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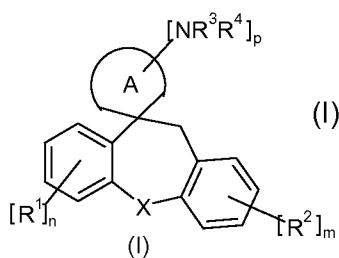
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(54) Title: SPIRO COMPOUNDS USEFUL AS ANTAGONISTS OF THE H1 RECEPTOR



(57) Abstract: The invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for treating diseases and conditions of the central nervous system (CNS), in particular sleep disorders.

SPIRO COMPOUNDS USEFUL AS ANTAGONISTS OF THE H₁ RECEPTOR

This invention relates to novel spiro derivatives. The invention also relates to the use of the derivatives in treating diseases and conditions of the central nervous system (CNS), in particular sleep disorders. In addition, the invention relates to compositions containing the derivatives and processes for their preparation.

Common symptoms for those suffering with a sleep disorder include abnormal sleep behaviour and difficulties in one or more of falling asleep, remaining asleep, sleeping for adequate lengths of time and achievement of restorative sleep.

Available treatments for sleep disorders include the use of prescription hypnotics, e.g., benzodiazepines. However, these may be habit-forming, lose their effectiveness after extended use, and metabolise more slowly for certain designated groups, resulting in persisting medicative effects.

Other treatments include over-the-counter antihistamines, e.g., diphenhydramine or dimenhydrinate. These are not designed to be strictly sedative in their activity and as such, this method of treatment has been associated with a number of adverse side effects, e.g., persistence of the sedating medication after the prescribed time of treatment, or the so-called "hangover effect". Many of these side effects result from nonspecific activity in both the periphery as well as the CNS during this period of extended medication.

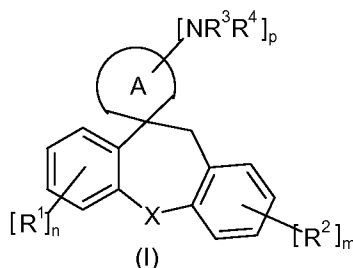
Therefore, a need exists for the development of new compounds useful for the improved treatment of sleep disorders.

It has been suggested that brain histamine is involved in the regulation of the sleep-wake cycle, arousal, cognition and memory mainly through H₁ receptors, producing a reduction of the sleep latency in both preclinical (Shigemoto et al., (2004), Eur J Pharmacol., 494(2-3):161-5) and clinical studies (Simons et al., (1996), Clin Exp Allergy, 26(9):1092-7).

In parallel, selective blockade of the 5-HT_{2A} receptor has been proved in both preclinical studies (Popa et al., (2005), J. Neurosci., 25(49): 11231-8) and clinical studies (Viola A. et al, (2002), Clin. Neurophysiol., 113(3) 429-434) to be efficacious in reducing Wake After

Sleep Onset, increasing Slow Wave Sleep and Total Sleep Time therefore providing consolidation of sleep.

In a first aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

10 X is CH₂, O, or S;

n is 0, 1 or 2;

m is 0, 1 or 2;

p is 0 or 1;

when present, R¹ is independently selected from the group consisting of halogen, C₁-3alkyl and C₁-3alkoxy;

15 when present, R² is independently selected from the group consisting of halogen, C₁-3alkyl and C₁-3alkoxy;

when p is 0, A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional heteroatom selected from N, S and O, the ring being optionally substituted by one or more groups independently selected from oxo and C₁-3alkyl;

20 when p is 1, A is a spiro 5-6 membered saturated or partially unsaturated carbocyclic ring;

when present, R³ and R⁴ are each independently selected from the list consisting of hydrogen and C₁-3alkyl; or

25 R³ and R⁴ together with the nitrogen to which they are attached, form a 4-6 membered saturated or partially unsaturated ring optionally containing one or more additional heteroatoms selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁-3alkyl.

30 The term "halogen" and its abbreviation "halo" refer to fluorine, chlorine, bromine or

iodine. In an embodiment unless otherwise indicated such a halo substituents is fluoro or chloro.

As used herein, a C₁₋₃alkyl substituent is a univalent radical derived by removal of a hydrogen atom from an acyclic C₁₋₃alkane. Such C₁₋₃alkyl substituents include methyl and ethyl, may be straight chain (i.e. n-propyl) or branched chain (for example isopropyl). In an embodiment, unless otherwise indicated, any C₁₋₃alkyl substituent is methyl, ethyl, n-propyl or isopropyl.

As used herein, a C₁₋₃alkoxy substituent is group of formula "R-O-" where R is C₁₋₃alkyl as defined above. Such alkoxy substituents include methoxy and ethoxy and may be straight chain (i.e. n-propoxy) or branched chain (for example isopropoxy). In an embodiment, unless otherwise indicated, any C₁₋₃alkoxy substituent is methoxy, ethoxy, n-propoxy or isopropoxy.

As used herein, the term "oxo" is the bivalent radical =O.

In an embodiment X is CH₂ or S.

In an embodiment n is 0 or 1.

In an embodiment n is 0.

In an embodiment, when n is 1, R¹ is halogen.

In an embodiment m is 0 or 1.

In an embodiment m is 0.

In an embodiment, when m is 1, R² is halogen.

In an embodiment, when p is 1, R³ and R⁴ together with the nitrogen to which they are attached, form a 4-6 membered saturated ring optionally containing one additional heteroatom selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

In a further embodiment, when p is 1, R³ and R⁴ together with the nitrogen to which they are attached, form a 5-6 membered saturated ring optionally containing one or more additional heteroatoms selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

5

In a further embodiment, when p is 1, R³ and R⁴ together with the nitrogen to which they are attached, form a 4- 5- or 6-membered ring selected from the list consisting of oxazolidinyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, thiomorpholinyl and azetidiny where the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

10

In an embodiment, when p is 1, A is either cyclopentyl or cyclohexyl. In a further embodiment, A is cyclopentyl.

15

In an embodiment, when p is 0, A is a spiro 5-6 membered saturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional heteroatom atom selected from O, N and S, the ring being optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

20

In a further embodiment, when p is 0, A is a spiro 5- or 6-membered saturated or partially unsaturated heterocyclic ring selected from the list consisting of oxazolidinyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and thiomorpholinyl, the ring being optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

25

In an embodiment, the compound is selected from:

N,N-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine;
4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)morpholine;
1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)pyrrolidine;
1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)-4-

30

methylpiperazine;

N-methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine;
4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)thiomorpholine;
1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine;
1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)piperidine;

35

N,N-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine (Isomer 1);

- N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 2);
- N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 3);
- 5 *N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 4);
- 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)morpholine (Isomer 1);
- 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)morpholine
- 10 (Isomer 2);
- 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)pyrrolidine (Isomer 1);
- 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)pyrrolidine (Isomer 2);
- 15 *N*-Methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 1);
- N*-Methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 2);
- 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)azetidine (Isomer
- 20 1);
- 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)azetidine (Isomer 2);
- 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine;
- 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 1);
- 25 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 2);
- 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)thiomorpholine 1-oxide;
- 5,11-dihydro-6'*H*-spiro[dibenzo[*a,d*]cycloheptene-10,3'-piperidin]-6'-one;
- 5,11-dihydro-2'*H*-spiro[dibenzo[*a,d*]cycloheptene-10,4'-piperidin]-2'-one;
- 30 5,11-dihydrospiro[dibenzo[*a,d*]cycloheptene-10,3'-piperidine];
- 1'-methyl-5,11-dihydrospiro[dibenzo[*a,d*]cycloheptene-10,3'-piperidine];
- 3',4'-dihydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazin]-5'(6'*H*)-one;
- 3',4',5',6'-tetrahydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazine];
- 8-fluoro-3',4'-dihydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazin]-5'(6'*H*)-one;
- 35 8-fluoro-3',4',5',6'-tetrahydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazine]; and
- 1'-methyl-5,11-dihydrospiro[dibenzo[*a,d*]cycloheptene-10,4'-piperidine];

or a pharmaceutically acceptable salt thereof.

For the avoidance of doubt, unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected
5 from a number of alternative groups, the selected groups may be the same or different. For the avoidance of doubt, the term independently means that where more than one substituent is selected from a number of possible substituents, those substituents maybe the same or different.

10 The compounds of formula (I) may form pharmaceutically or veterinarily acceptable salts, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, saccharate,
15 fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York 1996, Volume
20 13, page 453-497.

Hereinafter, the compounds of formula (I) and their pharmaceutically acceptable salts, are referred to as " the compounds of the invention".

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

example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compound defined in the first aspect.

- 5 The compounds of the invention may exist in solvated or hydrated form.

The compounds of the invention or solvates/hydrates of the compounds or salts, may exist in one or more polymorphic forms.

- 10 Therefore, according to a further aspect, the invention includes a solvate, hydrate or prodrug of the compounds of the invention.

Certain compounds of the invention may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

- 15 Certain compounds of the invention possess one or more chiral centres and so exist in a number of stereoisomeric forms. Compounds having one chiral centre may exist as enantiomers or a racemic mixture containing enantiomers. Compounds having two or more chiral centres may exist as diastereoisomers or enantiomers. All stereoisomers (for example enantiomers and diastereoisomers) and mixtures thereof are included in the
- 20 scope of the present invention. Racemic mixtures may be separated to give their individual enantiomer using preparative HPLC using a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare individual enantiomers.

25

The invention also includes all suitable isotopic variations of the compounds of the invention. An isotopic variation of the compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of

- 30 isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{35}S , ^{18}F and ^{36}Cl respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e.,
- 35 ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e.,

^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

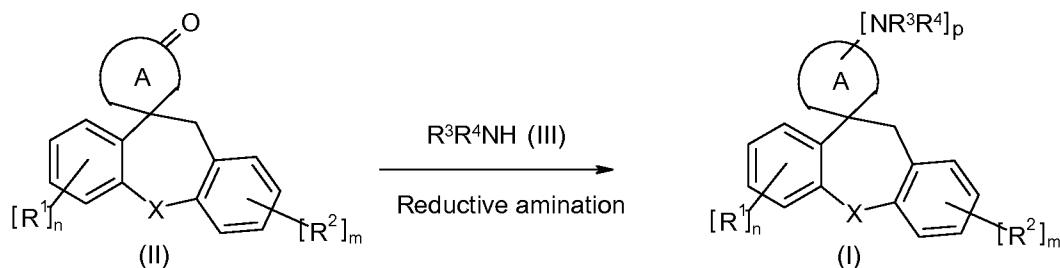
Compounds of the invention may be prepared in a variety of ways. In the following reaction schemes and hereinafter, unless otherwise stated R^1 to R^4 , A, X, n, m and p are as defined in the first aspect of the invention. These processes form further aspects of the invention.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic), etc...(IVa), (IVb), (IVc) etc.

Generally, compounds of formula (I), where A is a spiro 5-6 membered saturated or partially unsaturated carbocyclic ring and p is 1 may be prepared according to general reaction Scheme 1. Methods suitable for Scheme 1 are known in the literature (eg. J. Org. Chem. 1996, 61, 3849-3862). For example, by reacting a compound of formula (II) with a compound of formula (III) in the presence of an acid (eg glacial acetic acid) and a reducing agent (eg $\text{NaBH}(\text{OAc})_3$ or NaBH_4) in a suitable solvent (eg DCE) at room temperature for 12-24 hours.

Compounds of formula (III) are either commercially available or may be prepared by procedures known to the skilled person.

Scheme 1

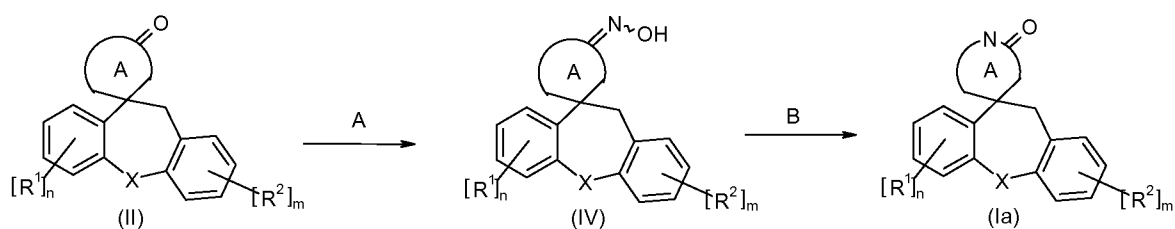


In the case of compounds of general formula (I), wherein A is a spiro 5-6 membered saturated or partially unsaturated carbocyclic ring, p is 1 and R³ and R⁴ are both hydrogen, the compounds may be prepared in two steps. Firstly, by reductive amination of a compound of formula (II) with benzylamine according to Scheme I. Secondly, by removing the benzilic protection with one of the methods described in literature (eg J. Org. Chem. 2001, 66, 5317-5328). For example by refluxing the compound with a reducing agent (eg ammonium formate) in presence of a catalyst (eg Pd/C) in a suitable solvent (eg MeOH) for 2 hours.

In the case of compounds of general formula (I), wherein A is a spiro 5-6 membered saturated or partially unsaturated carbocyclic ring, p is 1 and R³ and R⁴ together with the nitrogen to which they are attached, form a 4-6 membered saturated or partially unsaturated ring containing a sulfinyl or a sulfonyl functional group, the compounds may be prepared in two steps. Firstly, by reductive amination of a compound of formula (II) with thiomorpholine according to Scheme I. Secondly, by oxidising the sulphur atom with one of the procedures described in literature (eg Organic Process Research & Development, 10(6), 1157-1166; 2006; PCT Int. Appl., 2007000432, 04 Jan 2007) by reacting the compound with an oxidant (eg Oxone[®] solution) in a suitable solvent (eg MeOH, DCM and water) at low temperature (eg -8/10°C) for 10 mins.

Compounds of formula (Ia), i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom, the ring being substituted by oxo and p is 0, may be prepared according to reaction Scheme 2.

Scheme 2



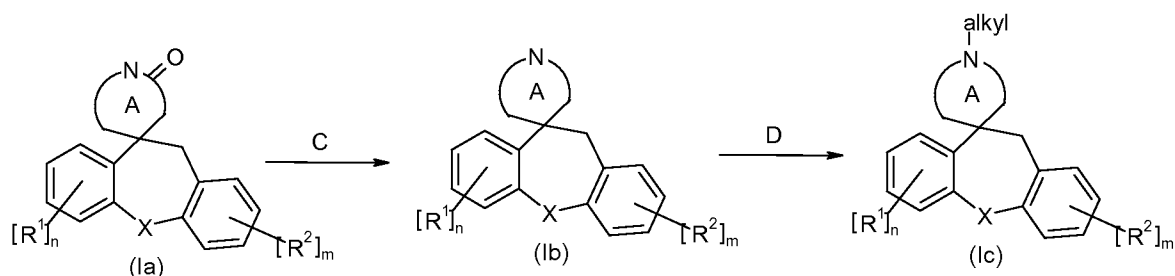
The synthesis (A) of the oxime (IV) and the Beckmann rearrangement (B) may be performed according to procedures described in literature (eg Org. Lett. 2005; 7(8), 1617 – 1619; J. Am. Chem. Soc. 1952, 74(10); 2680-2681). For example:

A) By reacting compounds of formula (II) with hydroxylamine hydrochloride and sodium acetate in a suitable solvent (eg MeOH, DCM and water) at room temperature for 3 days to give compounds of formula (IV);

B) By reacting compounds of formula (IV) with an acid (eg PPA) at elevated temperature (eg 100°C) for 10 minutes.

Further compounds of general formula (I) may be prepared according to reaction Scheme 3.

10 Scheme 3



Compounds of formula (Ia), i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom, the ring being substituted by oxo, and wherein p is 0, may be reduced (C) according to one of the procedures described in literature (eg Brown, H. C.; Heim, P. Selective reductions; J. Org. Chem. 1973, 38(5); 912-916) to give compounds of formula (Ib) i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom and wherein p is 0. Compounds of formula (Ib) may be optionally alkylated (D) (eg J. Med. Chem. 1979, 22(7), 834-839) to give compounds of formula (Ic), i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom, the ring being substituted by alkyl and wherein p is 0. For example:

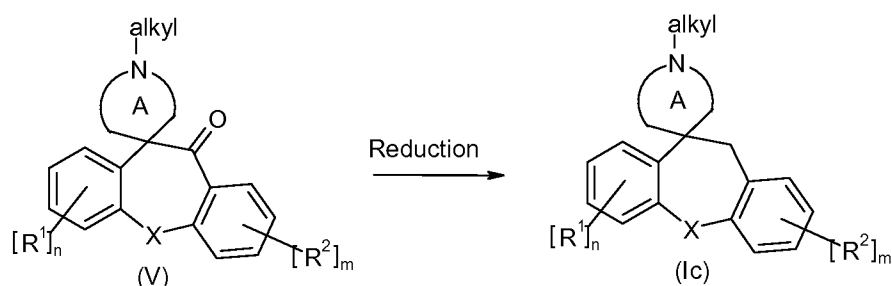
C) By reacting compounds of formula (Ia) with a reducing agent (eg borane) in a suitable solvent (eg THF) at reflux for 2 hours;

D) By reacting compounds of formula (Ib) with formalin in a suitable solvent (eg formic acid) at reflux for 16-18 hours.

