-OH)⁺].

Example 2

(1S)-1-[2-({4-[(E)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol
Prepared as described in Example 1, substituting Intermediate 2 for Intermediate 1
 δ_{H} (500 MHz, d⁶ DMSO): 8.03 (1H, d, J 7.9), 7.90-7.80 (6H, m), 7.72 (1H, t, J 7.4), 7.53 (1H, t, J 7.7), 7.40 (2H, q, J 12.7), 7.34-7.28 (1H, m), 7.16 (1H, t, J 8.5), 5.43-5.39 (1H, m), 5.30 (1H, d, J 4.0), 1.09 (3H, d, J 6.2). m/z (ES⁺) 383 [(M-OH)⁺]

Example 3

(1S)-1-[2-({4-[(E)-2-(4-fluorophenyl)vinyl]-3-methylphenyl}sulfonyl)phenyl]ethanol

Step 1

4-Bromo-3-methylbenzenesulfonyl chloride (1.145 g, 4.25 mmol) was added portion wise to a solution of sodium sulfite (0.578 g, 2.29 mmol) and sodium hydrogen carbonate (0.749 g, 2.4 mmol) in water (10 mL) at 80 °C. The reaction was heated to 90 °C for 3 h. The cooled reaction mixture was evaporated *in vacuo* to half-volume, at which point a precipitate appeared. This was removed by filtration. The filtrate was concentrated further then cooled to 5 °C and the precipitate removed by filtration. The combined residues were washed with water and dried to give sodium 4-bromo-3-methylbenzenesulfinate (0.54 g).

Step 2

(1S)-1-[2-({4-bromo-3-methylphenyl}sulfonyl)phenyl]ethanol was prepared as described in Example 1 Step 2 using sodium 4-bromo-3-methylbenzenesulfinate in place of Intermediate 1.

Step 3

An Emrys microwave vial containing (1*S*)-1-[2-({4-bromo-3-methylphenyl}sulfonyl)phenyl]ethanol (71 mg, 0.2 mmol), [(*E*)-2-(4-fluorophenyl)vinyl]boronic acid (43 mg, 0.26 mmol), *tetrakis*(triphenylphosphine) palladium (0) (23 mg, 0.020 mmol), THF (2 mL) and 2M aqueous sodium carbonate (1 mL) was heated in an Emrys microwave reactor at 150 °C for 10 minutes. On cooling, the mixture was partitioned between EtOAc (15 mL) and water (15 mL) and the organic phase was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica (eluant 30% EtOAc/isohexane) to afford the title compound as a white solid (45 mg). δ_H (500 MHz, d⁶ DMSO): 8.01 (1H, d, J 7.9), 7.88 (1H, d, J 8.2), 7.80 (1H, d, J 7.8), 7.73-7.63 (5H, m), 7.52 (1H, t, J 7.6), 7.37 (1H, d, J 16.3), 7.29 (1H, d, J 16.2), 7.22 (2H, t, J 8.7), 5.45 (1H, s), 5.30 (1H, s), 2.46 (3H, s), 1.11 (3H, d, J 5.9). m/z (ES⁺) 379 [(M-OH)⁺].

Example 4

[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol

Step 1

2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)benzaldehyde was prepared according to the method of Example 1, Step 2 using 2-iodobenzaldehyde in place of (*S*)-1-(2-iodophenyl)ethanol and Intermediate 2 in place of Intermediate 1.

Step 2

Sodium borohydride (89 mg, 1.8 mmol) was added to a solution of 2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)benzaldehyde (Step 1; 233 mg, 0.61 mmol) in MeOH (7 mL) and CH₂Cl₂ (3 mL). After 2 h, the mixture was partitioned between CH₂Cl₂ (10 mL) and water (10 mL), the phases were separated and the aqueous portion extracted with further CH₂Cl₂ (10 mL). The combined organics were then dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (eluant 40% EtOAc/isohexane) gave the title compound as a white solid (208 mg). δ_H (500 MHz, d⁶ DMSO): 8.08 (1H, d, J 7.7), 7.89-7.83 (5H, m), 7.77 (1H, d, J 7.6), 7.72 (1H, t, J 7.4), 7.55 (1H, t, J 7.5), 7.42-7.34 (2H, m), 7.33-7.27 (1H,

m), 7.15 (1H, td, J 2.1, 8.4), 5.39 (1H, t, J 5.7), 4.69 (2H, d, J 5.7). m/z (ES^+) 369 [(M-OH) $^+$].

