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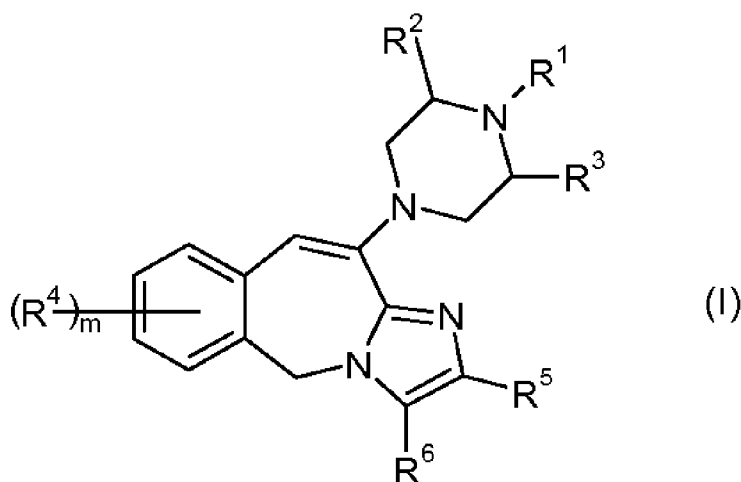
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(54) **Title:** IMIDAZOBENZAZEPINE COMPOUNDS FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) DISEASES



(57) **Abstract:** This invention relates to novel novel imidazobenzazepine derivatives of formula (I) or a pharmaceutically acceptable salt thereof, for treating diseases and conditions of the central nervous system (CNS), in particular sleep disorders.

IMIDAZOBENZAZEPINE COMPOUNDS FOR THE TREATMENT OF
CENTRAL NERVOUS SYSTEM (CNS) DISEASES

This invention relates to novel imidazobenzazepine 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 of 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.

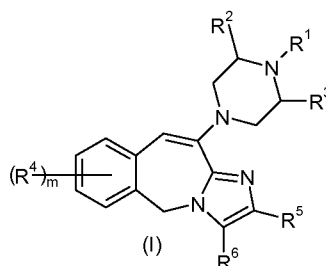
Other treatments include over-the-counter antihistamines, e.g. diphenhydramine and dimenhydrinate. These are not designed to be strictly sedative in their activity and as such, this method of treatment has been associated with a number of adverse side effects, e.g. persistence of the sedating medication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

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.

Therefore, a need exists for the development of improved drug therapies useful for the treatment of sleep disorders.

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



wherein

R^1 is carboxyC₃₋₆cycloalkyl, carboxyC₃₋₆cycloalkylmethyl, carboxymethylC₃₋₆cycloalkyl, $-(CR^{1a}R^{1b})_{2-6}CO_2H$ or $-(CR^{1a}R^{1b})_x(CR^{1c}R^{1d})(CR^{1a}R^{1b})_yCO_2H$;

R^{1a} and R^{1b} which may be the same or different are H or C₁₋₄alkyl or R^{1a} and R^{1b} can together form methylene (=CH₂);

R^{1c} and R^{1d} together with the C atom to which they are attached form a ring independently selected from C₃₋₄cycloalkane, oxirane and oxetane;

R^2 and R^3 are each independently selected from H, C₁₋₃alkyl and C₁₋₃haloalkyl;

each R^4 is independently selected from halo, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃haloalkyl and C₁₋₃haloalkoxy, cyano;

R^5 and R^6 are each independently selected from H, F, Cl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, trifluoromethyl and trifluoromethoxy;

x is 0-6;

y is 0-6 provided that x+y is 1-6; and

m is 0, 1 or 2.

The term “halogen” and its abbreviation “halo” refer to fluorine, chlorine, bromine or iodine. In an embodiment unless otherwise indicated such a halo substituent is fluoro or chloro.

- 5 As used herein, a C₁₋₄alkyl substituent is a univalent radical derived by removal of a hydrogen atom from an acyclic C₁₋₄alkane. Such C₁₋₄alkyl substituents include methyl and ethyl, and may be straight chain (i.e. n-propyl, n-butyl) or branched chain (for example, isopropyl, isobutyl).
- 10 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).

- As used herein, a C₁₋₃haloalkyl substituent is an C₁₋₃alkyl group substituted by one or
 15 more halo substituents, which halo substituents may be the same or different. Such C₁₋₃haloalkyl substituents include monofluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

- As used herein, a C₁₋₃haloalkoxy substituent is of formula “R^X-O-” where R^X is C₁₋₃haloalkyl as defined above. Such C₁₋₃haloalkoxy substituents include
 20 monofluoromethoxy, difluoromethoxy, trifluoromethoxy and 1-chloro-2-fluoroethoxy and may be straight chain or branched chain.

- As used herein unless otherwise indicated, a carboxy substituent is -C(O)-OH.
 25

As used herein unless otherwise indicated, a carboxyC₃₋₆cycloalkyl substituent is for example, HO-C(O)-C₆H₉-.

- In an embodiment R¹ is carboxyC₃₋₆cycloalkyl or -(CR^{1a}R^{1b})₂₋₆-CO₂H. In a further
 30 embodiment R¹ is carboxycyclohexyl, carboxycyclobutyl-CO₂H or -(CR^{1a}R^{1b})₂-CO₂H. In a further embodiment R¹ is -CH₂(CR^{1a}R^{1b})-CO₂H.

- In an embodiment R^{1a} and R^{1b} which may be the same or different are H or methyl or
 35 together form methylene (=CH₂). In another embodiment R^{1a} and R^{1b} which may be the same or different are H or methyl. In a further embodiment R^{1a} and R^{1b} are both methyl.

In an embodiment R^2 and R^3 are each independently selected from H and C_{1-3} alkyl. In a further embodiment R^2 and R^3 are each H.

In an embodiment R^5 and R^6 are each independently selected from H, Cl, F and methyl.

- 5 In a further embodiment R^5 and R^6 are each independently selected from H, Cl, F and methyl provided that at least one of R^5 and R^6 is H. In another embodiment R^5 and R^6 are each independently selected from H, Cl and F. In a further embodiment R^5 and R^6 are each independently selected from H, Cl and F provided that at least one of R^5 and R^6 is H. In a further embodiment R^5 and R^6 are each H. In a yet further embodiment R^5 and R^6 are each independently selected from H, Cl and F provided that at least one of R^5 and R^6 is Cl or F. In a yet further embodiment one of R^5 and R^6 is selected from Cl and F and the other of R^5 and R^6 is H.

- 15 It has been found that compounds in which one of R^5 and R^6 is selected from Cl or F show improved brain penetration. For example the brain penetration of the compounds of Examples 12, 13 and 14 described below was improved compared to that of the compound of Example 1.

- 20 In an embodiment x is 1 and y is 0. In an embodiment x is 0 and y is 1.

In an embodiment m is 0 or 1. In a further embodiment m is 0.

In an embodiment the compound is selected from

- 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
 25 Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1;
 Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2;
 3-[4-(2,3-Dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-
 30 dimethylpropanoic acid;
 2,2-Dimethyl-3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid;
 3-[(2R,6S)-4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-2,6-dimethyl-1-piperazinyl]propanoic acid;
 35 2,2-Dimethyl-3-{4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl}propanoic acid;
 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid;
 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 1;

3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 2;

2-{[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl}-2-propenoic acid;

3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-

5 dimethylpropanoic acid;

3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid; and

3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;

10 or a pharmaceutically acceptable salt thereof.

In a further embodiment, the compound is 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid or a pharmaceutically acceptable salt thereof.