Alternatively, compounds of formula (Ic), i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom, the ring being substituted by alkyl and wherein p is 0, may be synthesised according to

5 Scheme 4 by reducing the corresponding ketone, a compound of formula (V), whose synthesis is described in literature (eg Chemical & Pharmaceutical Bulletin, 27(9), 2056-64; 1979).

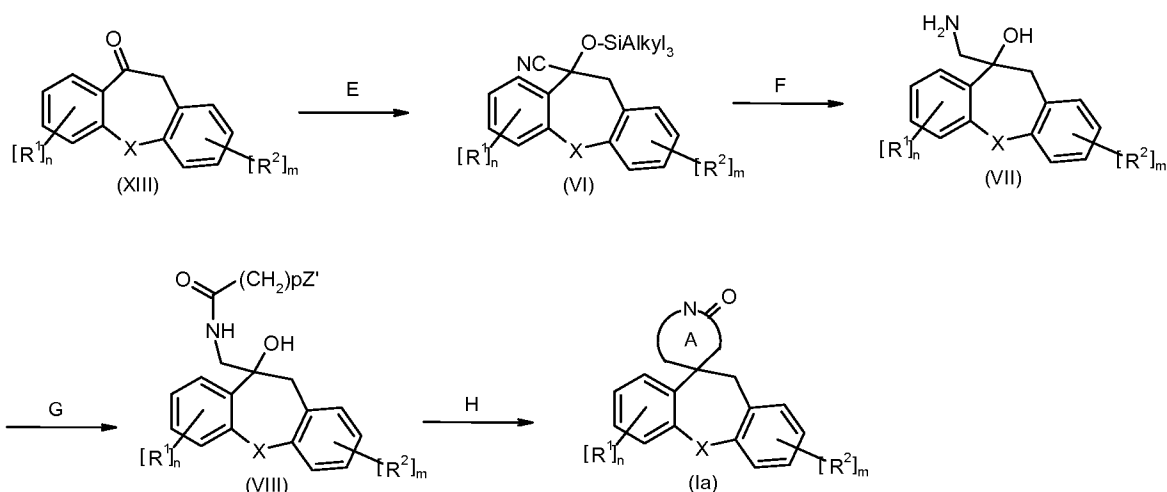
Scheme 4



Compounds of formula (Ia), i.e. compounds of general formula (I) wherein A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional nitrogen or oxygen atom and wherein

15 p is 0, may be prepared according to reaction Scheme 5.

Scheme 5



For example:

- 20 E) By reacting a compound of formula (XIII) with a suitable silyl cyanide (eg trimethylsilyl cyanide) and a zinc salt (eg zinc iodide) in a suitable solvent (eg toluene) at 40°C for 3-24 hours to give a compound of formula (VI);

F) By reacting a compound of formula (VI) with a reducing agent (eg LiAlH_4) in a suitable solvent (eg THF or diethyl ether) at reflux for 2-24 hours to give a compound of formula (VII);

G) By reacting a compound of formula (VII) with $\text{Z}'-(\text{CH}_2)_p-\text{CO}-\text{Z}$ wherein Z and Z' are leaving groups such as chlorine, bromine, etc. and wherein p is 0, 1, etc., in the presence of a suitable base (eg DIPEA, triethylamine) in a suitable solvent (eg DCM) at $0/25^\circ\text{C}$ for 2-3 hours to give a compound of formula (VIII);

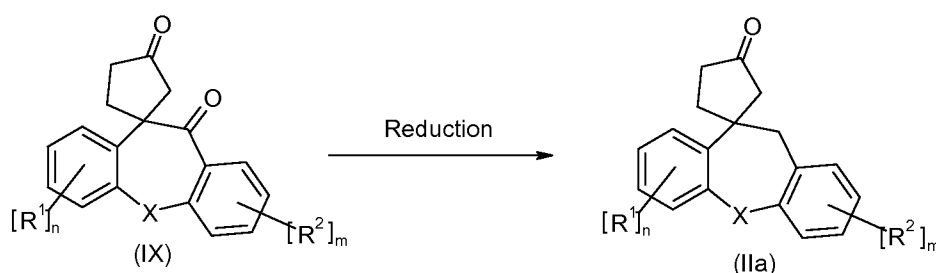
H) By reacting a compound of formula (VIII) with a base (eg KOH) in a suitable solvent (eg dioxane) at reflux for 1-2 hours to give a compound of formula (Ia).

10

Compounds of formula (IIa), i.e compounds of general formula (II) wherein A is cyclopentyl, may be prepared according to reaction Scheme 6 by reducing compounds of formula (IX) using one of the methods well described in literature (see for example Chem. Pharm. Bull. 2004, 52 (1), 79-88). For example, by reacting a compound of formula (IX) in the presence of an acid (eg acetic acid) with a catalyst (eg Pd/C) in a suitable solvent (eg THF) at a suitable H_2 pressure (eg 4-5 atm) at room temperature for 1-4 days.

15

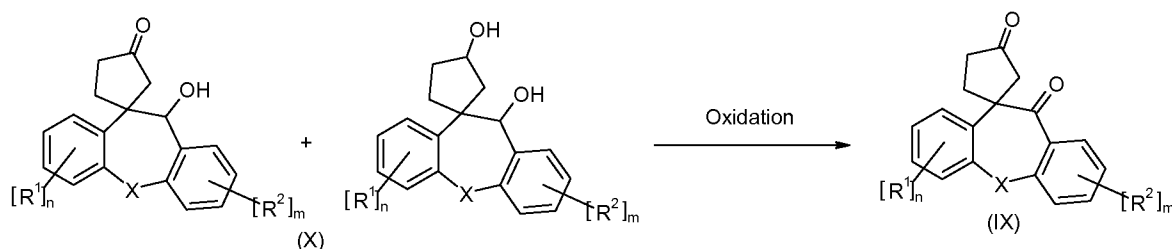
Scheme 6



20

Compounds of formula (IX) may be prepared according to reaction scheme 7 by reacting the mixture of compounds of formula (X) with a suitable oxidant (eg Dess-Martin periodinane) in a suitable solvent (eg DCM) at room temperature for 3-12 hrs.

Scheme 7

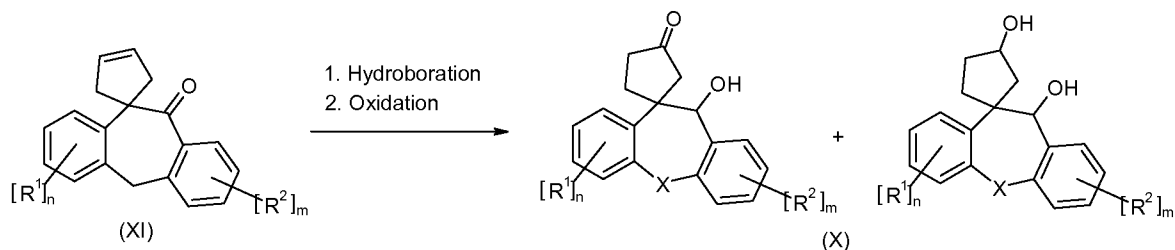


25

The mixture of compounds of formula (X) may be prepared according to reaction scheme 8 in 2 steps:

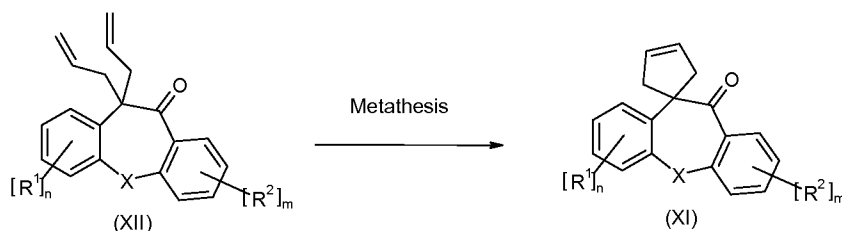
1. By reacting compounds of formula (XI) with borane in a suitable solvent (eg THF) at room temperature for 2-3 hours.
2. Adding water and sodium hydroxide followed by hydrogen peroxide at room temperature for 16 hours.

Scheme 8



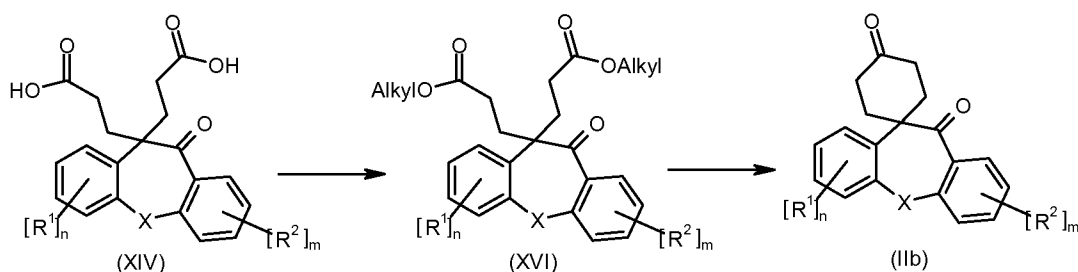
Compounds of formula (XI) may be prepared according to reaction scheme 9 by reacting compounds of formula (XII) with a suitable catalyst (eg Grubbs catalyst 2nd generation) in degassed solvent (eg CH_2Cl_2) at room temperature or reflux temperature for several hours (eg 1 day).

Scheme 9



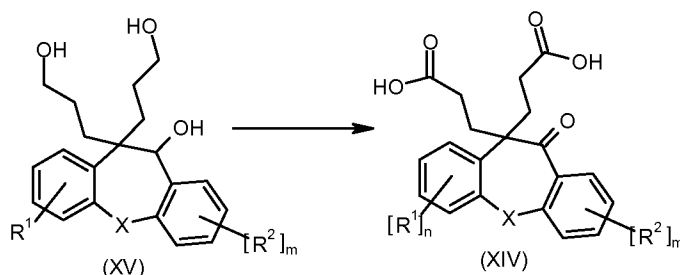
Compounds of formula (IIb), i.e. compounds of general formula (II), wherein A is cyclohexyl may be prepared according to reaction scheme 10 by esterification of the compound of formula (XIV) (see as an example Journal of the American Chemical Society, 127(50), 17877-17887; 2005), to a compound of formula (XVI), followed by cyclization to get (IIb) (see for example Bioorganic & Medicinal Chemistry Letters, 17(11), 3006-3009, 2007; Heterocycles, 65(6), 1359-1371, 2005; Synlett, (12), 2224-2226, 2004).

Scheme 10



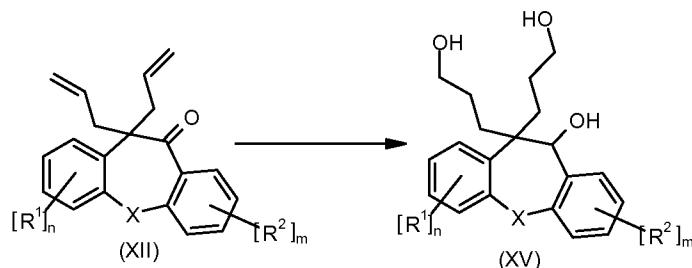
Compounds of formula (XIV) may be prepared according to reaction scheme 11 by reacting compounds of formula (XV) with an oxidant (eg Jones reagent) in a suitable solvent (eg acetone) at room temperature.

Scheme 11



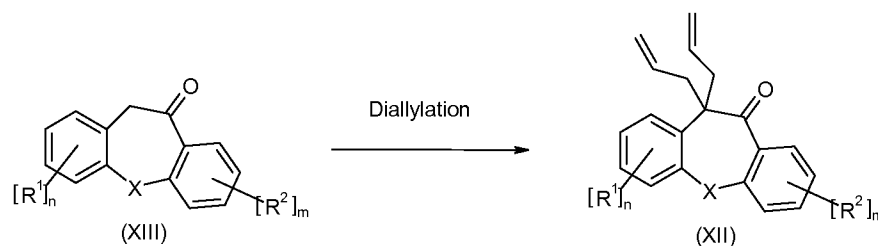
Compounds of formula (XV) may be prepared according to reaction scheme 12 by reacting compounds of formula (XII) with $\text{BH}_3\text{-THF}$ followed by H_2O_2 oxidation in a suitable organic solvent (eg THF).

Scheme 12



Compounds of formula (XII) may be prepared according to reaction scheme 13 by reacting compounds of formula (XIII) with a base (eg K-t-butoxide freshly prepared) and an allylating agent (eg allyl bromide) in a suitable solvent (eg t-butyl alcohol and toluene) at a moderate temperature (eg 55-60°C) for 40-60 minutes.

Scheme 13



Compounds of general formula (XIII) when X is CH₂, can be prepared following a literature procedure (Journal of Medicinal Chemistry (1981), 24(9), 1021-6).

5

Compounds of general formula (XIII) when X is S, are either commercially available from Specs (when n, m are 0) or can be made following a literature procedure (Chemical & Pharmaceutical Bulletin (1975), 23(10), 2223-31).

10 Compounds of general formula (XIII) when X is O, can be made following a literature procedure (Organic Letters, 5(25), 4911-4913; 2003)

15 The compounds of the invention are antagonists of the H₁ receptor . In addition, some of the compounds of the invention are antagonists of the 5HT_{2A} receptor.

The compounds of the invention are useful for the treatment of diseases and conditions mediated by antagonism of the H₁ receptor and optionally by antagonism of the 5HT_{2A} receptor.

20

Therefore, according to an embodiment, the invention provides the compounds of the invention for use as a medicament, preferably a human medicament.

25 The compounds of the invention may treat diseases or conditions selected from the list consisting of: [the numbers in brackets after the listed diseases below refer to the classification code in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10)]:

30 i) Psychotic disorders for example Schizophrenia (including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60)); Schizophreniform Disorder (295.40);

Schizoaffective Disorder (295.70) (including the subtypes Bipolar Type and Depressive Type); Delusional Disorder (297.1) (including the subtypes Erotomantic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type); Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic
 5 Disorder due to a General Medical Condition (including the subtypes with Delusions and with Hallucinations); Substance-Induced Psychotic Disorder (including the subtypes with Delusions (293.81) and with Hallucinations (293.82)); and Psychotic Disorder Not Otherwise Specified (298.9).

10 ii) Depression and mood disorders for example Depressive Episodes (including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode); Depressive Disorders (including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311)); Bipolar Disorders (including Bipolar I
 15 Disorder, Bipolar II Disorder (i.e. Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80)); Other Mood Disorders (including Mood Disorder due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features);
 Substance-Induced Mood Disorder (including the subtypes With Depressive Features,
 20 With Manic Features and With Mixed Features); and Mood Disorder Not Otherwise Specified (296.90).

iii) Anxiety disorders for example Social Anxiety Disorder; Panic Attack; Agoraphobia, Panic Disorder; Agoraphobia Without History of Panic Disorder (300.22); Specific Phobia
 25 (300.29) (including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type); Social Phobia (300.23); Obsessive-Compulsive Disorder (300.3); Posttraumatic Stress Disorder (309.81); Acute Stress Disorder (308.3); Generalized Anxiety Disorder (300.02); Anxiety Disorder Due to a General Medical Condition (293.84); Substance-Induced Anxiety Disorder; and Anxiety
 30 Disorder Not Otherwise Specified (300.00).

iv) Substance-related disorders for example Substance Use Disorders (including Substance Dependence, Substance Craving and Substance Abuse); Substance-Induced Disorders (including Substance Intoxication, Substance Withdrawal, Substance-Induced
 35 Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood

Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders (including Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81),

5 Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9)); Amphetamine (or Amphetamine-Like)-Related

10 Disorders (for example Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and

15 Amphetamine-Related Disorder Not Otherwise Specified (292.9)); Caffeine Related Disorders (including Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9)); Cannabis-Related Disorders (including Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium,

20 Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9)); Cocaine-Related Disorders (including Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-

25 Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9)); Hallucinogen-Related Disorders (including Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder,

30 Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9)); Inhalant-Related Disorders (including Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder,

35 Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9)); Nicotine-Related Disorders (including Nicotine Dependence (305.1), Nicotine

- Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9)); Opioid-Related Disorders (including Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9)); Phencyclidine (or Phencyclidine-Like)-Related Disorders (including Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9)); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders (including Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic-Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9)); Polysubstance-Related Disorder (including Polysubstance Dependence (304.80)); and Other (or Unknown) Substance-Related Disorders (including Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide).
- v) Sexual dysfunction for example Sexual Desire Disorders (including Hypoactive Sexual Desire Disorder (302.71) and Sexual Aversion Disorder (302.79)); sexual arousal disorders (including Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72)); orgasmic disorders (including Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75)); sexual pain disorder (including Dyspareunia (302.76) and Vaginismus (306.51)); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias (including Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9)); gender identity disorders (including Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85)); and Sexual Disorder Not Otherwise Specified (302.9).