Example 5

5 [2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol

Prepared according to the method of Example 4 using Intermediate 1 in place of Intermediate 2. δ_H (400 MHz, d^6 DMSO): 8.10 (1H, dd, J 1.0, 7.8), 7.86-7.68 (8H, m), 7.57-7.55 (1H, m), 7.44 (1H, d, J 16.5), 7.32-7.22 (3H, m), 5.41 (1H, t, J 5.7), 4.72 (2H, d, J 5.7). m/z (ES^+) 351 [(M-OH) $^+$].

10

Example 6

2-[2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]propan-2-ol

Step 1

(1S)-1-[2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol (Example
15 1; 100 mg, 0.26 mmol), *N*-methylmorpholine-*N*-oxide (46 mg, 0.39 mmol), 4 Å
activated molecular sieves (100 mg) and CH_2Cl_2 (2.6 mL) were combined under N_2
and stirred for 20 minutes prior to addition of tetra(*n*-propyl)ammonium perruthenate
(4.6 mg, 0.013 mmol). After a further 20 minutes, the mixture purified by flash
chromatography (eluant 40% EtOAc/isohexane) to afford 1-[2-({4-[(E)-2-(4-
20 fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanone as a white solid (84 mg). δ_H (400
MHz, d^6 DMSO): 8.10 (1H, d, J 7.8), 7.88 (2H, d, J 8.5), 7.80 (3H, dd, J 0.0, 8.7),
7.72-7.68 (3H, m), 7.62 (1H, d, J 6.6), 7.46 (1H, d, J 16.5), 7.32-7.22 (3H, m), 2.61
(3H, s). m/z (ES^+) 380 [MH $^+$].

Step 2

25 A stirred THF (1 mL) solution of 1-[2-({4-[(E)-2-(2,4-
difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanone (Step 1; 65 mg, 0.17 mmol)
was treated with methyl magnesium bromide (3 N in Et_2O ; 0.17 mL, 0.51 mmol) at
ambient temperature. After 75 minutes, the mixture was partitioned between water
(20 mL) and EtOAc (20 mL). The phases were separated and the organic phase dried
30 ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash
chromatography on silica (eluant 35% EtOAc/isohexane). The material thus obtained
was washed with hexane to afford the title compound as a white solid (53 mg). δ_H

(500 MHz, d^6 DMSO): 8.25 (1H, d, J 8.1), 7.71-7.64 (8H, m), 7.53 (1H, t, J 6.1), 7.40 (1H, d, J 16.4), 7.30-7.22 (3H, m), 4.98 (1H, s), 1.56 (6H, s). m/z (ES^+) 419 $[(M+Na)^+]$.

5 **Example 7**

2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol

Step 1

In each of two identical vessels, a mixture of 2-(2-bromophenyl)ethanol (750 mg, 3.7 mmol), sodium iodide dihydrate (1.39 g, 7.5 mmol), CuI (71.0 mg, 0.37 mmol) and
10 *N,N'*-dimethylethylenediamine (79.4 μ L, 65.8 mg, 0.75 mmol) in 1,4-dioxane (8 mL) was heated to 150 °C in a microwave reactor for 4 h. The two reaction mixtures were combined, diluted with water (90 mL) and concentrated ammonium hydroxide (20 mL), then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL) then brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow oil (1.62 g) was found to be a 3:1 mixture of 2-(2-iodophenyl)ethanol : 2-(2-bromophenyl)ethanol and was used without further purification. Data for major compound: δ_H (360 MHz, $CDCl_3$): 7.84 (1H, d, J 8.2), 7.32-7.24 (2H, m), 6.94-6.86 (1H, m), 3.87 (2H, br s), 3.02 (2H, t, J 7.0), 1.43 (1H, s).