15 In a further embodiment, the compound is selected from 3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid; 3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid; and 3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid, or a pharmaceutically acceptable salt thereof.

20

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 from a number of alternative groups, the selected groups may be the same or different.

25 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 may be the same or different.

The compounds of formula (I) may form pharmaceutically 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, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. In addition, pharmaceutically acceptable base addition salts can be formed with a suitable inorganic

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or organic base such as triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine, optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Other suitable pharmaceutically acceptable salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as sodium, potassium, calcium or magnesium salts; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the compound of formula (I). 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 13, page 453-497.

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

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 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 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.

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.

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

The compounds of the invention may exist in zwitterionic form.

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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.

10 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 scope of the present invention. Racemic mixtures may be separated to give their
15 individual enantiomers 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.

20 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 isotopes that can be incorporated into compounds of the invention include isotopes of
25 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., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of
30 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
35 methods or by the preparations described in the Examples and Preparations hereafter using appropriate isotopic variations of suitable reagents.

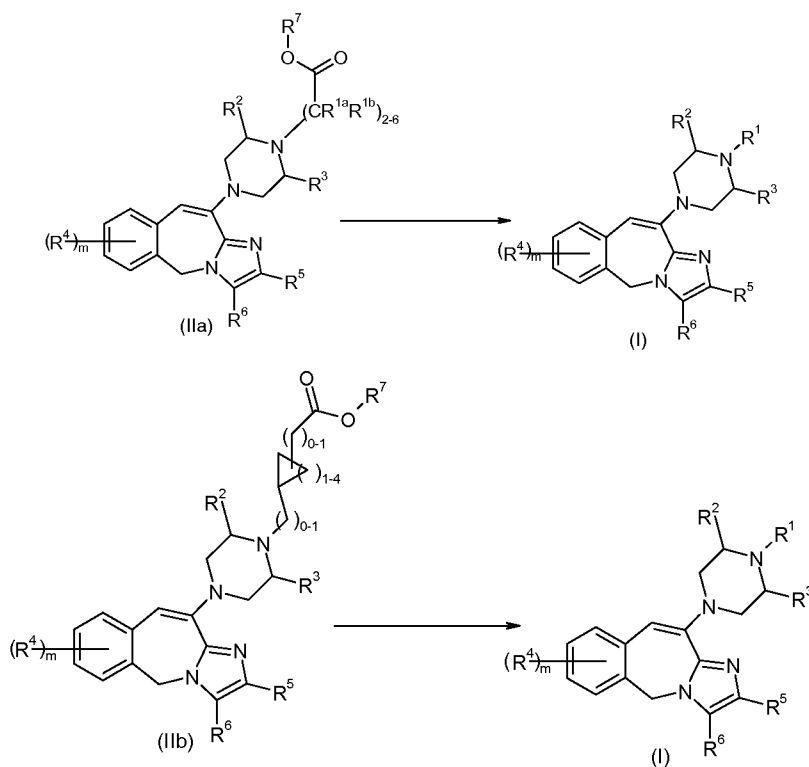
Compounds of the invention may be prepared in a variety of ways. In the following reaction schemes and hereinafter, unless otherwise stated R^1 to R^6 , x , y and m are as defined in the first aspect. These processes form further aspects of the invention.

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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.

- 10 Compounds of formula (I) may be prepared according to reaction scheme 1 by hydrolysis of compounds of formula (IIa) or (IIb), wherein $R^7 = C_{1-2}$ alkyl, with an alkali metal hydroxide or an alkali earth metal hydroxide, such as lithium hydroxide or potassium hydroxide, in a mixture of water and a water miscible organic solvent, such as methanol, at room temperature. For the avoidance of doubt, compounds of formula (I) wherein R^1 is
- 15 $-(CR^{1a}R^{1b})_x(CR^{1c}R^{1d})(CR^{1a}R^{1b})_yCO_2H$ may be prepared following similar procedures as those prepared from compounds of formula (IIa).

Scheme 1



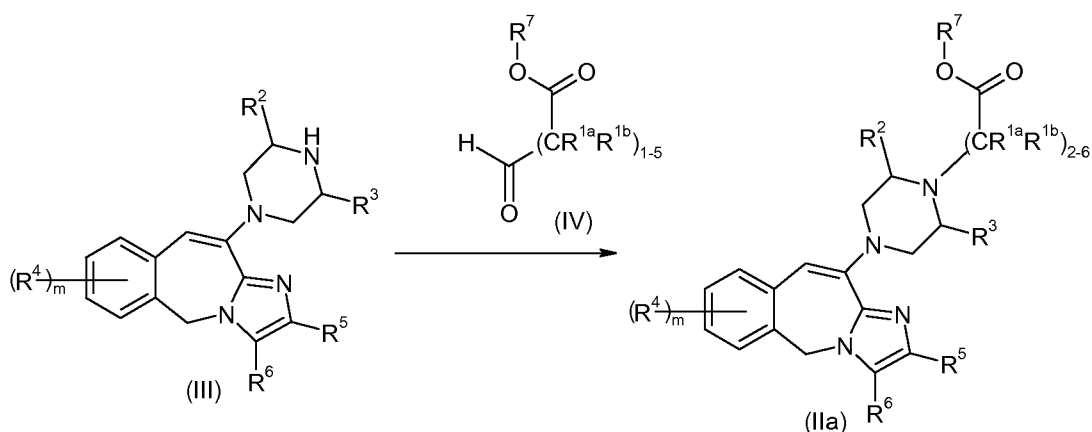
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Compounds of formula (IIa) may be prepared from compounds of formula (III) according to reaction scheme 2 by reaction with aldehydes of formula (IV) in the presence of a

reducing agent such as $\text{NaBH}(\text{OAc})_3$ in an organic solvent, such as DCE, at room temperature.

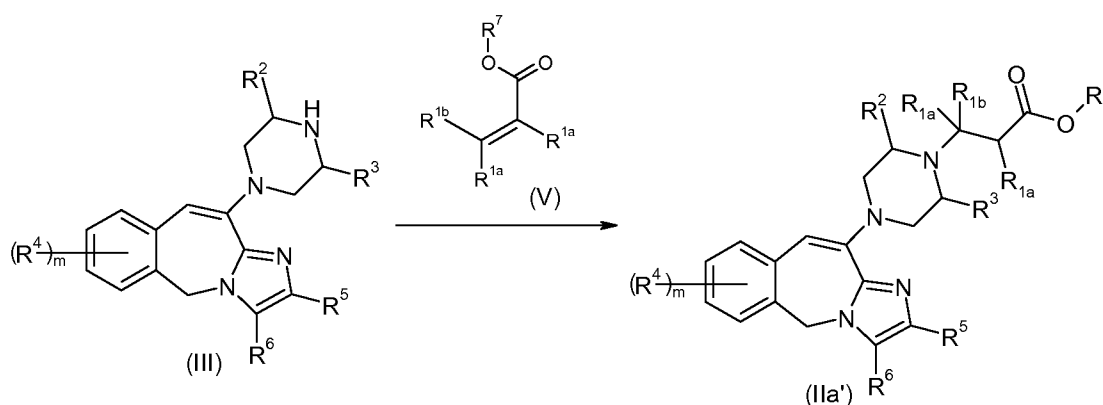
Aldehydes of formula (IV) are either commercially available or may be prepared by procedures known to the skilled person.

Scheme 2



Alternatively, compounds of formula (IIa'), which represent a subset of compounds of formula (IIa), may be prepared from compounds of formula (III) according to reaction scheme 3 by reaction with α,β -unsaturated esters of formula (V) in the presence of a base, such as DBU, in an organic solvent such as DMF.