- vi) Sleep disorder for example primary sleep disorders such as Dyssomnias (including Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47)); primary sleep disorders such as
- 5 Parasomnias (including Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47)); Sleep Disorders Related to Another Mental Disorder (including Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44)); Sleep Disorder Due to a General Medical Condition; and Substance-Induced
- 10 Sleep Disorder (including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type).
- vii) Eating disorders such as Anorexia Nervosa (307.1) (including the subtypes Restricting Type and Binge-Eating/Purging Type); Bulimia Nervosa (307.51) (including the subtypes
- 15 Purging Type and Nonpurging Type); Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50).
- viii) Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder, Rett's Disorder, Childhood Disintegrative Disorder and Pervasive Developmental Disorder
- 20 Not Otherwise Specified.
- ix) Attention-Deficit /Hyperactivity Disorder (including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder
- 25 Hyperactive-Impulse Type (314.01) and Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified (314.9)); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder (including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders
- 30 such as Tourette's Disorder (307.23).
- x) Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83),
- 35 Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301.81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6),

Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9).

xi) Enhancement of cognition including the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease.

In an embodiment, the invention provides the use of the compounds of the invention in the manufacture of a medicament for treating or preventing sleep disorders.

In an embodiment the sleep disorder is selected from the list consisting of: primary sleep disorders such as Dyssomnias (including Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47)); primary sleep disorders such as Parasomnias (including Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47)); Sleep Disorders Related to Another Mental Disorder (including Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44)); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder (including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type).

The compounds of the invention may be used in combination with the following agents to treat or prevent psychotic disorders: i) antipsychotics; ii) drugs for extrapyramidal side effects, for example anticholinergics (such as benztropine, biperiden, procyclidine and trihexyphenidyl), antihistamines (such as diphenhydramine) and dopaminergics (such as amantadine); iii) antidepressants; iv) anxiolytics; and v) cognitive enhancers for example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

The compounds of the invention may be used in combination with antidepressants to treat or prevent depression and mood disorders.

The compounds of the invention may be used in combination with the following agents to treat or prevent bipolar disease: i) mood stabilisers; ii) antipsychotics; and iii) antidepressants.

The compounds of the invention may be used in combination with the following agents to treat or prevent anxiety disorders: i) anxiolytics; and ii) antidepressants.

- The compounds of the invention may be used in combination with the following agents to treat or prevent male sexual dysfunction: i) phosphodiesterase V inhibitors, for example vardenafil and sildenafil; ii) dopamine agonists/dopamine antagonists/dopamine transport inhibitors for example apomorphine and bupropion; iii) alpha adrenoceptor antagonists for example phentolamine; iv) prostaglandin agonists for example alprostadil; v) androgen receptor modulators such as testosterone; vi) serotonin agonists/antagonists/modulators/serotonin transporter inhibitors for example serotonin reuptake inhibitors; vii) noradrenaline transport inhibitors for example reboxetine; viii) oxytocin receptor antagonists; (ix) sodium and calcium channel inhibitors/blockers; and (x) opioid receptor antagonists.
- 15 The compounds of the invention may be used in combination with the same agents specified for male sexual dysfunction to treat or prevent female sexual dysfunction, and in addition an estrogen agonist such as estradiol.

- Antipsychotic drugs include Typical Antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine); and Atypical Antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone and amisulpride).

- 25 Antidepressant drugs include serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, indalpine and zimeldine); dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran); Noradrenaline reuptake inhibitors (such as reboxetine and venlafaxine); tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine); monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine); and others (such as bupropion, mianserin, mirtazapine, nefazodone and trazodone).
- 30 Mood stabiliser drugs include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate and tiagabine.
- 35

Anxiolytics include benzodiazepines such as alprazolam and lorazepam.

It will be appreciated that the compound of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations),
5 separately or sequentially.

It will be appreciated that references herein to "treatment" extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions. The compound of
10 the invention may be administered as the raw chemical but the active ingredient is suitably presented as a pharmaceutical formulation.

The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient by an appropriate route.
15 Accordingly, in another aspect, the invention provides pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically-acceptable excipients.

As used herein, "pharmaceutically-acceptable excipient" means any pharmaceutically
20 acceptable material present in the pharmaceutical composition or dosage form other than the compound or compounds of the invention. Typically the material gives form, consistency and performance to the pharmaceutical composition.

The pharmaceutical compositions of the invention typically contain one compound of the
25 invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. In addition, the pharmaceutical compositions of the invention may comprise one or more additional pharmaceutically active compounds.

Such pharmaceutical compositions of the invention may be prepared and packaged in
30 bulk form wherein a safe and therapeutically effective amount of a compound of the invention can be dispensed and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged as dosage forms wherein each physically discrete dosage form contains a safe
35 and effective amount of a compound of the invention. Accordingly, in another aspect, the

invention provides dosage forms comprising pharmaceutical compositions of the invention.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the nature of the composition, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of formula (I) for the treatment of disorders or diseases associated with H₁ antagonist activity will generally be in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. Thus, for a 70 kg adult mammal, the actual amount per day would usually be from 70 to 700 mg and this amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a pharmaceutically acceptable salt thereof may be determined as a proportion of the effective amount of the compound of formula (I) per se. It is envisaged that similar dosages would be appropriate for treatment of the other conditions referred to above.

It will be recognised by one of skill in the art that the optimal quantity and spacing of individual dosages of compounds of the invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of compounds of the invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The compositions of the invention will typically be formulated into dosage forms which are adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, lozenges, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets and cachets; (2) parenteral administration such as sterile solutions, suspensions, implants and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal and vaginal administration such as suppositories, pessaries and foams; (5) inhalation and intranasal such as dry powders, aerosols,

suspensions and solutions (sprays and drops); (6) topical administration such as creams, ointments, lotions, solutions, pastes, drops, sprays, foams and gels; (7) ocular administration such as drops, ointment, sprays, suspensions and inserts; (8) buccal and sublingual administration such as lozenges, patches, sprays, drops, chewing gums and tablets.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the release of the compound of the invention at the appropriate rate to treat the condition.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavouring agents, flavour masking agents, colouring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, rate modifying agents, antioxidants, preservatives, stabilizers, surfactants and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to determine suitable pharmaceutically-acceptable excipients in appropriate amounts for use with the compounds of the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples

include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press). The pharmaceutical compositions of the invention may be prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a safe and effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. hydroxypropyl methyl cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include starches, croscopovidone, sodium starch glycolate, croscarmellose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and sodium dodecyl sulphate. The oral solid dosage form may further comprise a glidant such as talc and colloidal silicon dioxide. The oral solid dosage form may further comprise an outer coating which may have cosmetic or functional properties.

It will be appreciated that the invention includes the following further aspects. The diseases and conditions described above extend, where appropriate, to these further aspects.

- i) A compound of the invention for use in treating or preventing a disease or condition mediated by antagonism of the H₁ receptor.
- ii) A method of treatment or prevention of a disease or condition mediated by antagonism of the H₁ receptor in a mammal comprising administering an effective amount of a compound of the invention.

Supporting Compounds and Intermediates

The invention is supported by the following compounds described below.

- 5 In the procedures that follow, after each starting material, reference to an intermediate or compound is often provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

- Compounds are named using ACD/Name PRO 6.02 chemical naming software
10 (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

- Reagents were obtained from commercial suppliers (Sigma–Aldrich and Lancaster) and used without further purifications. According to standard procedures DCM and DCE were dried over calcium hydride; THF, toluene and diethyl ether were dried over
15 Na/benzophenone and EtOH was dried over Mg/I₂ prior to use. DMF was bought already anhydrous. Anhydrous reactions were run under a positive pressure of dry N₂ or Argon.

IR spectra were recorded on a Perkin Elmer BX FT-IR system using CH₃Cl as solvent.

- 20 Thin-layer chromatography was carried out using Merck TLC plates Kieselgel 60F-254, visualised with UV light, 5%phosphomolybdic acid, aqueous potassium permanganate. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 23-400 mesh, for flash technique.
- 25 Preparative TLC was carried out using Merck pre-coated plates Kieselgel 60F-254, layer thickness 2.0 mm and layer thickness 0.20-0.25 mm.

- Melting points were taken using a Gallenkamp Melting Point Apparatus and are uncorrected. Melting point determination was conducted after recrystallization of solids
30 from appropriate solvents.

- ¹H-NMR were obtained at 298K, at the frequency stated using a Bruker AC200F 200 MHz or a Varian Oxford 300 MHz or a Bruker 400 Ultra Shield or a Varian INOVA 400 MHz or 500 MHz or a Bruker™ 400 MHz machine and run as a dilute solution of CDCl₃, CD₂Cl₂,
35 CD₃OD and DMSO-d₆. All NMR spectra were reference to tetramethylsilane (TMS δ_H 0, δ_C 0). Chemical shift are expressed in parts per million (ppm, δ units). All coupling

constants are reported in units of hertz (Hz), and multiplicities are labelled s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet).

- 5 The purity of compounds was assessed by reversed-phase liquid chromatography and mass spectrometer (Agilent series 1100 LC/MSD) with an UV detection range of 200-245 nm and an electrospray ionization source (ESI). The LC elution method (using Zorbax Eclipse XDB, 4.6 x 150 mm, 5 μ m C8 column) was the following: 15-35 min method at 25 °C, mobile phase composed of different CH₃CN/H₂O-HCOOH 0.1% mixtures at a flow rate
- 10 of 1 mL/min (all solvent were HPLC grade, Fluka). Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254nm. Mass spectra were acquired in positive mode scanning over the mass range of 50-1500. The following ion source parameters were used: drying gas flow, 10 mL/min;
- 15 nebulizer pressure, 40 psig; drying gas temperature, 350 °C.

Alternatively HPLC spectra were performed using a reversed-phase liquid chromatography (ProStar 210/215 PrepStar218) and UV-Vis Detector (ProStar 325) with an UV detection range of 200-245 nm. The LC elution method (using Varian Polaris 5 C-

20 18, 150 x 4.6 mm) was the following: 15-35 min method at 25 °C, mobile phase composed of different CH₃CN/H₂O-HCOOH 0.1% mixtures at a flow rate of 1 mL/min (all solvent were HPLC grade, Fluka).

Where required GC-MS were performed after dissolution in DCM (using GC Varian

25 Star3400Cx- MS Varian Saturn 3) adapted for capillary column (Factor Four™, VF-5ms, 30m, 0.25mm, 0.25 μ m, Part NumberCP8944). Oven temperature at injection and for 20 minutes 60°C and then a programmed temperature run at 20°C/min to 280°C, a final isothermal period of 20 min.

- 30 For the chiral separation and the chiral quality control two different techniques were used:
- 1) Supercritical Fluid Chromatography (SFC): analytical chromatography was performed on a Berger SFC Analytix, while for the preparative SFC, a Gilson SFC series SF3 was used.
- 2) High Performance Liquid Chromatography (HPLC): chiral Preparative HPLC was
- 35 performed using a Waters 600 HPLC system and Agilent series 1100 instrument, while for analytical chromatography an Agilent series 1100 HPLC was used.

Abbreviations

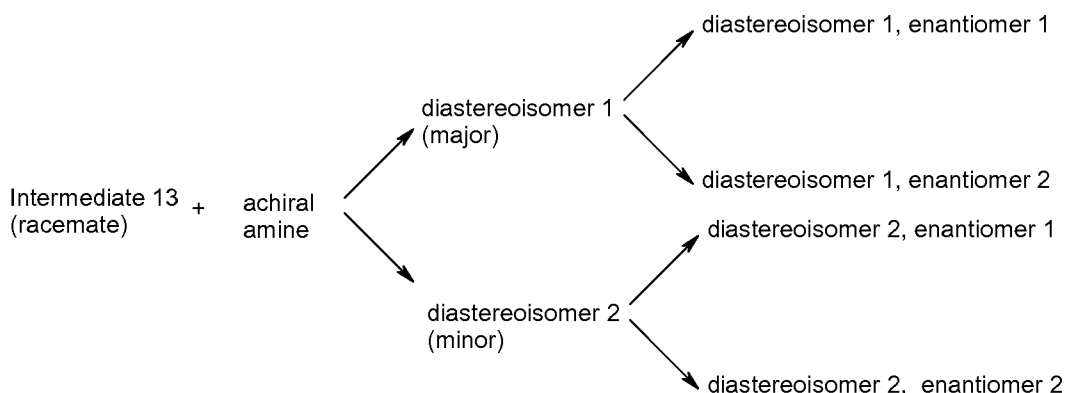
The following lists the abbreviations used:

NaOH	sodium hydroxide
NaHCO ₃	sodium bicarbonate
NaBH ₄	sodium borohydride
NaBH(OAc) ₃	sodium triacetoxyborohydride
KOH	potassium hydroxide
KCN	potassium cyanide
CHCl ₃	chloroform
MeOH	methanol
EtOH	ethanol
DCM	dichloromethane
DCE	dichloroethane
THF	tetrahydrofuran
DMF	dimethylformamide
PPA	polyphosphoric acid
EtOAc	Ethyl acetate
Et ₃ N	triethylamine
DMSO	dimethyl sulfoxide
CDCl ₃	chloroform-d
CD ₂ Cl ₂	dichloromethane-d ₂
CD ₃ OD	methanol-d ₄
DMSO-d ₆	dimethyl sulfoxide-d ₆
cHex	cyclohexane
BOC ₂ O	di-tert-butyl dicarbonate
SCX	strong cation resin
TEA	triethyl amine
TFA	trifluoro acetic acid
AcOH	acetic acid
e.e.	enantiomeric excess
d.e.	diastereoisomeric excess

From reductive amination reaction (Scheme 1 in the description) of Intermediate 13 (racemate) with achiral amines, 4 products were obtained: 2 diastereoisomers (ratio usually in the range between 75/25 and 92/8) and the corresponding enantiomers.

- 5 Conventionally, the major diastereoisomer is named diastereoisomer 1 and the minor diastereoisomer is named diastereoisomer 2. Each diastereoisomer exists in the two enantiomeric forms: they are named enantiomer 1 and enantiomer 2 after the order of elution from chiral chromatography. An exemplary scheme is provided starting from Intermediate 13.

10



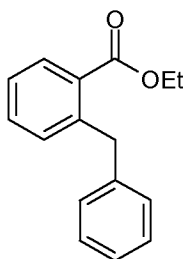
- 15 Apart from Compound 1, whose purification by chiral chromatography led to the isolation of all the four products as single enantiomers, only the enantiomers relative to the major diastereoisomer (“diastereoisomer 1, enantiomer 1” and “diastereoisomer 1, enantiomer 2”) were collected.

For the reader's benefit the term:

- 20 (diastereoisomer 1, enantiomer 1) will be named from now on isomer 1,
(diastereoisomer 1, enantiomer 2) will be named from now on isomer 2;
(diastereoisomer 2, enantiomer 1) will be named from now on isomer 3;
(diastereoisomer 2, enantiomer 2) will be named from now on isomer 4.

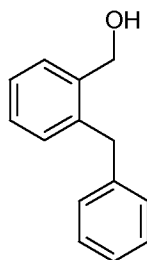
Intermediate 1: Ethyl 2-(phenylmethyl)benzoate

25



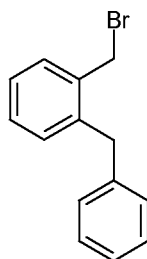
O-benzylbenzoic acid (5g, 23.6 mmol; Sigma-Aldrich) in ethanol (50mL) and conc. sulfuric acid (2.5mL) was refluxed for five hours. After cooling, the major part of the solvent was evaporated to get a residue redissolved in the least amount of water and extracted using diethyl ether. The organic phase was washed using a diluted solution of NaOH, then washed with brine and dried. The organic phase was evaporated to dryness to give the title compound (4.86 g) which was used in the next step without further purification; MS (ESI) m/z : 263 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1261, 1713, 3012, 3028; 1H NMR ($CDCl_3$): δ 1.28 (t, 3 H), 4.26 (q, 2 H), 4.37 (s, 2 H), 7.10-7.44 (m, 8 H), 7.85-7.89 (m, 1 H).

Intermediate 2: [2-(Phenylmethyl)phenyl]methanol



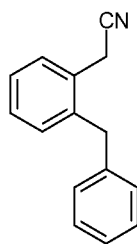
Ethyl 2-(phenylmethyl)benzoate (Intermediate 1, 4.8g, 20mmol) in dry ether (10mL) was added to a solution of $LiAlH_4$ (0.85 g, 22mmol) in dry ether (30mL) under N_2 atm at $0^\circ C$. The solution was heated to reflux for 2.5 hours. After cooling, ice and diluted sulfuric acid were added and the mixture was filtered through a pad of Celite® to remove aluminum salts. The filtrate was extracted with diethyl ether and the organic layer was dried and evaporated to dryness affording the title compound as an oily product (3.96g). It was used in the next step without further purification; MS (ESI) m/z : 221 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1217, 1453, 1494, 3013, 3608; 1H NMR ($CDCl_3$): δ 4.08 (s, 2 H), 4.64 (s, 2 H), 7.11 - 7.42 (m, 9 H).