Step 2

20 The 3 : 1 mixture of 2-(2-iodophenyl)ethanol : 2-(2-bromophenyl)ethanol (Step 1; 200 mg) was reacted with Intermediate 1 (275 mg, 0.97 mmol) and CuI (461 mg, 2.4 mmol) in DMSO (5 mL) by the procedure of Example 1 Step 2. The crude product was purified by flash chromatography on silica (eluant 25% then 40% EtOAc/isohexane) yielding the title compound as a white solid (65 mg): δ_H (400 MHz, $CDCl_3$): 8.16 (1H, d, J 8.0), 7.84 (2H, d, J 8.4), 7.61-7.37 (7H, m), 7.17 (1H, d, J 16.3), 7.07 (2H, t, J 8.6), 7.00 (1H, d, J 16.3), 3.83 (2H, q, J 6.2), 3.14 (2H, t, J 6.5), 1.99 (1H, t, J 5.7). m/z (ES^+) 365 $[(M-OH)^+]$.

Example 8

30 Methyl 2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)benzoate

Step 1

Methyl 2-[(4-bromophenyl)sulfonyl]benzoate was prepared according to the method of Example 1, Step 2 using methyl 2-bromobenzoate (2.8 mL, 20 mmol) in place of (S)-1-(2-iodophenyl)ethanol and sodium 4-bromophenylsulfinate dihydrate (5.6 g, 20 mmol) in place of Intermediate 1, together with CuI (19 g, 100 mmol) and DMSO (40 mL), affording product as a white solid (3.8 g).

Step 2

1-Ethynyl-2,4-difluorobenzene (9.6 g, 69.5 mmol) was warmed to 40 °C and catechol borane (8.3 g, 69.2 mmol) was added. The dark reaction mixture was stirred at 40 °C for 3 h before stirring at 80 °C for 24 h. Room temperature was attained and the mixture left to stand for 2 days. Water was added and the resulting dark solid collected by filtration. The solid was washed on the sinter with toluene to leave a beige solid, identified as [(E)-2-(2,4-difluorophenyl)vinyl]boronic acid and a mixture of anhydrides (3.8 g).

Step 3

The title compound was prepared according to the method described in Example 3, Step 3 using methyl 2-[(4-bromophenyl)sulfonyl]benzoate (Step 1) in place of (1S)-1-[2-(4-bromo-3-methylphenyl)sulfonyl]phenylethanol and [(E)-2-(2,4-difluorophenyl)vinyl]boronic acid (Step 2) in place of [(E)-2-(4-fluorophenyl)vinyl]boronic acid. δ_H (500 MHz, d^6 DMSO): 8.22-8.20 (1H, m), 7.94-7.80 (7H, m), 7.69-7.63 (1H, m), 7.44 (1H, d, J 16.4), 7.39 (1H, d, J 16.4), 7.35-7.30 (1H, m), 7.19-7.15 (1H, m), 3.87 (3H, s). m/z (ES^+) 383 [(M-MeO) $^+$].

Example 9

Methyl 2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate

A suspension of the methyl 2-iodobenzoate (8.8 mL, 60 mmol), Intermediate 1 (20.4 g, 72 mmol) and CuI (17.1 g, 90 mmol) in DMSO (300 mL) was degassed by repeated evacuation and release to N₂, then heated in an oil bath at 100 °C for 4 h. The cooled mixture was partitioned between water (1 L) and EtOAc (600 mL) and the dense suspension stirred for 10 minutes before being filtered through a plug of Hyflo[®]. The residue was extracted with EtOAc (400 mL) and the filtrate transferred to a separating funnel containing aqueous ammonium hydroxide solution (200 mL). The phases were separated and the aqueous phase extracted with EtOAc (twice). The combined

organic fractions were washed with water, then brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product loaded onto silica and purified by flash chromatography (eluant 1% Et₂O/CH₂Cl₂) and the resulting material recrystallised from 50% EtOAc/hexane to afford the title compound as colourless crystals (13.9 g);
5 m.p. 125 °C. δ_H (500 MHz, d⁶ DMSO): 8.22-8.20 (1H, m), 7.93 (2H, d, J 8.5), 7.84-7.78 (4H, m), 7.72-7.66 (3H, m), 7.46 (1H, d, J 16.4), 7.30 (1H, d, J 16.4) 7.27-7.21 (2H, m), 3.86 (3H, s). m/z (ES⁺) 365 [(M-MeO)⁺].