Scheme 3

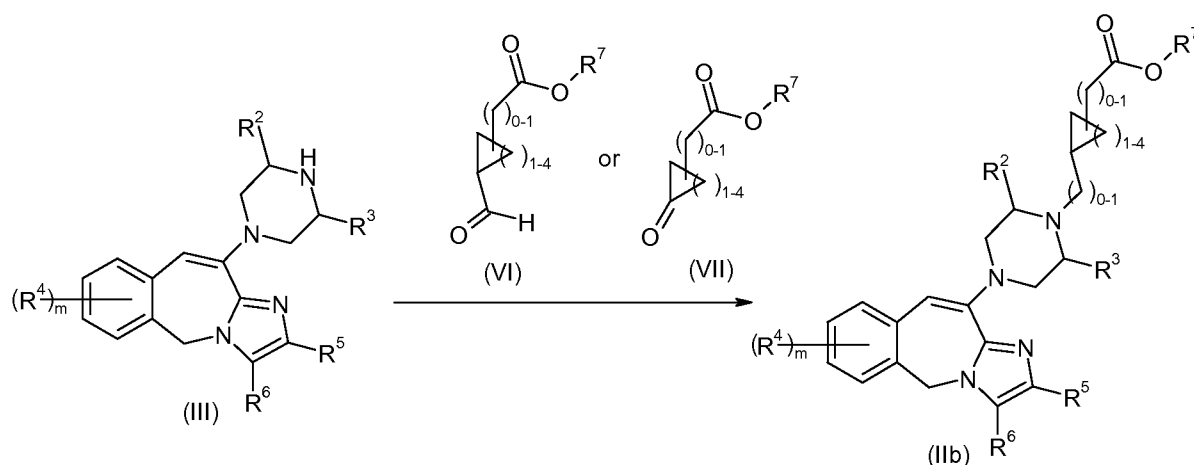


Compounds of formula (IIb) may be prepared from compounds of formula (III) according to reaction scheme 4 by reaction with aldehydes of formula (VI) or ketones of formula (VII)

in the presence of a reducing agent, such as $\text{NaBH}(\text{OAc})_3$, in an organic solvent such as DCE at room temperature.

- Aldehydes of formula (VI) and ketones of formula (VII) are either commercially available
5 or may be prepared by procedures known to the skilled person.

Scheme 4

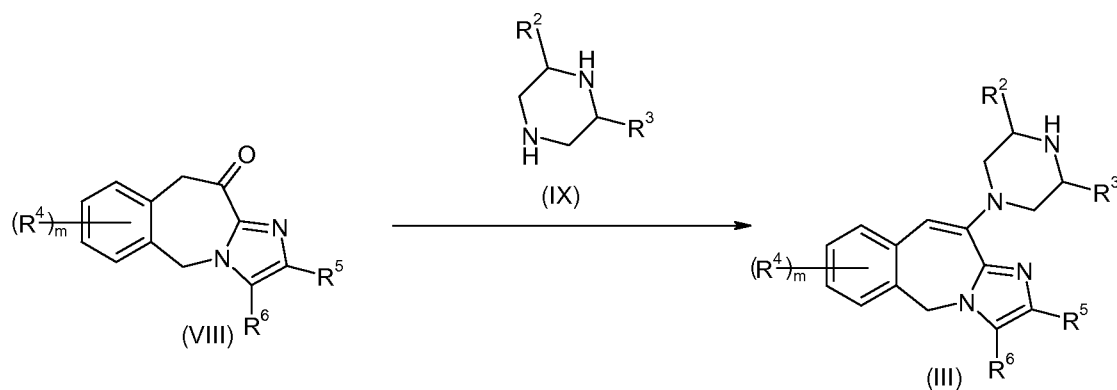


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Compounds of formula (III) may be prepared from compounds of formula (VIII) according to reaction scheme 5 by reaction with a piperazine of formula (IX) in the presence of trimethylsilyl trifluoromethylsulphonate at a temperature of 130°C .

- 15 Piperazines of formula (IX) are either commercially available or may be prepared by procedures known to the skilled person.

Scheme 5

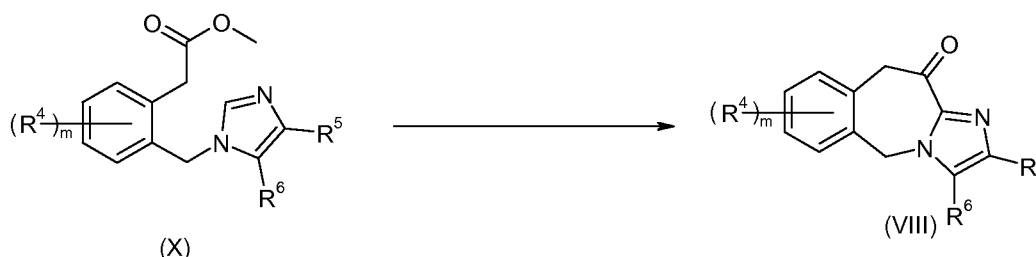


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Compounds of formula (VIII) may be prepared from compounds of formula (X) according to reaction scheme 6 by intramolecular cyclisation with a strong base such as lithium diisopropylamide in an aprotic organic solvent, such as THF, at low temperature (eg. -78°C).

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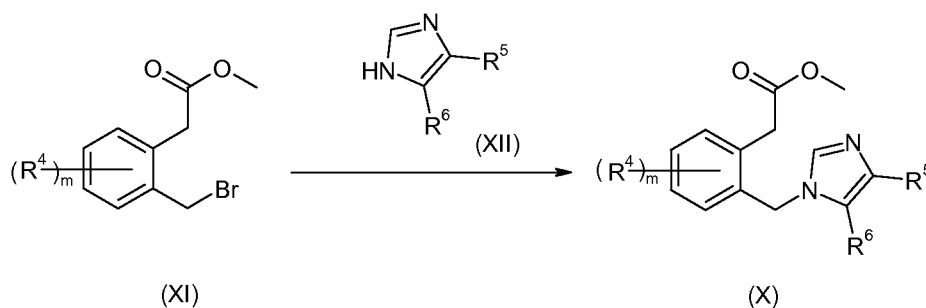
Scheme 6



Compounds of formula (X) may be prepared from compounds of formula (XI) according to reaction scheme 7 by reaction with an imidazole of formula (XII) in the presence of a suitable base, such as potassium carbonate, 2,8,9-trisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane or an excess of imidazole (XII), at room temperature in an aprotic organic solvent such as THF or DMF.

Imidazoles of formula (XII) and compounds of formula (XI) are either commercially available or may be prepared by procedures known to the skilled person.

Scheme 7



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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.

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

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)]:

- 10 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 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
15 Otherwise Specified (298.9).
- 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),
25 Depressive Disorder Not Otherwise Specified (311)); Bipolar Disorders (including Bipolar I 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
30 Major Depressive-like Episode, With Manic Features and With Mixed Features); Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features); and Mood Disorder Not Otherwise Specified (296.90).
- 35 iii) Anxiety disorders for example Social Anxiety Disorder; Panic Attack; Agoraphobia, Panic Disorder; Agoraphobia Without History of Panic Disorder (300.22); Specific Phobia

(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
5 General Medical Condition (293.84); Substance-Induced Anxiety Disorder; and Anxiety 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
10 Disorders (including Substance Intoxication, Substance Withdrawal, Substance-Induced 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
15 (Flashbacks); Alcohol-Related Disorders (including Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), 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-
20 Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9)); Amphetamine (or Amphetamine-Like)-Related 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,
25 Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and 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
30 (292.9)); Cannabis-Related Disorders (including Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, 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),
35 Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-

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),
5 Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, 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
10 Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, 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),
15 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),
20 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
25 (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
30 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-
35 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 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).