Intermediate 3: 1-(Bromomethyl)-2-(phenylmethyl)benzene



A mixture of [2-(phenylmethyl)phenyl]methanol (Intermediate 2, 3.70g, 19mmol) and 48% aqueous hydrobromic acid (15mL) was refluxed for 3 hours. After cooling the reaction mixture was diluted with distilled water. The oil which was separated, was collected by dichloromethane extraction and then washed with water, dried and evaporated to give the title compound (4.53g). It was used in the next step without further purification;
 GC-MS: 181 [M-Br]⁺; IR (CHCl₃) (ν, cm⁻¹): 1454, 1494, 3011; ¹HNMR (CDCl₃): δ 4.15 (s, 2 H), 4.44 (s, 2 H), 7.12 - 7.36 (m, 9 H).

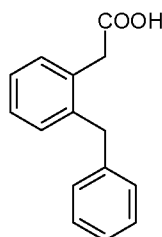
10 Intermediate 4: [2-(Phenylmethyl)phenyl]acetonitrile



A solution of KCN (0.90g, 14mmol) and 1-(bromomethyl)-2-(phenylmethyl)benzene (Intermediate 3, 3.0g, 11mmol) in absolute ethanol (30mL) was heated to reflux for 8 hours. After cooling the reaction mixture was diluted with water (50mL) and then extracted with diethyl ether. The organic phase was washed with brine, dried and evaporated to give the title compound as an oil (1.95g). It was used in the next step without further purification;

MS (ESI) *m/z*: 230 [M+Na]⁺; IR (CHCl₃) (ν, cm⁻¹): 1454, 1494, 2252, 2926, 3024; ¹HNMR (CDCl₃): δ 3.54 (s, 2 H), 4.03 (s, 2 H), 7.06 - 7.43 (m, 9 H).

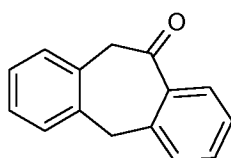
20 Intermediate 5: [2-(Phenylmethyl)phenyl]acetic acid



To a solution of [2-(phenylmethyl)phenyl]acetonitrile (Intermediate 4, 1.7g, 8.04mmol) in absolute ethanol (10mL) was added a solution of KOH (1.22g, 22mmol) in distilled water (1.4mL). The reaction mixture was heated to reflux for 20 hours. After cooling, the major part of the ethanol was evaporated and the residue was washed using DCM. The alkaline aqueous phase was acidified and extracted using DCM. The organic layer was washed with brine, dried and concentrated under reduced pressure providing the title compound (1.09g). It was used in the next step without further purification;

MS (ESI) m/z : 249 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1453, 1495, 1710, 3013, 3493; 1H NMR ($CDCl_3$): δ 3.61 (s, 2 H), 4.04 (s, 2 H), 7.08 - 7.30 (m, 9 H).

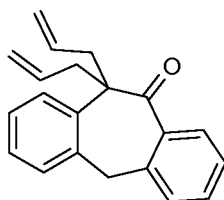
Intermediate 6: 5,11-Dihydro-10H-dibenzo[a,d]cyclohepten-10-one



[2-(Phenylmethyl)phenyl]acetic acid (Intermediate 5, 0.100g, 0.44mmol) was added in small portions to PPA (0.5mL) and stirred at 90°C. The reaction mixture was left under vigorous magnetic stirring for 30 minutes at 90°C. After cooling, water (5mL) was added and the mixture was extracted with DCM. The organic phase was washed with saturated $NaHCO_3$ and dried. Evaporation of the organic solvent gave a solid residue that was recrystallized from ethanol to give the title compound (0.082g);

MS (ESI) m/z : 231 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1283, 1447, 1598, 1673, 3013; 1H NMR ($CDCl_3$): δ 4.11 (s, 2 H), 4.19 (s, 2 H), 7.17 - 7.48 (m, 7H), 8.09 - 8.13(m, 1 H).

Intermediate 7: 11,11-Di-2-propen-1-yl-5,11-dihydro-10H-dibenzo[a,d]cyclohepten-10-one



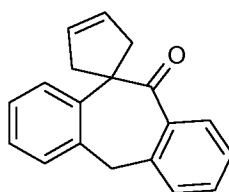
The starting material (5,11-dihydro-10H-dibenzo[a,d]cyclohepten-10-one) used in this step was derived from the combination of the previous batch (Intermediate 6) with another one prepared using the same procedure.

To a solution of K-*t*-butoxide, prepared by dissolving potassium metal (0.093g, 2.4mmol) in a mixture of *t*-butyl alcohol (9mL) and dry toluene (2mL), were added 5,11-dihydro-10H-dibenzo[a,d]cyclohepten-10-one (Intermediate 6, 0.166g, 0.80 mmol) and allyl bromide

(0.21mL, 2.4mmol) dropwise. When the addition was complete the reaction was left at room temperature for 1 hour, then it was heated to 50-60°C for 45 minutes. Then it was cooled to room temperature, water was added and the mixture was extracted with diethyl ether. Recrystallization from methanol afforded the title compound (0.156g);

- 5 MS (ESI) m/z : 311 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1241, 1451, 1598, 1669, 2927, 3077; 1H NMR ($CDCl_3$): δ 2.75 - 2.96 (m, 4 H), 3.94 (s, 2 H), 4.92 - 5.04 (m, 4 H), 5.42 - 5.55 (m, 2 H), 7.10 - 7.35 (m, 8 H).

Intermediate 8: Spiro[cyclopent-3-ene-1,10'-dibenzo[a,d]cyclohepten]-11'(5'H)-one



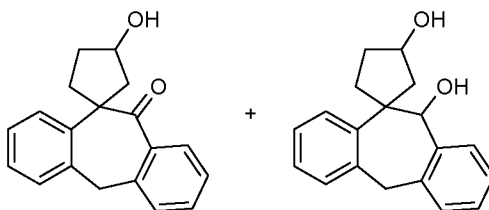
10

The starting material 11,11-di-2-propen-1-yl-5,11-dihydro-10*H*-dibenzo[a,d]cyclohepten-10-one used in this step was derived from the combination of the previous batch (Intermediate 7) with another one prepared with the same procedure.

- To a solution of 11,11-di-2-propen-1-yl-5,11-dihydro-10*H*-dibenzo[a,d]cyclohepten-10-one (Intermediate 7, 0.300g, 1.05mmol) in degassed CH_2Cl_2 (300mL) was added under Argon atmosphere at room temperature Grubbs catalyst 2nd generation (0.09g, 10mol%). After 7 hours starting material was still present (TLC check: 9/1 petroleum ether/diethyl ether), so further catalyst (0.09g, 10mol%) was added. The reaction mixture was left at room temperature under magnetic stirring overnight, it was then refluxed for 1 hour. After cooling the solution was absorbed on silica gel (10eq wt relative to catalyst) and passed through a pad of silica gel, washing with 6/1 petroleum ether/diethyl ether. The resulting solution was stirred with activated charcoal (50eq wt relative to the crude) for 12h. The carbon was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (9/1 petroleum ether/ diethyl ether) to give the title compound (0.224g);
- 15
- 20
- 25

MS (ESI) m/z : 283 $[M+Na]^+$; IR ($CHCl_3$) (ν , cm^{-1}): 1270, 1451, 1674, 3012; 1H NMR ($CDCl_3$): δ 2.92 - 2.99 (m, 2 H), 3.56 - 3.63 (m, 2 H), 4.36 (m, 2 H), 5.71 - 5.74 (m, 2 H), 7.09 - 7.51 (m, 7 H), 7.78 - 7.88 (m, 1 H).

- 30 Intermediate 9: 3-Hydroxyspiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-11'(5'H)-one and Intermediate 10: 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cycloheptene]-3,11'-diol



1M borane solution in THF (0.77mL, 0.77mmol) was added dropwise to a stirred solution of spiro[cyclopent-3-ene-1,10'-dibenzo[a,d]cyclohepten]-11'(5'H)-one (Intermediate 8, 0.200g, 0.77mmol) in anhydrous THF (1.6mL) at room temperature under N₂ atmosphere. The mixture was stirred at room temperature for 2.5 hours, and then water (0.08mL) was added dropwise, followed by 3M sodium hydroxide (0.10mL). Hydrogen peroxide (0.12mL, 35%) was then added at such a rate that the temperature of the mixture stayed between 30 and 50°C. After the addition was complete, the reaction mixture was stirred for 16 hours at room temperature. Diethyl ether (1.6mL) was added to the reaction mixture and the organic phase was washed with brine and water. The organic solvent was evaporated to give a residue which was purified by silica gel column chromatography (from 3/1 to 1/1 petroleum ether/diethyl ether) to afford the title compounds.

Intermediate 9 (0.091g):

MS (ESI) *m/z*: 279 [M+1]⁺, 301 [M+Na]⁺; 261 [M-H₂O]⁺; 579 [2M+Na]⁺;

IR (CHCl₃) (ν, cm⁻¹): 1451, 1596, 1670, 2929, 3011, 3612;

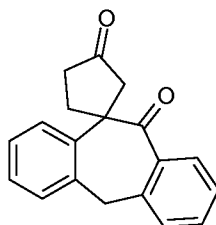
¹HNMR (CDCl₃): δ 1.66 - 1.92 (m, 2 H), 2.12 - 2.21 (m, 1 H), 2.32 - 2.48 (m, 1 H), 2.85 - 2.95 (m, 1 H), 3.21 - 3.30 (m, 1 H), 4.35 - 4.44 (m, 3 H), 7.10 - 7.46 (m, 7 H), 7.91 - 7.95 (m, 1 H).

Intermediate 10 (0.079g):

MS (ESI) *m/z*: 303 [M+Na]⁺;

¹HNMR (CDCl₃): δ 1.83 - 2.43 (m, 5 H), 2.61 - 2.71 (m, 1 H), 3.81 - 3.89 (m, 1 H), 4.47 - 4.61 (m, 2 H), 5.03 (s, 1 H), 7.03 - 7.61 (m, 8H).

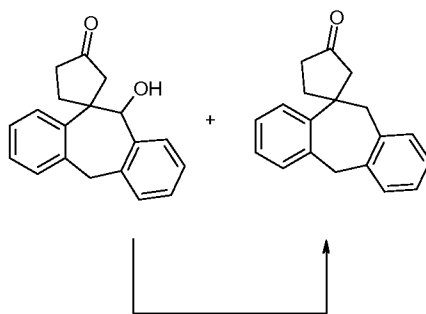
Intermediate 11: 3H-Spiro[cyclopentane-1,10'-dibenzo[a,d]cycloheptene]-3,11'(5'H)-dione



A mixture of 3-hydroxyspiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-11'(5'H)-one and 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cycloheptene]-3,11'-diol (Intermediates 9 & 10, 0.100g) was added to a solution of Dess-Martin periodinane (0.38g, 0.9mmol) in dry CH₂Cl₂ (8mL). The reaction mixture was stirred at 25°C for 3.5 hours. It was then diluted with DCM and washed with 1N sodium hydroxide solution. The organic phase was removed under reduced pressure and the mixture was purified by silica gel column chromatography (1/1 petroleum ether/diethyl ether) to give the title compound (0.093g);

MS (ESI) *m/z*: 299 [M+Na]⁺; ¹HNMR (CDCl₃): δ 2.26 - 2.49 (m, 3 H), 2.76 - 2.84 (m, 1 H), 3.26 - 3.46 (m, 2 H), 4.32 - 4.51 (m, 2 H), 7.16 - 7.48 (m, 7 H), 7.92 - 7.96 (m, 1 H).

Intermediate 12: 11'-Hydroxy-5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one and Intermediate 13: 5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one



To a solution of 3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cycloheptene]-3,11'(5'H)-dione (Intermediate 11, 0.092g, 0.33mmol) in THF (5mL) and acetic acid (1mL) was added Pd/C 10% (20mg) and the reaction mixture was stirred under a hydrogen atmosphere (4 atm) for 16 hours. After this time further catalyst (Pd/C) was added (20mg) and the reaction mixture was stirred again under a hydrogen atmosphere (4 atm) for 24 hours. Then the mixture was filtered and the solution was evaporated. The mixture was purified by preparative TLC (1/1 petroleum ether/diethyl ether) to afford the title compounds.

Intermediate 12 (0.032g):

MS (ESI) *m/z*: 301 [M+Na]⁺;

¹HNMR (CDCl₃): δ 2.27 - 3.10 (m, 6 H), 3.67 - 3.75 (m, 1 H), 4.48 - 4.57 (m, 1 H), 5.49 (s, 1 H), 7.05 - 7.59 (m, 8 H).

Intermediate 13 (0.016g):

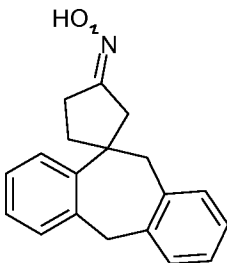
MS (ESI) m/z : 285 $[M+Na]^+$;

^1H NMR (CDCl_3): δ 2.24 - 2.32 (m, 2 H), 2.51 - 2.62 (m, 4 H), 3.09 - 3.16 (m, 2 H), 4.11 - 4.21 (m, 2 H), 7.04 - 7.35 (m, 8 H).

- 5 Intermediate 12 was then converted into Intermediate 13 using the typical procedure described below.

To a solution of 11'-hydroxy-5',11'-dihydro-3H-spiro[cyclopentane-1,10'-
dibenzo[a,d]cyclohepten]-3-one (Intermediate 12, 0.160g, 0.57mmol) in THF (18mL) and
10 acetic acid (4mL) was added Pd/C 10% (160mg) and the mixture was stirred under
hydrogen atmosphere (5 atm) for 24 hours to room temperature. After this time, further
catalyst (160mg) was added and the reaction mixture was stirred under a hydrogen
atmosphere (5 atm) for 24 hours. Then the mixture was filtered and the solution was
evaporated. The mixture was purified by preparative TLC (1/1 petroleum ether/diethyl
15 ether) affording Intermediate 13 (0.057g).

Intermediate 14 and Intermediate 15: (3E-Z)-5',11'-Dihydro-3H-spiro[cyclopentane-1,10'-
dibenzo[a,d]cyclohepten]-3-one oxime



20 To a solution of 5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one (Intermediate 13, 0.150g, 0.57mmol), in MeOH (8mL) and DCM (4mL) was added sodium acetate (0.23g, 2.87mmol) and hydroxylamine hydrochloride (0.20g, 2.86mmol). The reaction mixture was stirred at room temperature for 72 hours and then quenched
25 with phosphate buffer pH 7 (8mL). The organic solvent was removed under reduced pressure and the residue was diluted with DCM (10mL). The two phases were separated and the aqueous phase was extracted with DCM. The organic phase was evaporated to dryness and the mixture was purified by silica gel column chromatography (1/1 petroleum ether/ diethyl ether) affording Intermediate 14 (0.076g) and Intermediate 15 (0.052g).

30

NMR analysis performed on the two isomers did not allow to define the geometry of the double bond. The two intermediates were combined to carry out the next step.

Intermediate 14:

5 MS (ESI) m/z : 278 $[M+1]^+$;

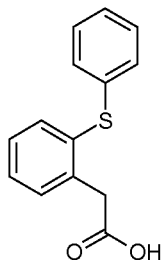
^1H NMR (300 MHz, DMSO- d_6): δ 1.86 - 1.98 (m, 1 H), 1.97 - 2.13 (m, 1 H), 2.49 (d, 1 H), 2.54 - 2.69 (m, 2 H), 2.71 (d, 1 H), 2.93 (d, 1 H), 3.05 (d, 1 H), 4.12 (d, 1 H), 4.22 (d, 1 H), 7.03 - 7.10 (m, 1 H), 7.12 - 7.22 (m, 5 H), 7.24 - 7.29 (m, 1 H), 7.49 (d, 1 H), 10.39 (s, 1 H).

Intermediate 15:

10 MS (ESI) m/z : 278 $[M+1]^+$;

^1H NMR (400 MHz, DMSO- d_6): δ 1.77 - 2.01 (m, 2 H), 2.44 (d, 1 H), 2.45 - 2.57 (m, 1 H), 2.59 - 2.71 (m, 1 H), 2.77 (d, 1 H), 2.90 (d, 1 H), 3.06 (d, 1 H), 4.01 (d, 1 H), 4.19 (d, 1 H), 6.97 - 7.03 (m, 1 H), 7.06 - 7.15 (m, 5 H), 7.20 (dd, 1 H), 7.31 (d, 1 H), 10.31 (s, 1 H).