Example 10

10 Methyl 3-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate

Prepared according to the method of Example 8, Step 1 using methyl 3-bromobenzoate, in place of methyl 2-bromobenzoate, and Intermediate 1 in place of sodium 4-bromophenylsulfinate dihydrate. δ_H (500 MHz, d⁶ DMSO): 8.42 (1H, s), 8.25 (2H, dd, J 8.0, 12.9), 7.98 (2H, t, J 8.0), 7.83-7.79 (3H, m), 7.70 (2H, dd, J 5.7,
15 8.7), 7.45 (1H, d, J 16.4), 7.31-7.23 (3H, m), 3.90 (3H, s). m/z (ES⁺) 397 [MH⁺].

Example 11

Methyl 2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)-3-methylbenzoate

Prepared according to the method of Example 9 using methyl 2-iodo-3-methylbenzoate in place of methyl 2-iodobenzoate. δ_H (400 MHz, d⁶ DMSO): 7.95 (2H, d, J 8.5), 7.85 (2H, d, J 8.6), 7.71-7.67 (3H, m), 7.48 (3H, dd, J 6.7, 12.9), 7.31 (1H, d, J 16.5), 7.25 (2H, t, J 8.9), 3.89 (3H, s), 2.43 (3H, s). m/z (ES⁺) 433 [(M+Na)⁺].

25 Example 12

2-[2-({4-[(E)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1H-imidazole **Step 1**

2-(2-bromophenyl)-1H-imidazole (WO 9407486; 1.0 g, 4.48 mmol) was dissolved in THF (11 mL) and DMF (11 mL) and cooled to 0 °C. Sodium hydride (60% dispersion
30 in mineral oil, 197 mg, 4.93 mol) was added and the reaction stirred for 20 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (0.79 mL, 4.93 mmol) was added and the reaction stirred overnight at room temperature. The reaction was quenched with

MeOH then partitioned between water and Et₂O. The organic layer was dried (MgSO₄) and concentrated *in vacuo* and the residue was purified by flash column chromatography to afford 2-(2-bromophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole as an off-white solid (1.5 g).

5 Step 2

2-[2-({4-[(*E*)-2-(2,4-Difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole was prepared according to the method of Example 1 using 2-(2-bromophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (Step 1) in place of (*S*)-1-(2-iodophenyl)ethanol and Intermediate 2 in place of Intermediate 1.

10 Step 3

A solution of 2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (Step 2, 110 mg) in CH₂Cl₂ (5 mL) was treated with trifluoroacetic acid (5 mL) and the solution stirred for 16 h, then concentrated *in vacuo* and partitioned between saturated aqueous NaHCO₃ (20 mL) and EtOAc (20 mL). The phases were separated and the organic phase dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (eluant 75% EtOAc/isohexane) to afford a colourless oil, which solidified on treatment with Et₂O. The solid was washed with 50% EtOAc/isohexane and dried, to afford the title compound as a white solid (47 mg). δ_{H} (500 MHz, d⁶ DMSO): 12.11 (1H, s), 8.25 (1H, t, J 4.6), 7.85 (1H, q, J 8.1), 7.77-7.71 (2H, m), 7.69 (2H, d, J 8.4), 7.58 (2H, d, J 8.4), 7.51 (1H, t, J 4.4), 7.39-7.29 (3H, m), 7.23 (1H, s), 7.15 (1H, td, J 2.5, 8.5), 6.94 (1H, s); *m/z* (ES⁺) 422 [MH⁺].