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 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 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 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 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), 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).

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

10 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.

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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
20 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)
25 opioid receptor antagonists.

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.

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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
35 amisulpride).

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).

Mood stabiliser drugs include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate and tiagabine.

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), 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 the invention may be administered as the raw chemical but 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. 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 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 invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. In addition, the

5 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 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 and effective amount of a compound of the invention. Accordingly, in another aspect, the invention provides dosage forms comprising pharmaceutical compositions of the

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15 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. 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

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25 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.

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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

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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, crospovidone, 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.

- 5 i) A compound of the invention for use in treating or preventing sleep disorders.
- ii) A method of treatment or prevention of sleep disorders in a mammal comprising administering an effective amount of a compound of the invention.
- 10 iii) A compound of the invention for use in the treatment of sleep disorders.
- iv) Use of a compound of the invention in the manufacture of a medicament for use in the treatment of sleep disorders.

15 Supporting Compounds and Intermediates

The invention is illustrated by the Compounds described below.

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

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

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Reagents were obtained from commercial suppliers (for example Sigma–Aldrich and Lancaster) and used without further purification. Solvents were obtained in dry form or were dried according to standard procedures. For example, DCM and DCE were dried over calcium hydride; THF, toluene and diethyl ether were dried over Na/benzophenone;
30 and EtOH was dried over Mg/I₂. Anhydrous reactions were run under a positive pressure of dry N₂ or argon.

Proton Nuclear Magnetic Resonance (¹H NMR) spectra were recorded either on Varian instruments at 300, 400, 500 or 600 MHz, or on Bruker instruments at 300, 400 or 500
35 MHz. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m,

multiplet; b, broad. The NMR spectra were recorded at a temperature ranging from 25 to 90°C.

Mass spectra (MS) were run on a 4 II triple quadrupole Mass Spectrometer on an Agilent
5 MSD 1100 Mass Spectrometer, operating in ES(+) and ES(-) ionization mode. The usage of this methodology is indicated by "MS".

HPLC-Mass spectra (HPLC/MS) were run on an Agilent LC/MSD 1100 Mass Spectrometer, operating in ES(+) and ES(-) ionization mode coupled with HPLC
10 instrument Agilent 1100 Series [LC/MS - ES (+): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3m) (mobile phase: 100% [water + 0.1% formic acid] for 1 min, then from 100% [water +0.1% formic acid] to 5% [water +0.1% formic acid] and 95% [acetonitrile] in 5 min, finally under these conditions for 2 min; T=40°C; flow= 1 mL/min; LC/MS - ES (-): analysis performed on a Supelcosil ABZ +Plus (33x4.6 mm, 3m) (mobile
15 phase: 100% [water +0.05% ammonia] for 1 min, then from 100% [water +0.05% ammonia] to 5% [water +0.05% ammonia] and 95% [acetonitrile] in 5 min, finally under these conditions for 2 min; T=40 °C; flow= 1 mL/min]. In the mass spectra only one peak in the molecular ion cluster is reported. The usage of this methodology is indicated by "HPLC/MS" in the analytical characterization of the described compounds.

20 Alternatively mass directed analytical HPLC (Agilent technology HP1100) was carried out using a 19 mm × 100 mm or 30 mm × 100 mm, 5 µm, reversed phase Waters Atlantis column as the stationary phase and a gradient from water + 0.1% formic acid to acetonitrile + 0.1% formic acid as the eluent. The HPLC system was monitored by DAD
25 array detector and an Agilent 110MSD mass spectrometer. The LC elution method (using Zorbax Eclipse XDB, 4.6 x 150 mm, 5 µm C8 column) was the following: 15 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).

30 Alternatively HPLC spectra (HPLC) were performed using a reversed-phase liquid chromatography (ProStar 210/215 PrepStar218) and UV-Vis Detector (ProStar 325). The LC elution method (using Varian Polaris 5 C-18, 150 x 4.6 mm) was the following: 15 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).

Alternatively HPLC spectra (HPLC) were performed using a Waters 2690 apparatus at 25°C using a 3 mm × 100 mm, 3.5 µm, reversed phase X-Terra C-18 column as the stationary phase and a gradient from water + 0.1% formic acid 5% to acetonitrile + 0.1% formic acid 90% during 19.5 min or water + 0.1% formic acid 20% to acetonitrile + 0.1% formic acid 95% during 19 min as the eluent. Flow rate was 0.5 mL/min (all solvents were HPLC grade, Merck). The HPLC system was monitored by DAD array detector at 254 nm and a Micromass Quattro micro mass spectrometer.

Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken also on a UPLC/MS Acquity™ system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQ™ mass spectrometer operating in positive or negative electrospray ionisation mode. [LC/MS - ES (+/-): analyses performed using an Acquity™ UPLC BEH C18 column (50 x 21 mm, 1.7 µm particle size), column temperature 40 °C (mobile phase: A-water + 0.1% formic acid / B - acetonitrile + 0.075% formic acid, Flow rate: 1.0 mL/min, Gradient: t=0 min 3% B, t=0.05 min 6% B, t= 0.57 min 70% B, t=1.4 min 99% B, t=1.45 min 3% B)]. The usage of this methodology is indicated by "UPLC/MS" in the analytic characterization of the described compounds.

For reactions involving microwave irradiation, a Personal Chemistry Emrys™ Optimizer was used.

Flash silica gel chromatography was carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany) or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage or Isolute Flash™ silica cartridges. Alternatively chromatographic purifications were performed on columns packed with Merck 60 silica gel, 23-400 mesh, for flash technique. Flash modified silica gel chromatography was carried out over Biotage KP-NH (NH) or Varian Mega BE-NH2 (NH2) pre-packed aminoalkyl functionalised silica gel cartridges. Thin-layer chromatography was carried out using Merck TLC plates Kieselgel 60F-254, visualised with UV light, 5% phosphomolybdic acid, aqueous potassium permanganate. SCX cartridges (SCX) are ion exchange solid phase extraction columns supplied by Varian or Phenomenex. The eluent used with SCX cartridges is methanol followed by 2N ammonia solution in methanol. Mega BE-C18 (C18) cartridges are reverse phase extraction columns supplied by Varian. The eluent used with C18 columns is water followed by MeOH.

In a number of preparations, purification was performed using either Biotage manual flash chromatography (Flash+) or automatic flash chromatography (Horizon) systems. All these instruments work with standard Biotage Silica cartridges.

- 5 In a number of preparations, purification was performed on a Mass-Directed Autopurification (MDAP) system FractionlynxTM equipped with Waters 2996 PDA detector and coupled with a ZQTM mass spectrometer (Waters) operating in positive and negative electrospray ionisation mode ES⁺, ES⁻ (mass range 100-1000).
- 10 A set of acidic as well as basic semi-preparative gradients have been used:

METHOD A: Chromatographic Acidic conditions for up to 30 mg of crude:

Column: 100 x 21.2 mm SupelcosilTM ABZ +Plus (5 µm particle size)
Mobile phase: A[water + 0.1% formic acid] / B[acetonitrile + 0.1% formic acid]
15 Flow rate: 20 mL/min
Gradient: 5% B for 1 min, 95% B in 9 min, 100% B in 3.5 min

METHOD B: Chromatographic Acidic conditions for up to 100 mg of crude:

- Column: 150 x 30 mm XTerra Prep MS C18 (10 µm particle size)
20 Mobile phase: A[water + 0.1% formic acid] / B [acetonitrile + 0.1% formic acid]
Flow rate: 40 mL/min
Gradient: 1% B to 100%B in 7 min lasting for 7.5 min.