Intermediate 16: [2-(Phenylthio)phenyl]acetic acid



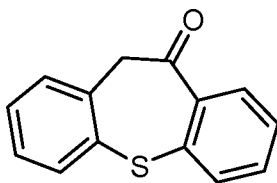
Equimolar amounts of 2-iodophenylacetic acid (200 mg, 0.763 mmol, Aldrich) and

20 Thiophenol (78 μL , 0.763 mmol, Aldrich) in a solution of KOH (475 mg) in water (5 mL) and copper bronze (5 mg, 0.0763 mmol, Aldrich) were refluxed for 5 hours. The reaction mixture was taken-up with EtOAc and it was washed with water, diluted HCl solution and brine. The aqueous phase was concentrated and filtered. 1N HCl was added to the filtered solution and a precipitate was formed. The title compound was collected after

25 filtration as a white solid (180 mg);

MS (ESI) m/z : 267 $[M+\text{Na}]^+$; ^1H NMR (200 MHz, CDCl_3): δ 3.88 (s, 2 H), 7.16 - 7.33 (m, 7 H), 7.41 - 7.45 (d, 2 H), 10.77 (s, 1 H).

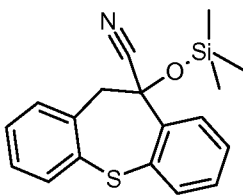
Intermediate 17: Dibenzo[b,f]thiepin-10(11H)-one



[2-(Phenylthio)phenyl]acetic acid (Intermediate 16, 100 mg, 0.410 mmol) was added portionwise to a stirred and refluxing solution of polyphosphoric acid (0.5 mL, Aldrich) in toluene (3 mL). The mixture was stirred at 110°C for 24hrs. After cooling, the solvent was evaporated to give a residue that was dissolved in EtOAc. The organic phase was washed with water, Na₂CO₃ aq. solution and brine and it was concentrated. The crude was purified by flash-chromatography (9/1 petroleum ether/diethyl ether) to give the title compound (30 mg);

MS (ESI) *m/z*: 249 [M+Na]⁺; ¹H NMR (200 MHz, CDCl₃): δ 4.34 (s, 2 H), 7.12 - 7.44 (m, 5 H), 7.55 - 7.62 (m, 2 H), 8.15 - 8.20 (m, 1 H).

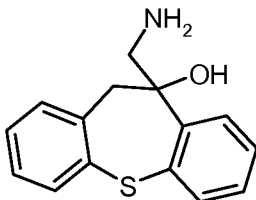
Intermediate 18: 10-[(Trimethylsilyl)oxy]-10,11-dihydrodibenzo[b,f]thiepin-10-carbonitrile



A solution of dibenzo[b,f]thiepin-10(11H)-one (Intermediate 17, 300 mg, 1.327 mmol), in anhydrous toluene (3mL) was treated with trimethylsilyl cyanide (498 μL, 3.98 mmol, Fluka) and zinc iodide (127 mg, 0.1398 mmol, Aldrich). The mixture was stirred at 40°C for 24hrs. After evaporation of the solvent, the residue was purified by silica gel chromatography (from 1/0 to 95/5 petroleum ether/diethyl ether) and by preparative TLC (5/1 petroleum ether/diethyl ether) to give the title compound;

MS (ESI) *m/z*: 326 [M+H]⁺, 348 [M+Na]⁺; ¹H NMR (200 MHz, CDCl₃): δ 0.19 (s, 9 H), 3.68 (d, 1 H), 4.21 (d, 1 H), 7.19 - 7.77 (m, 8 H).

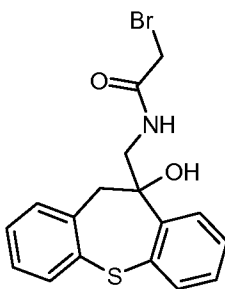
Intermediate 19: 10-(Aminomethyl)-10,11-dihydrodibenzo[b,f]thiepin-10-ol



To a cooled (ice bath) suspension of LiAlH_4 powder (121 mg, 3.2 mmol, Aldrich) in anhydrous THF (1 mL) was slowly added 10-[(trimethylsilyl)oxy]-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (Intermediate 18, 800 mg, 2.46 mmol) and the reaction mixture was refluxed with stirring for 4hrs. After cooling, the excess of LiAlH_4 was quenched with water and the mixture was diluted with diethyl ether and washed with 1N NaOH and brine. After evaporation of the organic layer, the crude product was purified by silica gel chromatography (from 1/0 to 98/2 EtOAc/MeOH) to give the title compound (140 mg);

MS (ESI) m/z : 258 $[\text{M}+\text{H}]^+$, 280 $[\text{M}+\text{Na}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.51 (br.s., 2 H), 2.45 (d, 1 H), 2.61 (d, 1 H), 3.38 (d, 1 H), 3.69 (d, 1 H), 5.44 (br.s., 1 H), 7.12 (t, 1 H), 7.17 (t, 1 H), 7.23 (t, 1 H), 7.29 (t, 1 H), 7.37 (d, 1 H), 7.50 (d, 2 H), 7.64 (d, 1 H).

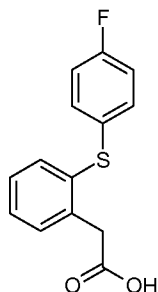
Intermediate 20: 2-Bromo-N-[(10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)methyl]acetamide



Freshly distilled DIPEA (34 μL , 0.194 mmol, Aldrich) was added to a solution of 10-(aminomethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (Intermediate 19, 50 mg, 0.194 mmol) in anhydrous DCM. Bromoacetyl chloride (18 μL , 0.214 mmol, Fluka) was added and the reaction mixture was stirred at room temperature for 3hrs. EtOAc was added, the two phases were separated and the organic layer was washed with water and brine. After evaporation of the solvent, the crude product was purified by silica gel chromatography (from 1/0 to 9:1 DCM/AcOEt) to give the title compound (50 mg);

MS (ESI) m/z : 401 $[\text{M}+\text{Na}]^+$; 779 $[2\text{M}+\text{Na}]^+$; ^1H NMR (200 MHz, CDCl_3): δ 3.43 (d, 2 H), 3.56 (d, 1 H), 3.84 (d, 1 H), 3.89 (s, 2 H), 6.83 (s, 1 H), 7.09 - 7.35 (m, 5 H), 7.45 - 7.56 (m, 2 H), 7.69 (d, 1 H).

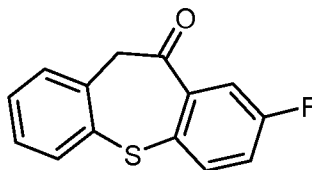
Intermediate 21: {2-[(4-Fluorophenyl)thio]phenyl}acetic acid



A solution of KOH (86 mg, 1.53 mmol) in water (7 mL) was reacted under N₂ atmosphere with 4-Fluorothiophenol (41 μ L, 0.382 mmol, Aldrich) and the reaction mixture was stirred at 50°C for 15 min. Then 2-iodophenylacetic acid (100 mg, 0.382 mmol, Fluka) and copper bronze (0.24 mg, 0.004 mmol, Aldrich) were added and the reaction mixture was heated at reflux overnight. The hot mixture was filtered through a fritted filter funnel and the filtrate was quenched with 1N HCl and extracted with diethyl ether. Evaporation of the solvent gave the title compound (50 mg);

MS (ESI) m/z : 285 [M+Na]⁺; IR (CHCl₃): 3066, 1713 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 3.87 (s, 2 H), 6.91 - 7.00 (m, 2 H), 7.18 - 7.36 (m, 5 H), 7.85 (d, 1 H), 10.22 (s, 1 H).

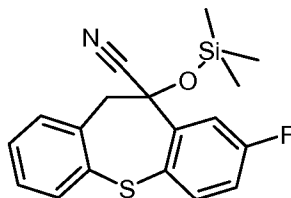
Intermediate 22: 8-Fluorodibenzo[b,f]thiepin-10(11H)-one



{2-[(4-fluorophenyl)thio]phenyl}acetic acid (Intermediate 21, 400 mg, 1.53 mmol) and polyphosphoric acid (4 mL) were refluxed for 2hrs. EtOAc was added and the organic phase was extracted with water, 2M NaOH aq. solution and brine. Evaporation of the solvent gave the title compound (280 mg);

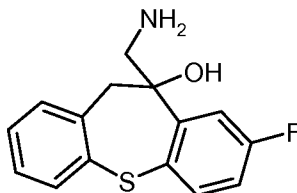
MS (ESI) m/z : 245 [M+H]⁺, 511 [2M+Na]⁺; ¹H NMR (200 MHz, CDCl₃): δ 4.36 (s, 2 H), 7.06 - 7.24 (m, 2 H), 7.30 - 7.44 (m, 2 H), 7.53 - 7.63 (m, 2 H), 7.84 - 7.90 (m, 1 H).

Intermediate 23: 8-Fluoro-10-[(trimethylsilyl)oxy]-10,11-dihydrodibenzo[b,f]thiepin-10-carbonitrile



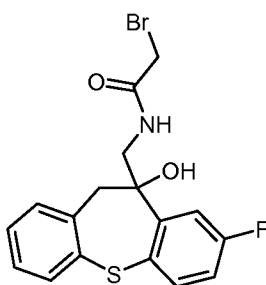
A solution of 8-fluorodibenzo[b,f]thiepin-10(11H)-one (Intermediate 22, 68 mg, 0.279 mmol) in anhydrous toluene (2 mL) was treated with trimethylsilyl cyanide (105 μ L, 0.836 mmol, Fluka) and zinc iodide (27 mg, 0.084 mmol, Aldrich). The reaction mixture was stirred at 40°C for 3.5hr. After evaporation of the solvent, the residue was purified by preparative TLC on silica (5/1 hexane/diethyl ether) to give the title compound; MS (ESI) m/z : 366 $[M+Na]^+$.

Intermediate 24: 10-(Aminomethyl)-8-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-ol



To a cooled (ice bath) suspension of $LiAlH_4$ powder (80 mg, 2.099 mmol, Aldrich) in anhydrous diethyl ether (2 mL) was slowly added a solution of 8-fluoro-10-[(trimethylsilyl)oxy]-10,11-dihydrodibenzo[b,f]thiepin-10-carbonitrile (Intermediate 23, 600 mg, 1.749 mmol) in anhydrous diethyl ether (3 mL) and the reaction mixture was heated at reflux for 2hr. After cooling, excess of $LiAlH_4$ was quenched with water and the mixture was diluted with diethyl ether. The two phases were separated and the organic layer was washed with 15% NaOH aq. solution and brine. After evaporation of the solvent, the residue was purified by flash-chromatography on silica gel (diethyl ether and then from 1/0 to 95/5 EtOAc/MeOH) to give the title compound (220 mg); MS (ESI) m/z : 276 $[M+H]^+$, 298 $[M+Na]^+$; 1H NMR (200 MHz, CD_3OD): δ 2.61 - 2.76 (m, 2 H), 3.38 - 3.46 (m, 1 H), 3.80 - 3.90 (m, 1 H), 6.80 - 6.91 (m, 1 H), 7.11 - 7.18 (m, 1 H), 7.22 - 7.30 (m, 1 H), 7.38 - 7.51 (m, 4 H).

Intermediate 25: 2-Bromo-N-[(8-fluoro-10-hydroxy-10,11-dihydrodibenzo[b,f]thiepin-10-yl)methyl]acetamide

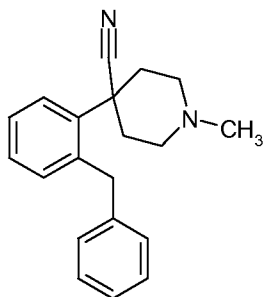


Freshly distilled DIPEA (139 μ L, 0.8 mmol, Aldrich) was added to a solution of 10-(aminomethyl)-8-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-ol (Intermediate 24, 220 mg,

0.8 mmol) in anhydrous DCM (5 mL). Bromoacetyl chloride (73 μ L, 0.88 mmol, Fluka) was added dropwise and the reaction mixture was stirred at room temperature for 2hr. Water was added and the mixture was extracted with EtOAc. The organic phase was washed with brine and the solvent was evaporated. The crude was purified by flash-

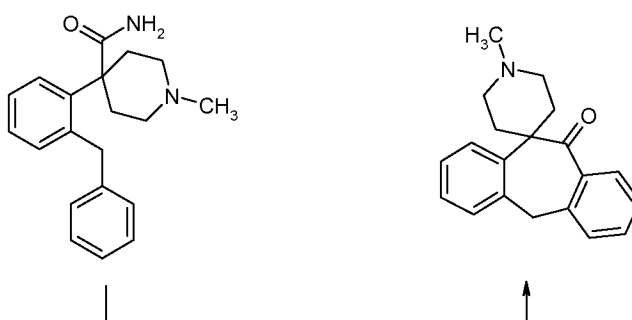
- 5 chromatography on silica gel (diethyl ether) to give the title compound (290 mg);
 ^1H NMR (200 MHz, CDCl_3): δ 3.32 - 3.62 (m, 4 H), 3.80 - 3.89 (m, 2 H), 6.80 - 6.90 (m, 1 H), 7.11 - 7.56 (m, 7 H).

Intermediate 26 : 1-Methyl-4-[2-(phenylmethyl)phenyl]-4-piperidinecarbonitrile



- 10 To a solution of [2-(phenylmethyl)phenyl]acetonitrile (Intermediate 4, 2.27g, 10.96mmol) in anhydrous DMSO (50mL) was added NaH (1.05g, 43.86mmol) in small portions. After stirring the reaction at room temperature for 30 minutes, a solution of methchloroethamine hydrochloride (2.00g, 10.42mmol) in dry DMSO (50 mL) was added dropwise and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was then
 15 poured into ice and extracted with diethyl ether. The organic layer was evaporated and the residue was purified by silica gel column chromatography (95/3/2 ethyl acetate/methanol/triethylamine) to give the title compound (0.636g);
 MS (ESI) m/z : 291[M+1] $^+$.

- 20 Intermediate 27: 1-Methyl-4-[2-(phenylmethyl)phenyl]-4-piperidinecarboxamide and
Intermedite 28: 1'-Methylspiro[dibenzo[a,d]cycloheptene-10,4'-piperidin]-11(5H)-one



- A mixture of 1-methyl-4-[2-(phenylmethyl)phenyl]-4-piperidinecarbonitrile (Intermediate
 25 26, 0.580, 2.00mmol) in 48% aqueous hydrobromic acid (20mL) was heated to 110°C for

1 day. TLC analysis (TLC check: 95/3/2 ethyl acetate/methanol/triethylamine) revealed the presence of starting material, so the reaction mixture was refluxed for 6 more days while further amounts of 48% aqueous hydrobromic acid (4x10mL) were added. The reaction mixture was cooled down to room temperature and major amount of volatiles were removed under reduced pressure. The aqueous phase was basified with 32% NH₄OH solution and then extracted with EtOAc. The aqueous phase was then acidified to pH=5.5-5 with 1N HCl and extracted using CHCl₃. The aqueous phase was evaporated to dryness to afford a white solid dried as much as possible under high vacuum, then washed three times using CHCl₃ and filtered over filtering paper. The filtered solution was combined with the previous organic phases (CHCl₃) and evaporated under vacuum to give a residue. This solid was added to the least amount of PPA previously heated to 90-95°C and heating was continued for 0.5 hour. After cooling, water was added and the solution was basified with 32% NH₄OH solution. The aqueous phase was then extracted with diethyl ether and the organic phase was dried and evaporated under reduced pressure. The major part of impurities were removed by silica gel column chromatography (95/3/2 ethyl acetate/ methanol/ Et₃N) to give an oil. The mixture was dissolved in diethyl ether and activated charcoal was added to the solution. The mixture was left under magnetic stirring at room temperature for 30 minutes. The mixture was filtered and the filtrate was evaporated to dryness to give Intermediate 27 (0.160g) and Intermediate 28 (0.157g).

Intermediate 27:

MS (ESI) *m/z*: 309 [M+1]⁺.

Intermediate 28:

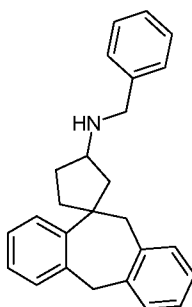
MS (ESI) *m/z*: 292 [M+1]⁺;

¹H NMR (CDCl₃): δ 1.97 - 2.22 (m, 4 H), 2.25 (s, 3 H), 2.81 - 2.85 (m, 4 H), 4.59 (s, 2 H), 7.17 - 7.47 (m, 7 H), 7.77 - 7.79 (m, 1 H); ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.74 - 1.99 (m, 4 H) 2.06 (s, 3 H) 2.60 - 2.69 (m, 4 H) 4.64 (s, 2 H) 7.22 (t, 1 H) 7.31 - 7.44 (m, 5 H) 7.54 (t, 1 H) 7.62 (d, 1 H)

Intermediate 27 was converted into Intermediate 28 using the following procedure: a mixture of Intermediate 27 (0.160g, 0.52mmol) in 48% aqueous hydrobromic acid (15mL) was irradiated by microwaves in a sealed tube (1st time: T=130°C, t=20 minutes; 2nd time T=180°C, t=25 minutes). After cooling, the mixture was reduced under vacuum, the aqueous phase was basified using 32% NH₄OH solution and then extracted with EtOAc.