25 Example 13

2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole

Prepared according to the method of Example 9 using 2-(2-bromophenyl)-1*H*-imidazole (WO 9407486; 1.0 g, 4.48 mmol) in place of methyl 2-iodobenzoate. δ_{H} (500 MHz, CDCl₃): 11.08 (1H, s), 8.35 (1H, d, J 8.0), 8.02 (1H, d, J 7.7), 7.69-7.67 (1H, m), 7.60 (1H, t, J 7.7), 7.46-7.38 (6H, m), 7.18 (1H, s), 7.10-7.03 (4H, m), 6.89 (1H, d, J 16.3). *m/z* (ES⁺) 405 [MH⁺].

Example 14**2-[2-({4-[(E)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole****Step 1**

5 Methyl 2-[(4-bromophenyl)sulfonyl]benzoate (Example 8 Step 1; 150 mg, 0.46 mmol) and hydrazine hydrate (0.06 mL, 2.32 mmol) were stirred together at room temperature for 1.5 h then at 90 °C for 2 h. The excess hydrazine was removed *in vacuo* and the residue was dissolved in triethylorthoformate (4.6 mL) with catalytic camphorsulfonic acid and the mixture heated at 90 °C overnight. The cooled reaction
10 mixture was partitioned between EtOAc and water and the organic layer was washed with brine and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica (eluant 50% EtOAc/isohexane) to yield 2-{2-[(4-bromophenyl)sulfonyl]phenyl}-1,3,4-oxadiazole (60 mg, 35%). δ_{H} (400 MHz, d^6 DMSO): 9.42 (1H, s), 8.35-8.33 (1H, m), 7.97-7.91 (2H, m), 7.86-7.84 (3H, m), 7.80-
15 7.78 (2H, m).

Step 2

The title compound was prepared according to the method of preparation of Intermediate 1, Step 2, using 2-{2-[(4-bromophenyl)sulfonyl]phenyl}-1,3,4-oxadiazole (Step 1) in place of 3-[(4-bromophenyl)sulfonyl]propanenitrile and 2,4-
20 difluorostyrene in place of 4-fluorostyrene. δ_{H} (500 MHz, d^6 DMSO): 9.45 (1H, s), 8.35 (1H, d, J 7.8), 7.97-7.85 (8H, m), 7.47-7.31 (3H, m), 7.17 (1H, t, J 8.6). m/z (ES^+) 425 [MH^+].

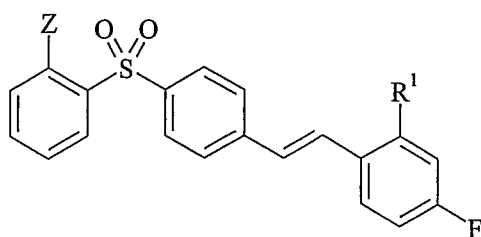
Example 15

25 **2-[2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole**
Prepared from methyl 2-({4-[(E)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate (Example 9) according to the method of Example 14 Step 1. δ_{H} (400 MHz, d^6 DMSO): 9.48 (1H, s), 8.36 (1H, dd, J 1.3, 8.0), 8.00-7.82 (7H, m), 7.74-7.70 (2H, m), 7.49 (1H, d, J 16.5), 7.34-7.24 (3H, m); m/z (ES^+) 407 [MH^+].

30

Examples 16 – 25

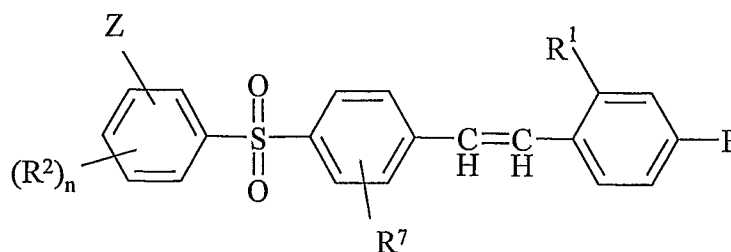
The following were prepared by methods analogous to those of Examples 12 and 13:



Example	R ¹	Z	<i>m/z</i> (ES ⁺) [MH ⁺]
16	H	thiazol-2-yl	422
17	H	1-Me-imidazol-2-yl	437
18	H	pyrazol-3-yl	405
19	F	pyrazol-3-yl	423
20	F	1,2,4-triazol-3-yl	424
21	H	1,2,4-triazol-3-yl	406
22	F	oxazol-2-yl	424
23	F	1,2,3-triazol-4-yl	424
24	F	2-pyridyl	434
25	H	3-pyridyl	416

CLAIMS

1. A compound of formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof; wherein:

n is 0 or 1;

R¹ represents H or F;

R² represents halogen, CN, CONH₂, C₁-₄alkyl or C₁-₄alkoxy;

R⁷ represents H or C₁-₄alkyl; and

Z represents hydroxyC₁-₆alkyl, or C₁-₆alkoxycarbonyl, or a 5- or 6-membered heteroaromatic ring which optionally bears a methyl substituent.

2. A compound according to claim 1 wherein Z represents hydroxyC₁-

₆alkyl.

3. A compound according to claim 1 wherein Z represents C₁-

₆alkoxycarbonyl.

4. A compound according to claim 1 wherein Z represents a 5- or 6-

membered heteroaromatic ring which optionally bears a methyl substituent.

5. A compound according to any previous claim wherein Z is *ortho* to the sulfone moiety in formula I.

6. A compound according to claim 1 selected from:

(1*S*)-1-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol;

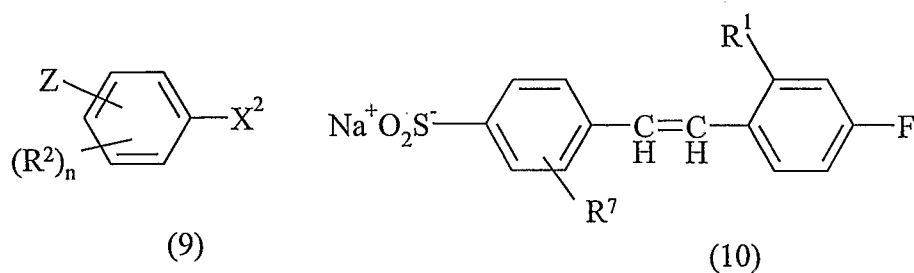
(1*S*)-1-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol;

- (1*S*)-1-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]-3-methylphenyl}sulfonyl)phenyl]ethanol;
 [2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol;
 [2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]methanol;
 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]propan-2-ol
 5 2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]propan-2-ol;
 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]ethanol;
 methyl 2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)benzoate;
 methyl 2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate;
 methyl 3-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)benzoate;
 10 — methyl 2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)-3-methylbenzoate;
 2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole;
 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole;
 2-[2-({4-[(*E*)-2-(2,4-difluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole;
 and
 15 2-[2-({4-[(*E*)-2-(4-fluorophenyl)vinyl]phenyl}sulfonyl)phenyl]-1,3,4-oxadiazole;
 and pharmaceutically acceptable salts and hydrates thereof.

7. A pharmaceutical composition comprising a compound according to any previous claim and a pharmaceutically acceptable carrier.
 20
8. A compound according to any of claims 1-6 for use in treatment of the human body.
9. The use of a compound according to any of claims 1-6 for the
 25 manufacture of a medicament for treatment of a condition mediated by 5-HT_{2A} receptor activity.
10. A pharmaceutical composition according to claim 7 which additionally comprises gaboxadol.

11. The combination of a compound according to any of claims 1-6 and gaboxadol for use in treatment or prevention of sleep disorders, schizophrenia or depression.

5 12. A process for preparing a compound of formula I as defined in claim 1 comprising reaction of a bromo- or iodobenzene derivative (9) with a stilbenesulfinic acid salt (10):



10 where X^2 represents Br or I and R^1 , R^2 , R^7 , n and Z are as defined in claim 1.