METHOD C: Chromatographic Basic conditions for up to 100 mg of crude

- 25 Column: 150 x 30 mm XTerra Prep MS C18 (10 µm particle size)
Mobile phase: A-water + 10 mM ammonium carbonate (adjusted to pH 10 with ammonia)/
B - acetonitrile
Flow rate: 40 mL/min
Gradient: 10%B for 0.5 min, 95%B in 12.5 min

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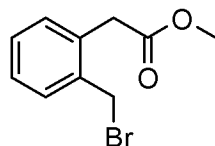
Abbreviations

The following lists the abbreviations used:

DCM	dichloromethane
DCE	1,2-dichloroethane
THF	tetrahydrofuran
DMF	dimethylformamide

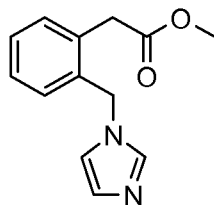
MeOH	methanol
PPA	polyphosphoric acid
cHex	cyclohexane
BOC ₂ O	di-tert-butyl dicarbonate
SCX	strong cation resin
TEA	triethylamine
TFA	trifluoroacetic acid
AcOH	acetic acid
RT	room temperature
Rt	retention time
EtOAc	ethyl acetate
Et ₂ O	diethyl ether
TBAF	tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
BuLi	n-butyllithium
LDA	lithium diisopropylamide
d ₆ -DMSO	deuterated dimethylsulfoxide

Intermediate 1: Methyl [2-(bromomethyl)phenyl]acetate



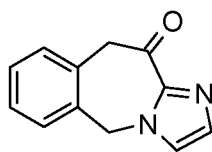
- A solution of (2-methylphenyl)acetic acid (2 g, 13.32 mmol) in chloroform (20 ml)
5 containing N-bromosuccinimide (2.370 g, 13.32 mmol) was heated under reflux for 8
hours, cooled, filtered and evaporated to give a crude containing 2-(bromomethyl)phenyl
acetic acid. This material was dissolved in dichloromethane (40 ml) and methanol (10 ml)
and the mixture was cooled at 0°C. A 2M solution of trimethylsilyl diazomethane in Et₂O
(9.99 ml, 19.98 mmol) was added dropwise and the temperature was allowed to rise to
10 ROOM TEMPERATURE and the mixture was stirred for 2 hours. The solvent was
evaporated and the residue was purified by flash chromatography on silica gel (Biotage
40 M column) eluting with ethyl acetate / cyclohexane (1/9) to afford the title compound
(1.9 g, 7.82 mmol) as a pale yellow oil; UPLC/MS Rt=0.73 min; m/z (ES): 243/245 [M+H]⁺
and 163 [M-Br]⁺; ¹H NMR (CDCl₃): δ 3.73 (s, 3H), 3.84 (s, 2H), 4.61 (s, 2H), 5.42-5.55 (m,
15 2H), 7.16-7.24 (m, 1H), 7.26-7.35 (m, 2H), 7.37-7.42 (m, 1H).

Intermediate 2: Methyl [2-(1H-imidazol-1-ylmethyl)phenyl]acetate



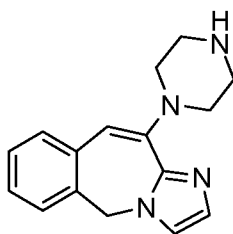
Methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 200 mg, 0.823 mmol) and imidazole (224 mg, 3.29 mmol) were dissolved in dry DMF (10 ml) and stirred at room temperature for 8 hours. After dilution with water the mixture was extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (20g) eluting with a gradient of EtOAc in cyclohexane from 30 to 100% to afford the title compound (145 mg, 0.630 mmol) as a colourless oil; UPLC/MS Rt=0.39 min; m/z (ES): 231 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.63 (s, 2H), 3.69 (s, 3H), 5.22 (s, 2H), 6.86-6.88 (m, 1H), 7.00-7.05 (m, 1H), 7.09-7.11 (m, 1H), 7.25-7.36 (m, 3H), 7.50 (s, 1H).

Intermediate 3: 5,10-Dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



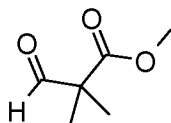
To a solution of methyl [2-(1H-imidazol-1-ylmethyl)phenyl]acetate (Intermediate 2, 950 mg, 4.13 mmol) in THF (5 ml), at -78°C under nitrogen, a 2M solution of LDA in THF (2.269 ml, 4.54 mmol) was slowly added. The temperature was allowed to reach room temperature and the reaction was stirred overnight. The reaction mixture was cooled to 0°C and further LDA (2M in THF, 1 ml, 2.0 mmol) was added. After 18 hours the reaction was quenched with saturated NH₄Cl solution and extracted with DCM. The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25g) eluting with a gradient of 2M methanolic NH₃ in DCM from 0 to 2% to afford a yellowish solid that was triturated in ethyl ether to give the title compound (305 mg, 1.539 mmol) as a white solid; UPLC/MS Rt=0.41 min; m/z (ES): 199 [M+H]⁺; ¹H NMR (CDCl₃): δ 4.21 (s, 2H), 5.36 (s, 2H), 7.19 (d, 1H), 7.27 (d, 1H), 7.29-7.42 (m, 4H).

Intermediate 4: 11-(1-Piperaziny)-5H-imidazo[1,2-b][2]benzazepine



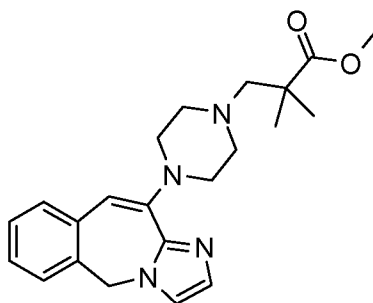
In a screw capped vial to 5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 3, 51 mg, 0.257 mmol) was added piperazine (111 mg, 1.286 mmol) and trimethylsilyl trifluoromethanesulfonate (139 μ l, 0.772 mmol). The mixture was then
 5 heated at 130 °C for 2 hours. The mixture was then cooled to room temperature and the crude product was purified by flash chromatography on modified silica gel (25g NH₂ cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (48 mg, 0.180 mmol) as a white solid; UPLC/MS Rt=0.42 min; m/z (ES): 267 [M+H]⁺ and 134 [M+2H]²⁺; ¹H NMR (d6-DMSO): δ 2.81-2.87 (m, 4H), 2.97-3.04 (m, 4H),
 10 4.96 (s, 2H), 6.15 (s, 1H), 7.00 (d, 1H), 7.19 (td, 1H), 7.25-7.30 (m, 2H), 7.32-7.38 (m, 2H).

Intermediate 5: Methyl 2,2-dimethyl-3-oxopropanoate



15 To a solution of methyl 3-hydroxy-2,2-dimethylpropanoate (2 g, 15.13 mmol) and TEMPO (0.236 g, 1.513 mmol) in dichloromethane (15 ml) was added iodobenzene diacetate (5.36 g, 16.65 mmol) and the solution was stirred for 3 hours at ROOM TEMPERATURE. The reaction was quenched with a saturated solution of NaHCO₃/5%Na₂S₂O₃ (10ml) and extracted with DCM (20ml). The organic layer was washed with brine and then dried
 20 (Na₂SO₄), filtered and evaporated to afford the title compound (4.8 g, 14.75 mmol) as an ~1:1 mixture with iodobenzene that was used in the following reaction without further purification; ¹H NMR (CDCl₃) only signals relating to title compound: δ 1.38 (s, 6H), 3.78 (s, 3H), 9.69 (s, 1H).