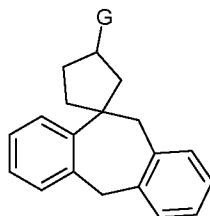
The aqueous phase was then acidified to pH=5.5-5 with 1N HCl and then it was extracted with CHCl₃. The aqueous phase was evaporated to dryness to give a white solid that was dried under high vacuum, washed with CHCl₃ (3X) and filtered over filtering paper. The filtered solution was combined with the previous organic phases (CHCl₃), dried and
5 evaporated under vacuum to get a light yellow solid. The solid was dissolved in the least amount of PPA previously heated to 90/95°C and heating was continued for 0.5 hour. After cooling, water was added and the solution was basified with 32% NH₄OH solution. The aqueous phase was then extracted using diethyl ether and the organic phase was dried and evaporated under reduced pressure. The major part of impurities were removed
10 by silica gel column chromatography (95/3/2 ethyl acetate/ methanol/ Et₃N) to get an oil that was dissolved in diethyl ether. Activated charcoal was added to the solution and the mixture was left under magnetic stirring at room temperature for 30 minutes. The mixture was filtered through filtering paper and the filtrate was evaporated to dryness to give Intermediate 28 (0.039g);
15 MS (ESI) *m/z*: 292 [M+1]⁺.

Intermediate 29: N-(Phenylmethyl)-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo [a,d] cyclohepten]-3-amine



20 Benzylamine (0.084mL, 0.76mmol) and 5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one (Intermediate 13, 0.10g, 0.38mmol) were mixed in DCE (16mL) and glacial acetic acid (0.028mL). After 1 hour NaBH(OAc)₃ (0.114g, 0.054mmol) was added. The reaction mixture was stirred for 24 hours at room temperature. Then 1N NaOH solution was added and the aqueous phase was extracted with DCM. The organic
25 phase was dried and evaporated to dryness and the crude was purified by preparative TLC (ethyl acetate) affording the title compound (0.134g);
MS (ESI) *m/z*: 354 [M+1]⁺; ¹HNMR (CDCl₃): δ 1.82 - 2.36 (m, 6 H), 3.22 - 3.42 (m, 2 H), 3.60 - 3.71 (m, 1 H), 3.90 (s, 2 H), 4.07 - 4.30 (m, 2 H), 7.07 - 7.66 (m, 13 H).

30 Compounds 1-8 of general structure:



General procedure for amine synthesis: Appropriate amine (G) (1-3 eq) and 5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one (Intermediate 13, 1 eq) were mixed in DCE and glacial acetic acid (1eq). After 1-24 hours at room temperature $\text{NaBH}(\text{OAc})_3$ (1.4-2.8 eq) was added and the resulting reaction mixture was stirred at room temperature from 12 to 24 hours, checking the reaction by TLC analysis. The work-up was done by adding 1N NaOH aq. and then by extracting with DCM. Products were purified by silica gel column chromatography or preparative TLC using appropriate eluent.

The use of NaBH_4 as reducing agent was necessary to get the compound *N*-methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine (Compound 5).

Compound	G	TLC and column chromatography	^1H NMR
1: N,N-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine	Dimethylamine	ethyl acetate/ methanol 98/2	^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.68 - 2.08 (m, 6 H), 2.20 (s, 6 H), 2.77 - 2.93 (m, 1 H), 3.07 (d, 1 H), 3.19 (d, 1 H), 4.04 (d, 1 H), 4.20 (d, 1 H), 6.99 - 7.06 (m, 1 H), 7.09 - 7.25 (m, 6 H), 7.24 - 7.31 (m, 1 H); Mixture of diastereoisomers

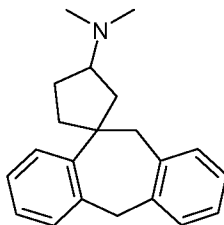
			ratio ca. 8:2.
2: 4-(5',11'- dihydrospiro[cyclopentane- 1,10'-dibenzo[a,d]cyclohepten]- 3-yl)morpholine	Morpholine	diethyl ether	¹ H NMR (500 MHz, DMSO-d ₆): δ 1.69 - 1.76 (m, 1 H), 1.76 - 1.85 (m, 2 H), 1.89 - 1.97 (m, 2 H), 1.96 - 2.03 (m, 1 H), 2.34 - 2.47 (m, 4 H), 2.86 - 2.97 (m, 1 H), 3.03 (d, 1 H), 3.20 (d, 1 H), 3.54 - 3.64 (m, 4 H), 3.99 (d, 1 H), 4.19 (d, 1 H), 7.00 (t, 1 H), 7.10 (dd, 2 H), 7.12 - 7.18 (m, 2 H), 7.21 (t, 2 H), 7.26 (d, 1 H). Mixture of diastereoisomers ratio ca. 7:1.
3: 1-(5',11'- dihydrospiro[cyclopentane- 1,10'-dibenzo[a,d]cyclohepten]- 3-yl)pyrrolidine	Pyrrolidine	ethyl acetate/ methanol 98/2	¹ H NMR (500 MHz, DMSO-d ₆): δ 1.65 - 1.72 (m, 4 H), 1.69 - 1.79 (m, 1 H), 1.82 - 1.95 (m, 4 H), 1.95 - 2.03 (m, 1 H), 2.38 - 2.48

			(m, 4 H), 2.77 - 2.90 (m, 1 H), 3.06 (d, 1 H), 3.19 (d, 1 H), 4.01 (d, 1 H), 4.17 (d, 1 H), 6.99 (t, 1 H), 7.07 - 7.13 (m, 2 H), 7.13 - 7.17 (m, 2 H), 7.17 - 7.23 (m, 2 H), 7.27 (d, 1 H). Mixture of diastereoisomers ratio ca. 6:1.
4: 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)-4-methylpiperazine	Methylpiperazine	ethyl acetate/ methanol 98/2	¹ H NMR (500 MHz, DMSO-d ₆): δ 1.65 - 2.03 (m, 6 H), 2.13 - 2.15 (m, 3 H), 2.15 - 2.68 (m, 8 H), 2.84 - 2.93 (m, 1 H), 3.00 (d, 1 H), 3.20 (d, 1 H), 3.98 (d, 1 H), 4.20 (d, 1 H), 6.96 - 7.28 (m, 8 H). Mixture of diastereoisomers ratio ca. 92:8
5: <i>N</i> -methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine	Methylamine	ethyl acetate/ methanol/ triethylamine 95/3/2	¹ H NMR (500 MHz, DMSO-d ₆): δ 1.63 - 1.78 (m, 2 H), 1.87 - 1.98 (m, 2 H), 2.08 - 2.09 (m, 2 H),

			2.28 - 2.31 (m, 3 H), 3.16 - 3.17 (m, 2 H), 3.28 - 3.34 (m, 1 H), 4.04 - 4.13 (m, 2 H), 6.94 - 7.27 (m, 8 H). Mixture of diastereoisomers ratio ca. 85:15.
6: 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)thiomorpholine	Thiomorpholine	petroleum ether/ diethyl ether 1/1	¹ H NMR (500 MHz, DMSO-d ₆): δ 1.56 - 2.04 (m, 6 H), 2.53 - 2.84 (m, 8 H), 3.00 (d, 1 H), 3.04 - 3.16 (m, 1 H), 3.18 (d, 1 H), 3.98 (d, 1 H), 4.20 (d, 1 H), 6.99 (t, 1 H), 7.07 - 7.18 (m, 4 H), 7.21 (t, 2 H), 7.26 (d, 1 H). Mixture of diastereoisomers ratio ca. 90:10
7: 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine	Azetidine	ethyl acetate/ methanol/ triethylamine 95/3/2	¹ H NMR (400 MHz, DMSO-d ₆): δ 1.58 - 1.86 (m, 4 H), 1.83 - 2.06 (m, 4 H), 3.02 (t, 1 H), 3.00 - 3.17 (m, 4 H), 3.11 (d, 2 H), 3.99 - 4.20 (m, 2 H), 6.94 -

			7.30 (m, 8 H). Mixture of diastereoisomers ratio ca. 85:15.
8: 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[<i>a,d</i>]cyclohepten]-3-yl)piperidine	Piperidine	EtOAc/MeOH 98/2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ 1.35 - 1.43 (m, 2 H), 1.46 - 1.58 (m, 4 H), 1.64 - 1.74 (m, 1 H), 1.72 - 1.87 (m, 2 H), 1.87 - 2.04 (m, 3 H), 2.32 - 2.49 (m, 4 H), 2.87 - 2.97 (m, 1 H), 3.01 (d, 1 H), 3.19 (d, 1 H), 3.98 (d, 1 H), 4.20 (d, 1 H), 6.99 (t, 1 H), 7.08 - 7.13 (m, 2 H), 7.12 - 7.18 (m, 2 H), 7.18 - 7.23 (m, 2 H), 7.25 (d, 1 H). Mixture of diastereoisomers ratio ca. 90:10.

Compound 9: *N,N*-Dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 1)



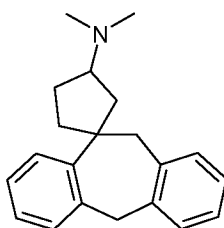
40 mg of *N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 1, 0.14 mmol) were purified by chiral chromatography [SFC chromatographic conditions column: CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1%

5 isopropylamine 10 %]: R_t = 11.68 min. Solvents were removed under reduced pressure to give the title compound (7.9 mg);

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.64 - 2.04 (m, 6 H), 2.17 (s, 6 H), 2.72 - 2.85 (m, 1 H), 3.05 (d, 1 H), 3.18 (d, 1 H), 4.02 (d, 1 H), 4.18 (d, 1 H), 6.91 - 7.32 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, pressure:

10 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 10 %]: R_t = 12.42 min. (100 % ee).

Compound 10: *N,N*-Dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 2)



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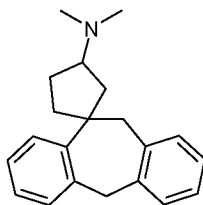
40 mg of *N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 1, 0.14 mmol) were purified by chiral chromatography [SFC chromatographic conditions column: CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1%

20 isopropylamine 10 %]: R_t = 13.23 min. Solvents were removed under reduced pressure to give the title compound (5.4 mg);

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.64 - 2.04 (m, 6 H), 2.17 (s, 6 H), 2.72 - 2.85 (m, 1 H), 3.05 (d, 1 H), 3.18 (d, 1 H), 4.02 (d, 1 H), 4.18 (d, 1 H), 6.91 - 7.32 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, pressure:

25 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 10 %]: R_t = 14.05 min. (100 % ee).

Compound 11: *N,N*-Dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 3)



40 mg of *N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 1, 0.14 mmol) were purified by chiral chromatography [SFC

chromatographic conditions column: CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar,

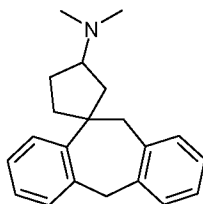
5 Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1%

isopropylamine 10 %]: *R*_t = 14.79 min. Solvents were removed under reduced pressure to give the title compound (1.5 mg);

¹H NMR (500 MHz, DMSO-*d*₆): δ 1.49 - 2.23 (m, 12 H), 2.70 - 2.91 (m, 1 H), 2.93 - 3.21 (m, 2 H), 3.94 - 4.23 (m, 2 H), 6.92 - 7.43 (m, 8 H).

10

Compound 12: *N,N*-Dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 4)



40 mg of *N,N*-dimethyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 1, 0.14 mmol) were purified by chiral chromatography [SFC

chromatographic conditions column: CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar,

Flow rate: 2.0 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1%

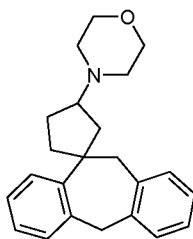
isopropylamine 10 %] *R*_t = 21.65 min. Solvents were removed under reduced pressure to give the title compound (0.7 mg);

¹H NMR (500 MHz, DMSO-*d*₆): δ 1.65 (dd, 1 H), 1.78 - 1.91 (m, 3 H), 2.04 (dd, 1 H), 2.07 - 2.13 (m, 1 H), 2.13 - 2.18 (m, 6 H), 2.76 - 2.84 (m, 1 H), 3.02 - 3.12 (m, 2 H), 4.04 - 4.15 (m, 2 H), 6.97 - 7.37 (m, 8 H).

20

Compound 13: 4-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-yl)morpholine (Isomer 1)

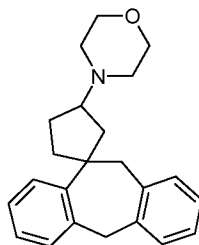
25



53 mg of 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)morpholine (Compound 2, 0.16 mmol) were purified by chiral chromatography [semipreparative chiral SFC conditions column: CHIRALCEL OJ-H, 25x2.1 cm, pressure: 176 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 8 %]. Solvents were removed under reduced pressure to give the title compound as a colourless oil (10.2 mg);

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.64 - 2.10 (m, 6 H), 2.30 - 2.58 (m, 4 H), 2.88 - 2.99 (m, 1 H), 3.01 - 3.12 (m, 1 H), 3.16 - 3.27 (m, 1 H), 3.51 - 3.71 (m, 4 H), 4.00 (d, 1 H), 4.21 (d, 1 H), 6.94 - 7.36 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALPAK OJ-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 240 nm, modifier: Ethanol + 0.1% isopropylamine 8 %]: R_t = 13.58 min. (100 % ee).

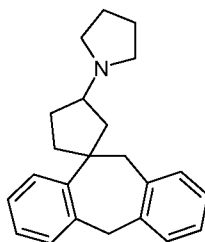
Compound 14: 4-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)morpholine (Isomer 2)



53 mg of 4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)morpholine (Compound 2, 0.16 mmol) were purified by chiral chromatography [semipreparative chiral SFC conditions column: CHIRALCEL OJ-H, 25x2.1 cm, pressure: 176 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 8 %]. Solvents were removed under reduced pressure to give the title compound as a colourless oil (10.6 mg);

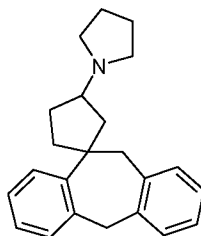
¹H NMR (400 MHz, DMSO-*d*₆): δ 1.62 - 2.10 (m, 6 H), 2.30 - 2.49 (m, 4 H), 2.88 - 2.99 (m, 1 H), 3.01 - 3.12 (m, 1 H), 3.16 - 3.27 (m, 1 H), 3.51 - 3.71 (m, 4 H), 4.00 (d, 1 H), 4.21 (d, 1 H), 6.94 - 7.36 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALPAK OJ-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 240 nm, modifier: Ethanol + 0.1% isopropylamine 8 %]: R_t = 15.16 min. (100 % ee).

Compound 15: 1-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)pyrrolidine (Isomer 1)



- 5 44 mg of 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)pyrrolidine (Compound 3, 0.14 mmol) were purified by chiral chromatography [semipreparative chiral SFC conditions column: CHIRALCEL OD-H, 25x2.1 cm, pressure: 173 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 13 %]. Solvents were removed under reduced pressure to give the title
- 10 compound as a colourless oil (4.6 mg);
¹H NMR (400 MHz, DMSO-*d*₆): δ 1.65 - 1.80 (m, 5 H), 1.80 - 2.05 (m, 5 H), 2.40 - 2.55 (m, 4 H), 2.80 - 2.92 (m, 1 H), 3.03 - 3.12 (m, 1 H), 3.17 - 3.25 (m, 1 H), 4.02 (d, 1 H), 4.18 (d, 1 H), 6.97 - 7.32 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 240 nm,
- 15 modifier: Ethanol + 0.1% isopropylamine 13 %]: R_t = 15.40 min. (100 % ee).

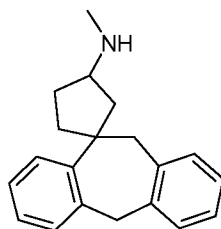
Compound 16: 1-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)pyrrolidine (Isomer 2)



- 20 44 mg of 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)pyrrolidine (Compound 3, 0.14 mmol) were purified by chiral chromatography [semipreparative chiral SFC conditions column: CHIRALCEL OD-H, 25x2.1 cm, pressure: 173 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 13 %]. Solvents were removed under reduced pressure to give the title
- 25 compound as a colourless oil (6.7 mg);
¹H NMR (400 MHz, DMSO-*d*₆): δ 1.65 - 1.80 (m, 5 H), 1.80 - 2.05 (m, 5 H), 2.40 - 2.55 (m, 4 H), 2.80 - 2.92 (m, 1 H), 3.03 - 3.12 (m, 1 H), 3.17 - 3.25 (m, 1 H), 4.02 (d, 1 H), 4.18 (d,

1 H), 6.97 - 7.32 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 240 nm, modifier: Ethanol + 0.1% isopropylamine 13 %]: R_t = 16.75 min. (81 % ee).