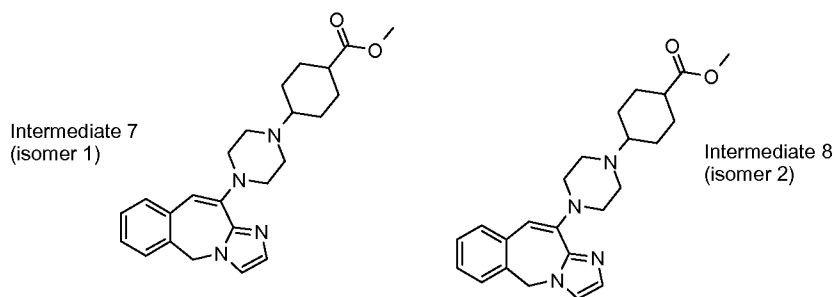
25 Intermediate 6: Methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



A mixture of 11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 4 together with another batch prepared in a similar fashion, 31 mg, 0.116 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 100 mg, 0.307 mmol) in dry

1,2-dichloroethane (2.5 ml) was stirred under nitrogen at room temperature for 30 min. Sodium triacetoxyborohydride (49.3 mg, 0.233 mmol) was then added and the resulting reaction mixture was stirred for 3 days, quenched with saturated aqueous NaHCO_3 solution and extracted with dichloromethane. The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10g) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (36 mg, 0.095 mmol); HPLC R_t =2.88 min; MS m/z (ES): 381.0 $[\text{M}+\text{H}]^+$, 403.2 $[\text{M}+\text{Na}]^+$ and 190.9 $[\text{M}+2\text{H}]^{2+}$; ^1H NMR (CDCl_3): δ 1.20 (s, 6H), 2.57 (s, 2H), 2.68-2.75 (m, 4H), 3.07-3.14 (m, 4H), 3.67 (s, 3H), 4.85 (s, 2H), 6.12 (s, 1H), 6.93 (d, 1H), 7.12 (d, 1H), 7.13-7.30 (m, 4H).

Intermediate 7 and Intermediate 8: Methyl 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1 and methyl 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2



To a mixture of 11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 4, 30 mg, 0.113 mmol) and ethyl 4-oxocyclohexanecarboxylate (38.3 mg, 0.225 mmol) in dry 1,2-dichloroethane (4 ml) under nitrogen, was added a drop of AcOH and the resulting reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (47.7 mg, 0.225 mmol) was then added and the resulting reaction mixture was stirred for 3 h, quenched with saturated aqueous NaHCO_3 solution and

extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified first by flash chromatography on silica gel (20g) eluting with a gradient of MeOH in DCM from 0.5 to 1%, then by flash chromatography on modified silica gel (20g NH₂ cartridge) eluting with a gradient of ethyl acetate in cyclohexane from 10 to 40% to afford the two title compounds:

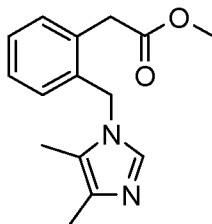
Intermediate 7 (15.6 mg, 0.037 mmol);

HPLC/MS Rt=1.90 min; m/z (ES): 421.2 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.27 (t, 3H), 1.48-1.66 (m, 4H), 1.67-1.80 (m, 2H), 2.14-2.23 (m, 2H), 2.27-2.40 (m, 1H), 2.50-2.60 (m, 1H), 2.76 (t, 4H), 3.16 (brs, 4H), 4.15 (q, 2H), 4.87 (s, 2H), 6.15 (s, 1H), 6.95 (d, 1H), 7.14 (d, 1H), 7.15-7.30 (m, 4H).

Intermediate 8 (7.5 mg, 0.018 mmol);

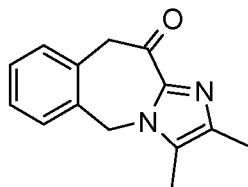
HPLC/MS Rt=1.82 min; m/z (ES): 421.2 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.26 (t, 3H), 1.40-1.80 (m, 4H), 1.98-2.14 (m, 4H), 2.17-2.29 (m, 1H), 2.29-2.43 (m, 1H), 2.77-2.87 (m, 4H), 3.17 (brs, 4H), 4.14 (q, 2H), 4.88 (s, 2H), 6.15 (s, 1H), 6.95 (d, 1H), 7.14 (d, 1H), 7.16-7.30 (m, 4H).

Intermediate 9: Methyl {2-[(4,5-dimethyl-1H-imidazol-1-yl)methyl]phenyl}acetate



Methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 750 mg, 3.09 mmol) and 4,5-dimethyl-1H-imidazole (326 mg, 3.39 mmol) were dissolved in dry DMF (5 ml) and stirred at room temperature for 8 hours. After dilution with water the mixture was extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25M) eluting with a gradient of MeOH in DCM from 0 to 4% to afford the title compound (260 mg, 1.007 mmol) as a colourless oil; UPLC/MS Rt=0.40 min; m/z (ES): 259 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.03 (s, 3H), 2.22 (s, 3H), 3.68 (s, 2H), 3.73 (s, 3H), 5.10 (s, 2H), 6.70 (d, 1H), 7.22-7.34 (m, 4H).

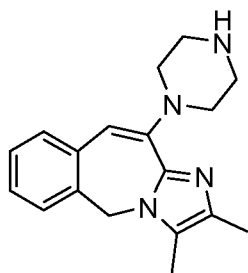
Intermediate 10: 2,3-Dimethyl-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



To a solution of methyl {2-[(4,5-dimethyl-1H-imidazol-1-yl)methyl]phenyl}acetate (Intermediate 9, 260 mg, 1.007 mmol) in THF (10 ml), at -70°C (external temperature) under nitrogen, a 1.8M solution of LDA in THF (0.839 ml, 1.510 mmol) was slowly added.

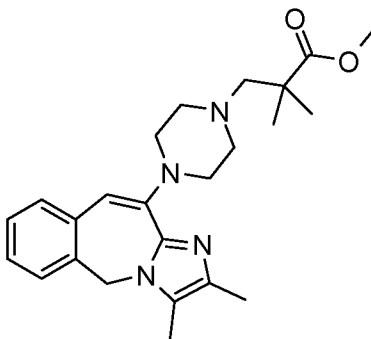
- 5 The temperature was allowed to reach -10°C in 2 hours then the reaction was quenched with saturated NH₄Cl solution, extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25g) eluting with a gradient of MeOH in DCM from 0 to 2%, to afford the title compound (51 mg, 0.225 mmol); HPLC/MS Rt=1.45 min; m/z (ES): 227.0
- 10 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.24 (s, 3H), 2.38 (s, 3H), 4.17 (s, 2H), 5.18 (s, 2H), 7.26-7.39 (m, 4H).

Intermediate 11: 2,3-Dimethyl-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



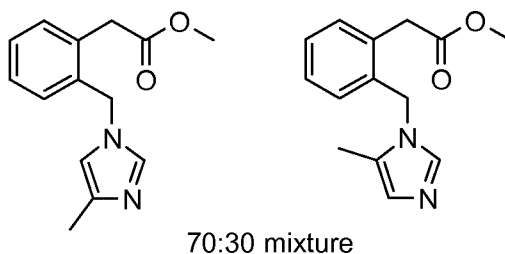
- 15 In a screw capped vial to 2,3-dimethyl-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 10, 51 mg, 0.225 mmol) was added piperazine (97 mg, 1.127 mmol) and trimethylsilyl trifluoromethanesulfonate (122 µl, 0.676 mmol). The mixture was then heated at 130 °C for 2 hours. The mixture was then cooled to room temperature and the crude product was purified by flash chromatography on modified silica gel (25g NH₂
- 20 cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (30 mg, 0.102 mmol) as a white solid; UPLC/MS Rt=0.37 min; m/z (ES): 295 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.18 (s, 3H), 2.27 (s, 3H), 3.07-3.17 (m, 8H), 4.72 (s, 2H), 6.12 (s, 1H), 7.15-7.21 (m, 1H), 7.23-7.31 (m, 3H).

- 25 Intermediate 12: Methyl 3-[4-(2,3-dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



To a mixture of 2,3-dimethyl-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 11, 27 mg, 0.092 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 59.7 mg, 0.183 mmol) in dry 1,2-dichloroethane (2 ml) under nitrogen, was added a drop of AcOH and then the mixture was stirred at room temperature for 30 min. Sodium triacetoxymethylborohydride (29.2 mg, 0.138 mmol) was then added and the resulting reaction mixture was stirred for 16 h, quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10g) eluting with a gradient of MeOH in dichloromethane from 0 to 2% to afford the title compound (28 mg, 0.069 mmol); HPLC/MS Rt=2.31 min; m/z (ES): 409.2 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.21 (s, 6H), 2.17 (s, 3H), 2.26 (s, 3H), 2.59 (s, 2H), 2.69-2.76 (m, 4H), 3.09-3.16 (m, 4H), 3.69 (s, 3H), 4.70 (s, 2H), 6.09 (s, 1H), 7.12-7.30 (m, 4H).

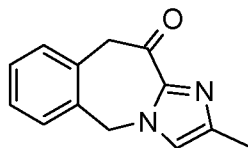
Intermediate 13: Methyl {2-[(methyl-1H-imidazol-1-yl)methyl]phenyl}acetate



Methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 500 mg, 2.057 mmol) and 4-methyl-1H-imidazole (675 mg, 8.23 mmol) were dissolved in DMF (20 ml) and stirred at room temperature for 3 hours. After dilution with water the mixture was extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25M) eluting with a gradient of MeOH in DCM from 0 to 4% to afford the title compound (313 mg, 1.281 mmol,) as a 70/30 mixture of two isomers; UPLC/MS Rt=0.38 min; m/z (ES): 245 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.10 (s, 3H minor isomer), 2.22 (s, 3H, major isomer), 3.62 (s, 2H,

major isomer), 3.66 (s, 2H minor isomer), 3.69 (s, 3H, major isomer), 3.71 (s, 3H minor isomer), 5.13 (s, 2H both isomers), 6.57 (s, 1H major isomer), 6.70 (d, 1H minor isomer), 6.87 (s, 1H minor isomer), 7.03 (d, 1H major isomer), 7.22-7.41 (m, 4H both isomers).

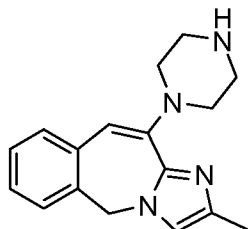
5 Intermediate 14: 2-Methyl-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



To a solution of methyl {2-[(4-methyl-1H-imidazol-1-yl)methyl]phenyl}acetate (Intermediate 13, 313 mg, 1.283 mmol) in THF (10 ml), at -10°C (external temperature) under nitrogen, a 1.8M solution of LDA in THF (1.069 ml, 1.924 mmol) was slowly added.

- 10 The temperature was allowed to reach -10°C in 2 hours then the reaction was quenched with saturated NH₄Cl solution, extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25g) eluting with a gradient of MeOH in DCM from 0 to 2%, to afford 62 mg of a mixture of isomers which was further purified by flash
- 15 chromatography on modified silica gel (20g NH₂ cartridge) eluting with a gradient of acetone in DCM from 0 to 1% to afford the title compound (32 mg, 0.151 mmol); HPLC/MS Rt=1.38 min; m/z (ES): 213.0 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.27 (s, 3H), 4.16 (s, 2H), 5.27 (s, 2H), 6.92 (s, 1H), 7.25-7.32 (m, 1H), 7.34-7.40 (m, 3H).

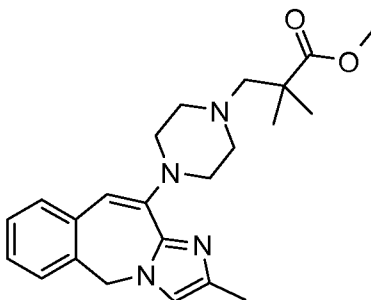
20 Intermediate 15: 2-Methyl-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



- In a screw capped vial to 2-methyl-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 14, 32 mg, 0.151 mmol) was added piperazine (64.9 mg, 0.754 mmol) and trimethylsilyl trifluoromethanesulfonate (82 µl, 0.452 mmol). The mixture was then heated
- 25 at 130 °C for 2 hours. The mixture was then cooled at room temperature and the crude product was purified by flash chromatography on silica gel (25g NH₂ cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (22 mg, 0.078 mmol) as a white solid; HPLC/MS Rt=1.65 min; m/z (ES): 281.1 [M+H]⁺; ¹H NMR (CDCl₃):

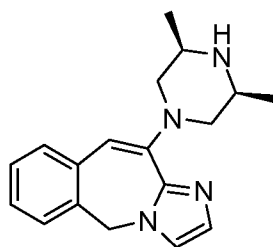
δ 2.22 (s, 3H), 3.07-3.19 (m, 8H), 4.81 (s, 2H), 6.13 (s, 1H), 6.67 (s, 1H), 7.16-7.28 (m, 4H).

Intermediate 16: Methyl 3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



To a mixture of 2-methyl-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (20 mg, 0.071 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 46.4 mg, 0.143 mmol) in dry 1,2-dichloroethane (2 ml) under nitrogen, a drop of AcOH was added and then the mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (30.2 mg, 0.143 mmol) was then added and the resulting reaction mixture was stirred for 3 h, quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10g) eluting with a gradient of MeOH in dichloromethane from 0 to 2% to afford the title compound (18 mg, 0.046 mmol); HPLC/MS Rt=2.17 min; m/z (ES): 395.1 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.21 (s, 6H), 2.22 (s, 3H), 2.59 (s, 2H), 2.70-2.76 (m, 4H), 3.09-3.15 (m, 4H), 3.69 (s, 3H), 4.79 (s, 2H), 6.10 (s, 1H), 6.66 (s, 1H), 7.16-7.30 (m, 4H).