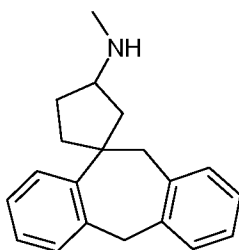
5 Compound 17: *N*-Methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 1)



40 mg of *N*-methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 5, 0.14 mmol) were purified by chiral chromatography [semipreparative
10 chiral SFC conditions column: CHIRALPAK AD-H, 25x2.1 cm, pressure: 180 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 13 %]. Solvents were removed under reduced pressure to give the title compound (6.2 mg) as a colourless oil;

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.50 - 2.20 (m, 6 H), 2.26 - 2.33 (m, 3 H), 3.11 - 3.26 (m,
15 2 H), 3.26 - 3.43 (m, 1 H), 4.03 - 4.16 (m, 2 H), 6.90 - 7.40 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALPAK AD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 225 nm, modifier: 2-Propanol+ 0.1% isopropylamine 13 %]: R_t = 12.37 min. (100 % ee).

20 Compound 18: *N*-Methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Isomer 2)

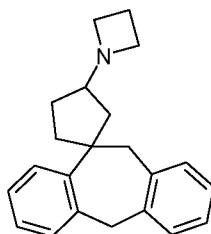


40 mg of *N*-methyl-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[*a,d*]cyclohepten]-3-amine (Compound 5, 0.14 mmol) were purified by chiral chromatography [semipreparative
25 chiral SFC conditions column: CHIRALPAK AD-H, 25x2.1 cm, pressure: 180 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: Ethanol + 0.1% isopropylamine 13

5 %]. Solvents were removed under reduced pressure to give the title compound (7.3 mg) as a colourless oil;

¹H NMR (500 MHz, DMSO-*d*₆): δ 1.50 - 2.20 (m, 6 H), 2.26 - 2.33 (m, 3 H), 3.11 - 3.26 (m, 2 H), 3.26 - 3.43 (m, 1 H), 4.03 - 4.16 (m, 2 H), 6.90 - 7.40 (m, 8 H); Chiral analysis, SFC
 5 chromatographic conditions [CHIRALPAK AD-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 225 nm, modifier: Ethanol + 0.1% isopropylamine 13 %]: R_t = 14.63 min. (100 % ee).

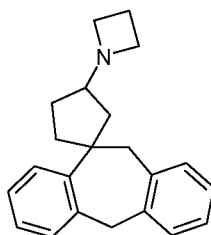
10 Compound 19: 1-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine (Isomer 1)



30 mg of 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine (Compound 7, 0.1 mmol) were purified by chiral chromatography [chromatographic
 15 conditions column: CHIRALCEL OD-H, 25x0.46 cm, n-Hexane/Ethanol 95/5 % v/v, Flow rate: 0.8 mL/min, UV detection: CD 225 nm]. Solvents were removed under reduced pressure to give the title compound (5.1 mg) as a colourless oil;

¹H NMR (400 MHz, DMSO-*d*₆): δ 1.62 - 1.81 (m, 4 H), 1.85 - 2.00 (m, 4 H), 2.93 - 3.14 (m, 5 H), 3.15 - 3.26 (m, 2 H), 4.01 - 4.15 (m, 2 H), 6.92 - 7.34 (m, 8 H); Chiral analysis, SFC
 20 chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, n-Hexane/Ethanol 95/5 % v/v, Flow rate: 0.8 mL/min, UV detection: CD 225 nm]: R_t = 6.2 min. (100 % ee).

Compound 20: 1-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine (Isomer 2)

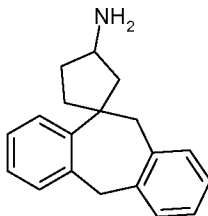


25 30 mg of 1-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)azetidine (Compound 7, 0.1 mmol) was purified by chiral chromatography [chromatographic conditions column: CHIRALCEL OD-H, 25x0.46 cm, n-Hexane/Ethanol 95/5 % v/v, Flow

rate: 0.8 mL/min, UV detection: CD 225 nm]. Solvents were removed under reduced pressure to give the title compound (6.6 mg) as a colourless oil;

^1H NMR (400 MHz, DMSO- d_6): δ 1.56 - 1.83 (m, 4 H), 1.83 - 2.06 (m, 4 H), 2.86 - 3.25 (m, 7 H), 3.98 - 4.19 (m, 2 H), 6.91 - 7.33 (m, 8 H), Chiral analysis, SFC chromatographic conditions [CHIRALCEL OD-H, 25x0.46 cm, n-Hexane/Ethanol 95/5 % v/v, Flow rate: 0.8 mL/min, UV detection: CD 225 nm]: R_t = 6.9 min. (100 % ee).

Compound 21: 5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine

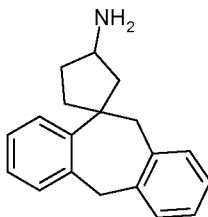


- 10 A solution of N-(phenylmethyl)-5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo [a,d] cyclohepten]-3-amine (Intermediate 29, 0.090g, 0.25mmol), Pd/C 10% (0.018g) and ammonium formate (0.080g, 1.27mmol) in methanol (1mL) and ethyl acetate (0.50mL) was heated to reflux for 2 hours. Then the reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite® and evaporated to dryness. The crude was purified by
15 silica gel column chromatography (95/3/2 ethyl acetate/ methanol/ triethylamine) to give the title compound (0.033g).

MS (ESI) m/z : 264 $[\text{M}+1]^+$; ^1H NMR (500 MHz, DMSO- d_6): δ 1.92 (br. s., 2 H), 1.58 - 1.75 (m, 2 H), 1.84 - 2.06 (m, 4 H), 3.16 (d, 1 H), 3.22 (d, 1 H), 3.58 - 3.68 (m, 1 H), 4.02 - 4.15 (m, 2 H), 6.98 (t, 1 H), 7.06 - 7.17 (m, 4 H), 7.17 - 7.28 (m, 3 H).

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Compound 22: 5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine (Isomer 1)

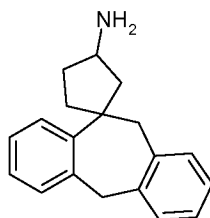


- 30 mg of 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine
25 (Compound 21, 0.11 mmol) were purified by chiral chromatography [SFC chromatographic conditions column: CHIRALPAK AS-H, 25x2.1 cm, pressure: 162 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: 2-Propanol + 0.1%

isopropylamine 17 %]. Solvents were removed under reduced pressure to give the title compound (1.6 mg) as a white solid;

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.40 - 2.30 (m, 8 H), 3.10 - 3.50 (m, 2 H), 3.56 - 3.69 (m, 1 H), 4.02 - 4.24 (m, 2 H), 6.90 - 7.41 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALPAK AS-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 225 nm, modifier: 2-Propanol + 0.1% isopropylamine 17 %]: R_t = 10.47 min; (100% e.e.).

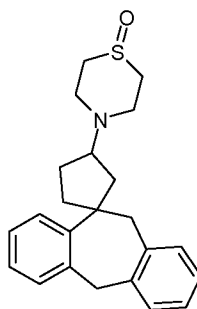
Compound 23: 5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine
(Isomer 2)



30 mg of 5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-amine (Compound 21, 0.11 mmol) were purified by chiral chromatography [SFC chromatographic conditions column: CHIRALPAK AS-H, 25x2.1 cm, pressure: 162 bar, Flow rate: 22 mL/min, UV detection: CD 220 nm, modifier: 2-Propanol + 0.1% isopropylamine 17 %]. Solvents were removed under reduced pressure to give the title compound (3.7 mg) as a white solid;

^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.44 - 2.30 (m, 8 H), 3.10 - 3.50 (m, 2 H), 3.56 - 3.69 (m, 1 H), 4.04 - 4.26 (m, 2 H), 6.91 - 7.41 (m, 8 H); Chiral analysis, SFC chromatographic conditions [CHIRALPAK AS-H, 25x0.46 cm, pressure: 100 bar, Flow rate: 2.0 mL/min, UV detection: CD 225 nm, modifier: 2-Propanol + 0.1% isopropylamine 17 %]: R_t = 11.66 min; (51% e.e.).

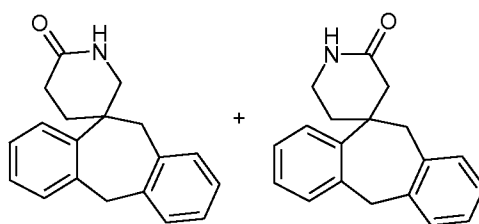
Compound 24: 4-(5',11'-Dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)thiomorpholine 1-oxide



4-(5',11'-dihydrospiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-yl)thiomorpholine (Compound 6, 0.044g, 0.13mmol) was dissolved in MeOH (2mL) and DCM (2mL) and the solution was cooled down to -8°C. The resulting slurry solution was treated with a solution of Oxone® (0.15g, 0.25mmol) in distilled water (2mL) in a slow stream while the temperature was maintained below 10°C. The reaction mixture was stirred for 10 mins at -10°C and then it was quenched using 5N NaOH solution (12mL). The aqueous phase was extracted with DCM. The organic phase was evaporated to dryness and the crude was purified by preparative TLC (95/5 dichloromethane/methanol) to give the title compound (0.032g). The sample which was tested was actually a recovered product from a failed reaction;

MS (ESI) m/z : 366 [M+1]⁺, 388 [M+Na]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.62 - 2.11 (m, 6 H), 2.63 - 2.82 (m, 4 H), 2.85 - 2.97 (m, 4 H), 3.02 (d, 1 H), 3.15 - 3.23 (m, 1 H), 3.19 (d, 1 H), 3.99 (d, 1 H), 4.19 (d, 1 H), 7.00 (t, 1 H), 7.07 - 7.19 (m, 4 H), 7.21 (t, 2 H), 7.28 (d, 1 H).

Compound 25: 5,11-dihydro-6'H-spiro[dibenzo[a,d]cycloheptene-10,3'-piperidin]-6'-one
and Compound 26: 5,11-dihydro-2'H-spiro[dibenzo[a,d]cycloheptene-10,4'-piperidin]-2'-one



A mixture of the two isomers 3E and 3Z-5',11'-dihydro-3H-spiro[cyclopentane-1,10'-dibenzo[a,d]cyclohepten]-3-one oxime (Intermediates 14 & 15, 0.067g, 0.24mmol) and PPA (1.34mL) was heated at 100°C for 10 minutes. After cooling to room temperature, cold water was added and the homogeneous solution was extracted using DCM. The combined organic phases were dried and concentrated. The crude product was purified by preparative TLC (1/2 petroleum ether / ethyl acetate) to give the two title compounds: 5,11-dihydro-6'H-spiro[dibenzo[a,d]cycloheptene-10,3'-piperidin]-6'-one and 5,11-dihydro-2'H-spiro[dibenzo[a,d]cycloheptene-10,4'-piperidin]-2'-one.

Compound 25 (0.015g):

MS (ESI) m/z : 300 [M+Na]⁺, 577 [2M+Na]⁺;

^1H NMR (500 MHz, DMSO- d_6): δ 1.62 - 1.71 (m, 1 H), 2.15 - 2.37 (m, 2 H), 2.38 - 2.50 (m, 1 H), 2.87 (dd, 1 H), 3.17 - 3.26 (m, 2 H), 3.47 (d, 1 H), 4.08 (d, 1 H), 4.20 (d, 1 H), 7.07 (t, 1 H), 7.11 - 7.18 (m, 3 H), 7.19 (d, 1 H), 7.23 (t, 2 H), 7.48 (d, 1 H), 7.62 (d, 1 H).

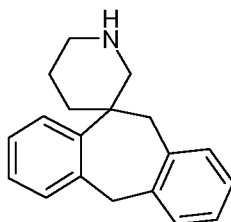
5 Compound 26 (0.019g):

MS (ESI) m/z : 300 $[\text{M}+\text{Na}]^+$, 577 $[2\text{M}+\text{Na}]^+$.

^1H NMR (500 MHz, DMSO- d_6): δ 1.50 - 1.74 (m, 1 H), 1.95 - 2.72 (m, 3 H), 2.96 - 3.60 (m, 4 H), 3.94 - 4.32 (m, 2 H), 7.00 - 7.70 (m, 9 H). The sample consists of a mixture of the target compound (~80% mol) and of the other regioisomer compound 25 (~20% mol).

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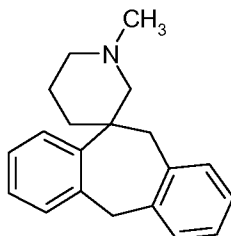
Compound 27: 5,11-Dihydrospiro[dibenzo[a,d]cycloheptene-10,3'-piperidine]



To 5,11-dihydro-6'*H*-spiro[dibenzo[a,d]cycloheptene-10,3'-piperidin]-6'-one (Compound 25, 0.018g, 0.066mmol) was added a solution of 1M borane THF complex (0.066mL) and the reaction mixture was heated at reflux for 2 hours. After cooling, water was added dropwise and the reaction mixture was stirred for 10 minutes at room temperature. The aqueous phase was extracted with DCM. The organic phase was evaporated under reduced pressure and the residue was purified by preparative TLC (95/3/2 ethyl acetate/methanol/triethylamine) affording the title compound (2.3mg);

20 MS (ESI) m/z : 264 $[\text{M}+1]^+$; ^1H NMR (500 MHz, DMSO- d_6): δ 1.18 - 1.30 (m, 1 H), 1.41 (d, 1 H), 1.55 (d, 1 H), 1.75 - 1.99 (m, 1 H), 2.61 (d, 1 H), 2.68 (t, 1 H), 2.91 (d, 1 H), 3.06 (d, 1 H), 3.24 - 3.50 (m, 2 H), 4.11 (s, 2 H), 7.03 (t, 1 H), 7.06 - 7.18 (m, 4 H), 7.20 (d, 1 H), 7.30 (d, 1 H), 7.51 (d, 1 H).

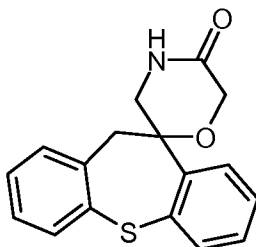
25 Compound 28: 1'-Methyl-5,11-dihydrospiro[dibenzo[a,d]cycloheptene-10,3'-piperidine]



5,11-Dihydrospiro[dibenzo[a,d]cycloheptene-10,3'-piperidine] (Compound 27, 10 mg, 0.04mmol) was dissolved in formic acid (1 mL) and the reaction mixture was refluxed for 2hrs. Formalin (37% HCHO in H₂O, 1mL) was added and the resulting mixture was stirred and refluxed for 16hrs. The excess of reagents were removed under vacuum, water was added to the residue and it was basified with diluted NaOH solution. The mixture was extracted using DCM, the organic phase was washed with water and finally it was evaporated to dryness. The crude was purified by preparative TLC (95/3/2 ethyl acetate/methanol/triethylamine) affording the title compound (2.1mg);

MS (ESI) *m/z*: 278 [M+1]⁺; ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.44 - 1.63 (m, 2 H), 1.58 - 1.73 (m, 1 H), 1.89 - 2.07 (m, 2 H), 2.10 (d, 1 H), 2.14 (s, 3 H), 2.40 (d, 1 H), 2.87 (d, 1 H), 3.36 (d, 1 H), 3.47 (d, 1 H), 4.04 - 4.18 (m, 2 H), 7.01 - 7.23 (m, 7 H), 7.47 (d, 1 H).

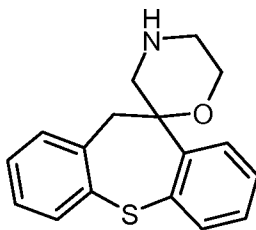
Compound 29: 3',4'-Dihydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazin]-5'(6'*H*)-one



A solution of KOH (74 mg, 1.32 mmol) in water (0.1 mL) was added to a solution of 2-bromo-N-[(10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)methyl]acetamide (Intermediate 20, 50 mg, 0.132 mmol) in dioxane (3 mL). The resulting mixture was heated at refluxing temperature for 2hrs. After evaporation of the solvent, the crude product was diluted with EtOAc and washed with water and brine. The organic phase was evaporated to dryness and the residue was purified by preparative TLC on silica (98/2 EtOAc/MeOH) to give the title compound (13 mg);

MS (ESI) *m/z*: 298 [M+H]⁺; 320 [M+Na]⁺; 617 [2M+Na]⁺; ¹H NMR (500 MHz, DMSO-*d*₆): δ 2.94 (dd, 1 H), 3.41 (d, 1 H), 3.62 (d, 1 H), 3.66 (d, 1 H), 4.29 (d, 1 H), 4.37 (d, 1 H), 7.20 - 7.26 (m, 2 H), 7.28 (t, 1 H), 7.36 (t, 1 H), 7.43 (d, 2 H), 7.56 (d, 1 H), 7.72 (d, 1 H), 8.19 - 8.25 (m, 1 H).

Compound 30: 3',4',5',6'-tetrahydro-11*H*-spiro[dibenzo[*b,f*]thiepin-10,2'-[1,4]oxazine]



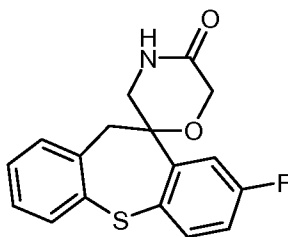
To a stirred and cooled (ice bath) suspension of LiAlH_4 (20 mg, 0.525 mmol, Aldrich) in anhydrous THF (1 mL) was added dropwise a solution of 3',4'-dihydro-11H-

spiro[dibenzo[b,f]thiepin-10,2'-[1,4]oxazin]-5'(6'H)-one (Compound 29, 130 mg, 0.438

5 mmol) in anhydrous THF (2 mL). The reaction mixture was heated to reflux for 3 hrs. After cooling, water was added and the mixture was extracted with ethyl acetate. After evaporation of the organic layer, the residue was purified by silica gel chromatography (from 1/0 to 95/5 EtOAc/MeOH) to give the title compound (50 mg);

MS (ESI) m/z : 306 $[\text{M}+\text{Na}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 2.57 (d, 1 H), 2.72 (d, 1 H),
 10 2.86 (d, 2 H), 3.62 (d, 1 H), 3.80 - 3.92 (m, 2 H), 4.09 - 4.21 (m, 1 H), 7.15 (t, 1 H), 7.19 (t, 1 H), 7.25 (t, 1 H), 7.32 (t, 1 H), 7.37 (d, 1 H), 7.52 (d, 1 H), 7.57 (d, 1 H), 7.79 (d, 1 H).

Compound 31: 8-Fluoro-3',4'-dihydro-11H-spiro[dibenzo[b,f]thiepin-10,2'-[1,4]oxazin]-5'(6'H)-one

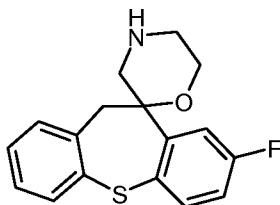


15 A solution of KOH (411 mg, 7.32 mmol) in water (1 mL) was added to a solution of 2-bromo-N-[(8-fluoro-10-hydroxy-10,11-dihydrodibenzo[b,f]thiepin-10-yl)methyl]acetamide (Intermediate 25, 290 mg, 0.73 mmol) in dioxane (10 mL). The resulting mixture was heated to reflux for 1hr. After evaporation of the solvents, water was added and a

20 precipitate was formed. The solid was collected after filtration, washing with water, and it was purified by silica gel chromatography (EtOAc) to give the title compound (150 mg);

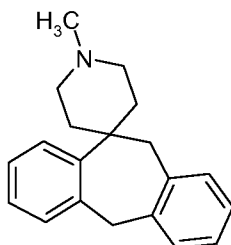
MS (ESI) m/z : 316 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 2.98 (dd, 1 H), 3.43 (d, 1 H), 3.64 (s, 2 H), 4.31 (d, 1 H), 4.37 (d, 1 H), 7.12 (td, 1 H), 7.25 (t, 1 H), 7.36 (t, 1 H), 7.43 (d, 1 H), 7.46 - 7.56 (m, 2 H), 7.55 (d, 1 H), 8.18 - 8.28 (m, 1 H).

25 Compound 32: 8-Fluoro-3',4',5',6'-tetrahydro-11H-spiro[dibenzo[b,f]thiepin-10,2'-[1,4]oxazine]



To a stirred and cooled (ice bath) suspension of LiAlH_4 powder (19 mg, 0.49 mmol, Aldrich) in anhydrous THF (2 mL) was added dropwise a solution of 8-fluoro-3',4'-dihydro-11H-spiro[dibenzo[b,f]thiepin-10,2'-[1,4]oxazin]-5'(6'H)-one (Compound 31, 130 mg, 0.41 mmol) in anhydrous THF (1 mL). The reaction mixture was refluxed for 1h. After cooling, water and diethyl ether were added, the two phases were separated and the organic phase was washed with water and brine. After evaporation of the organic layer, the residue was purified by silica gel chromatography (from 1/0 to 95/5 EtOAc/MeOH) to give the title compound (50 mg); MS (ESI) m/z : 302 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 2.61 (d, 1 H), 2.69 (d, 1 H), 2.81 - 2.94 (m, 2 H), 3.64 (dd, 1 H), 3.83 (d, 1 H), 3.88 (d, 1 H), 4.15 (td, 1 H), 7.04 (td, 1 H), 7.19 (t, 1 H), 7.33 (t, 1 H), 7.44 (dd, 1 H), 7.50 - 7.60 (m, 3 H).

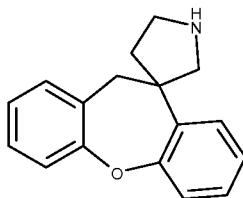
Compound 33: 1'-Methyl-5,11-dihydrospiro[dibenzo[a,d]cycloheptene-10,4'-piperidine]



A mixture of zinc (0.121g, 1.87mmol), HgCl_2 (9mg, 0.034mmol), concentrated HCl (0.043mL) was shaken for 5 minutes at room temperature. Then water (0.092mL), concentrated HCl (0.216mL) and a solution of 1'-methylspiro[dibenzo[a,d]cycloheptene-10,4'-piperidin]-11(5H)-one (Intermediate 28, 0.100g, 0.34mmol) in toluene (0.12mL) were added and the reaction mixture was refluxed for 16 hours. After cooling, water was added and the mixture was washed once with DCM. The aqueous phase was basified with 32% NH_4OH solution and extracted with ethyl acetate. The organic phase was evaporated to dryness to give a brown oil. Major impurities were removed by preparative TLC (95/3/2 ethyl acetate/methanol/triethylamine) and the resulting dark oil was purified by preparative Liquid Chromatography (MDAP FractionLynx Autopurification System™) [preparative chromatographic conditions Column: Gemini C18 AXIA, 50 x 21 mm, 5 μm ; Mobile phase: A: NH_4HCO_3 sol. 10 mM, pH10; B: CH_3CN ; Gradient:40% (B) for 1 min, 40% to 55% (B) in

9 min, 55% (B) for 2 min, 55% to 100% (B) in 0.1 min, 100% (B) for 1.9 min; Flow rate: 17 ml/min; UV range: 210-350 nm; Ionization: ES⁺; Mass range: 100-900 amu]. Two fractions containing a peak with the expected m/z ratio were collected and the evaporation of the solution containing the 1st peak (with the larger area) gave the title compound as a colourless oil (3.3 mg); ¹H NMR (500 MHz, DMSO-d₆): δ 1.47 (d, 2 H), 2.02 (dt, 2 H), 2.27 (s, 3 H), 2.42 (t, 2 H), 2.62 (d, 2 H), 3.26 (s, 2 H), 4.11 (s, 2 H), 6.97 - 7.24 (m, 7 H), 7.43 (d, 1 H). LC/MS analysis, analytical chromatographic conditions (MDAP FractionLynx Autopurification System™) [Column: Gemini C18, 50 x 4.6 mm, 5 μm; Mobile phase: A: NH₄HCO₃ sol. 10 mM, pH 10; B: CH₃CN; Gradient: 40% (B) for 0.5 min, 40% to 55% (B) in 4.5 min, 55% to 95% (B) in 0.1 min, 95% (B) for 1.4 min; Flow rate: 2 ml/min; UV range: 210-350 nm; Ionization: ES⁺; Mass range: 100-900 amu]: Rt = 4.55 min, m/z: 278 [M+H]⁺.

Compound 34: 11H-spiro[dibenzo[b,f]oxepin-10,3'-pyrrolidine]



The title compound was also prepared.

Biological Assay

a) 5HT_{2A} Antagonist Assay

Adherent SH-SY5Y cells stably expressing the recombinant human 5-HT_{2A} were maintained in culture at 37°C under 5% CO₂ in Alpha Minimum Essential Medium + ribonucleosides (Gibco Invitrogen,) supplemented with 10% dialysed foetal calf serum and 400 micrograms geneticin. SH-SY5Y are neuroblastoma and are commercially available from the American Type Culture Collection (ATCC). SH-SY5Y cells, expressing 5-HT_{2A} receptors, were seeded into black walled clear-base 384-well plates at a density of 16,000 cells per well and cultured overnight at 37°C under 5% CO₂. Media was aspirated off and the cells were then incubated with HBSS medium (CaCl₂·2H₂O 1.26mM, Glucose 5.55mM, KCl 5.36mM MgSO₄(anhyd) 0.81mM, NaCl 136.89mM, KH₂PO₄(anhyd) 0.41mM, HEPES 20mM, NaHCO₃ 4.16mM) containing the cytoplasmic calcium indicator, Fluo-4 in the acetylmethyl form (4 mM), 2.5mM Probenecid and 250uM Brilliant Black (Molecular Devices) at 37°C for 60 min. The loaded cells were then incubated with test compound for 30 min at 37°C. The plates were then placed into a FLIPR (Molecular

Devices, UK) for testing in antagonist mode, where a pre-determined concentration of 5-HT (approximately 4xEC₅₀) was added while cell fluorescence (λ_{ex} 488nm, λ_{em} 540nm) was monitored.

- 5 Using assay a), some of the supporting compounds gave an fpki against 5HT_{2A} of greater than 5.5.

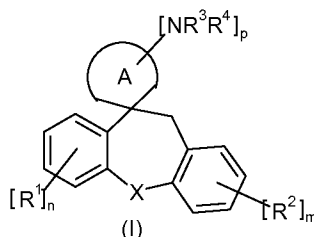
b) H₁ Antagonist Assay

- Adherent Chinese Hamster Ovary (CHO) cells stably expressing the recombinant human H₁ receptor were maintained in culture at 37°C under 5% CO₂ in Alpha Minimum Essential Medium without ribonucleosides (Gibco Invitrogen), supplemented with 10% dialysed foetal calf serum and 200mM Glutamine. These cells, expressing the human H₁ receptor, were snap frozen and stored ready for assay. 24 or 72 hours prior to assay the cells were seeded into black walled clear-base 384-well plates at a density of 12,000 or 4 000 cells per well (respectively) and cultured at 37°C under 5% CO₂. Cell seeding densities result in a confluent monolayer of cells at a time point of approximately 24 hours for 12 00 cells or 72 hours for 4 000 cells. Media was aspirated off and the cells were then incubated with HBSS medium (CaCl₂·2H₂O 1.26Mm, Glucose 5.55mM, KCl 5.36mM MgSO₄(anhyd) 0.81mM, NaCl 136.89mM, KH₂PO₄(anhyd) 0.41mM, HEPES 20mM, NaHCO₃ 4.16mM) containing the cytoplasmic calcium indicator, Fluo-4 in the acetylmethyl form (4 mM), 2.5mM Probenecid and 250uM Brilliant Black (Molecular Devices) at 37°C for 60 min. The loaded cells were then incubated with test compound for 30 min at 37°C. The plates were then placed into a FLIPR (Molecular Devices, UK) for testing in antagonist mode, where a pre-determined concentration of Histamine (approximately 4xEC₅₀) was added while cell fluorescence (λ_{ex} 488nm, λ_{em} 540nm) was monitored.

Using assay b), all the supporting compounds gave an fpki against H₁ of greater than 5.5.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein

X is CH₂, O, or S;

n is 0, 1 or 2;

m is 0, 1 or 2;

p is 0 or 1;

when present, R¹ is independently selected from the group consisting of halogen, C₁₋₃alkyl and C₁₋₃alkoxy;

when present, R² is independently selected from the group consisting of halogen, C₁₋₃alkyl and C₁₋₃alkoxy;

when p is 0, A is a spiro 5-6 membered saturated or partially unsaturated heterocyclic ring containing at least one nitrogen atom and optionally containing an additional heteroatom selected from N, S and O, the ring being optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl;

when p is 1, A is a spiro 5-6 membered saturated or partially unsaturated carbocyclic ring;

when present, R³ and R⁴ are each independently selected from the list consisting of hydrogen and C₁₋₃alkyl; or R³ and R⁴ together with the nitrogen to which they are attached, form a 4-6 membered saturated or partially unsaturated ring optionally containing one or more additional heteroatoms selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein X is CH₂ or S.

3. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.
4. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein n is 0.
5. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1.
6. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein m is 0.
7. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein R¹ is halogen.
8. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein R² is halogen.
9. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein when p is 1, R³ and R⁴ together with the nitrogen to which they are attached, form a 4-6 membered saturated ring optionally containing one additional heteroatom selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.
10. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein when p is 1, R³ and R⁴ together with the nitrogen to which they are attached, form a 5-6 membered saturated ring optionally containing one or more additional heteroatoms selected from O, N and S, wherein the ring is optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.
11. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein when p is 1, A is cyclopentyl.
12. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein when p is 0, A is a spiro 5-6 membered saturated heterocyclic

ring containing at least one nitrogen atom and optionally containing an additional heteroatom atom selected from N, S and O, the ring being optionally substituted by one or more groups independently selected from oxo and C₁₋₃alkyl.

- 5 13. A compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein when p is 0, A is a spiro 5- or 6-membered saturated or partially unsaturated heterocyclic ring selected from the list consisting of oxazolidinyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl and thiomorpholinyl, the ring being optionally substituted by one or more groups independently selected
10 from oxo and C₁₋₃alkyl.
14. A compound or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, for use in therapy.
- 15 15. The compound or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1-13, for use in the treatment of diseases or conditions mediated by antagonism of the H₁ receptor.
16. The compound or a pharmaceutically acceptable salt thereof, as claimed in claim
20 15, wherein the disease or condition is a sleep disorder.
17. A method of treatment or prevention of a disease or condition mediated by antagonism of the H₁ receptor in a mammal including a human, which comprises administering to the sufferer a therapeutically safe and effective amount of a
25 compound or a pharmaceutically acceptable salt thereof, as claimed in claim 1.
18. The method as claimed in claim 17, wherein the disease or condition is a sleep disorder.
- 30 19. Use of a compound or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, in the manufacture of a medicament for use in the treatment of a disease or condition mediated by antagonism of the H₁ receptor.
20. The use as claimed in claim 19, wherein the disease or condition is a sleep
35 disorder.

21. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, and a pharmaceutically acceptable carrier or excipient.
- 5 22. A process for preparing a pharmaceutical composition as defined in claim 21, the process comprising mixing a compound or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, and a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/059683

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C211/38 C07D498/10 C07D491/10 C07D295/02 C07D205/04
A61K31/131 A61P25/00

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)

C07C C07D 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, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAGAI, YASUTAKA ET AL: "Studies on psychotropic agents. V. Synthesis of 1-substituted spiro[dibenz[b,f]oxepin-11,4'-piperidine]-10(11H)-one and related compounds" CHEMICAL & PHARMACEUTICAL BULLETIN, 27(9), 2056-64 CODEN: CPBTAL; ISSN: 0009-2363, 1979, XP000941384 Compounds IV, 10, 11, 11E, 11A, 12, 17a,b, d, 18b, d, 19b, d, 20b,d ----- -/--	1-22

☒ 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

18 November 2008

Date of mailing of the international search report

19/12/2008

Name and mailing address of the ISA/

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Authorized officer

Bueno Torres, Pilar

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/059683

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ONG, HELEN H. ET AL: "Synthesis and analgesic activity of some spiro[dibenz[b,f]oxepin-10,4'-piperidine] derivatives" JOURNAL OF MEDICINAL CHEMISTRY, 22(7), 834-9 CODEN: JMCMAR; ISSN: 0022-2623, 1979, XP002504426 Compounds of formula II, 7a-c, 8a-c, 9a-c, 13a-c, Tables II and III -----	1-22
A	US 4 198 418 A (ONG HELEN H [US] ET AL) 15 April 1980 (1980-04-15) the whole document -----	1-22
A	US 4 198 420 A (ONG HELEN H [US] ET AL) 15 April 1980 (1980-04-15) the whole document -----	1-22
A	US 2003/232872 A1 (GLENNON RICHARD [US] ET AL) 18 December 2003 (2003-12-18) [0038], compounds 5, 16, 17, 30, 36, claims 24 and 26 -----	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/059683

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2008/059683

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4198418	A	15-04-1980	AR 229153 A1	30-06-1983
			AU 534512 B2	02-02-1984
			AU 5449080 A	17-07-1980
			CA 1142940 A1	15-03-1983
			DE 2964444 D1	03-02-1983
			EP 0016261 A1	01-10-1980
			ES 8101075 A1	01-03-1981
			JP 55094387 A	17-07-1980
			ZA 8000115 A	31-12-1980
US 4198420	A	15-04-1980	AU 5449180 A	17-07-1980
			CA 1142939 A1	15-03-1983
			DE 2964075 D1	23-12-1982
			EP 0013424 A1	23-07-1980
			ES 8100298 A1	16-01-1981
			JP 55094388 A	17-07-1980
			ZA 8000116 A	31-12-1980
US 2003232872	A1	18-12-2003	NONE	