Intermediate 17: 11-[(3R,5S)-3,5-Dimethyl-1-piperazinyl]-5H-imidazo[1,2-b][2]benzazepine

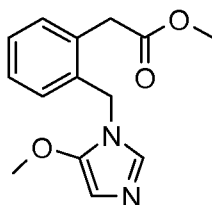


In a screw capped vial to 5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 3, 60 mg, 0.303 mmol) was added 2,6-dimethylpiperazine (predominantly cis) (173 mg, 1.513 mmol) and trimethylsilyl trifluoromethanesulfonate (164 μ l, 0.908 mmol). The mixture was then heated at 130 °C for 2 hours. Further 2,6-dimethylpiperazine

(predominantly cis) (173 mg, 1.513 mmol) was then added and the mixture was heated at 130°C for 10 hours. The mixture was then cooled to room temperature and the crude product was purified by flash chromatography on silica gel (25g NH₂ cartridge) eluting with a gradient of MeOH in DCM from 0 to 1% and then by Fraction Lynx (method:

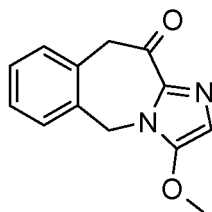
- 5 Gen_Basic_pH10), to afford the title compound (41 mg, 0.139 mmol) as a white solid; HPLC Rt=2.53 min; MS m/z (ES): 295.2 [M+H]⁺ and 148.1 [M+2H]²⁺; ¹H NMR (CDCl₃): δ 1.15 (d, 6H), 2.27 (t, 2H), 3.21-3.31 (m, 2H), 3.51-3.57 (m, 2H), 4.89 (s, 2H), 6.17 (s, 1H), 6.98 (d, 1H), 7.16 (d, 1H), 7.18-7.32 (m, 4H).

10 Intermediate 18: Methyl (2-([5-(methyloxy)-1H-imidazol-1-yl]methyl}phenyl)acetate



- Methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 2.5 g, 10.28 mmol) and 4-(methyloxy)-1H-imidazole (*J. Org. Chem.* (1984), 49(7), 1212-15) (2.018 g, 20.57 mmol) were dissolved in dry DMF (10 ml) and stirred at room temperature for 8 hours. After
 15 dilution with water the mixture was extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (65M) eluting with a gradient of MeOH in DCM from 0 to 5% to afford the title compound in 60% purity (917 mg, 3.52 mmol); UPLC/MS Rt=0.63 min; m/z (ES): 261 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.72 (s, 5H), 3.86 (s, 3H), 5.04 (s, 2H), 6.36 (d,
 20 1H), 7.05 (d, 1H), 7.26-7.36 (m, 3H).

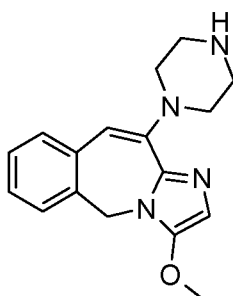
Intermediate 19: 3-(Methyloxy)-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



- To a solution of methyl (2-([5-(methyloxy)-1H-imidazol-1-yl]methyl}phenyl)acetate
 25 (Intermediate 18, 917 mg, 3.52 mmol) in THF (25 mL), at -70°C (external temperature) under nitrogen, a 1.8M solution of LDA in THF (2.94 mL, 5.28 mmol) was slowly added. The temperature was allowed to reach -20°C in 2 hours. Further LDA solution (1.5 ml, 2.7 mmol) was added. The reaction mixture was stirred for further 2 hours and the temperature was allowed to reach 0°C, then the reaction was quenched with saturated

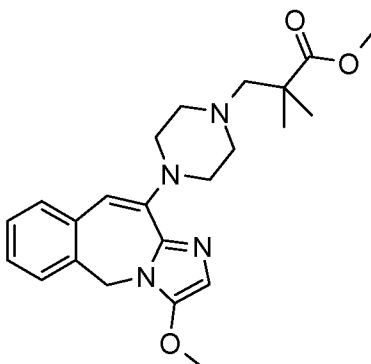
NH₄Cl solution, extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of MeOH in DCM from 0 to 2%, and then by trituration using diethyl ether, to afford the title compound (314 mg, 1.376 mmol) as an ~1:1 mixture with unreacted methyl (2-[[5-(methyloxy)-1H-imidazol-1-yl]methyl]phenyl)acetate. Intermediate 19 was used in the following reaction without further purification; UPLC/MS Rt=0.60 min; m/z (ES): 229 [M+H]⁺ and 457 [2M+H]⁺; ¹H NMR (CDCl₃) (only signals relating to the title compound): δ 4.05 (s, 3H), 4.15 (s, 2H), 5.19 (s, 2H), 6.71 (s, 1H), 7.23-7.39 (m, 4H).

Intermediate 20: 3-(Methyloxy)-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



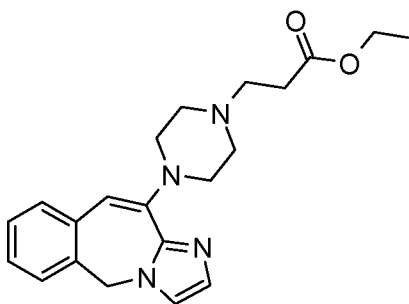
In a screw capped vial to 3-(methyloxy)-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 19, 314 mg, 1.376 mmol) was added piperazine (592 mg, 6.88 mmol) and trimethylsilyl trifluoromethanesulfonate (746 µl, 4.13 mmol). The mixture was then heated at 130 °C for 2 hours. The mixture was then cooled to room temperature and the crude product was purified by flash chromatography on modified silica gel (25g NH₂ cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (64 mg, 0.216 mmol) as a white solid; UPLC/MS Rt=0.65 min; m/z (ES): 297 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.07-3.20 (m, 8H), 3.92 (s, 3H), 4.77 (s, 2H), 6.10 (s, 1H), 6.50 (s, 1H), 7.16-7.38 (m, 4H).

Intermediate 21: Methyl 2,2-dimethyl-3-{4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl}propanoate



To a mixture of 3-(methoxy)-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 20, 64 mg, 0.216 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 281 mg, 0.864 mmol) in dry 1,2-dichloroethane (2 ml) under nitrogen, a drop of AcOH was added and then the mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (92 mg, 0.432 mmol) was then added and the resulting reaction mixture was stirred for 3 h, quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20g) eluting with a gradient of MeOH in dichloromethane from 0.5 to 1% to afford the title compound (30 mg, 0.073 mmol); UPLC/MS Rt=0.96 min; m/z (ES): 411 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.23 (s, 6H), 2.60 (s, 2H), 2.71-2.76 (m, 4H), 3.11-3.16 (m, 4H), 3.70 (s, 3H), 3.91 (s, 3H), 4.75 (s, 2H), 6.07 (s, 1H), 6.49 (s, 1H), 7.16-7.32 (m, 4H).

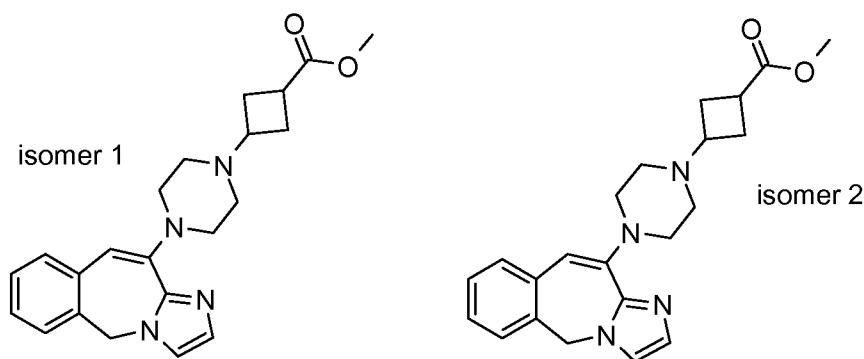
Intermediate 22: Ethyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoate



To a solution of 11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 4, 140 mg, 0.150 mmol) in chloroform (1 ml), ethyl 2-propenoate (0.024 ml, 0.225 mmol) was added. The reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (10g) eluting with a gradient of MeOH in DCM from 0 to 3%, to afford the title compound (40 mg, 0.109 mmol); UPLC/MS Rt=0.74 min; m/z (ES): 367

[M+H]⁺; ¹H NMR (CDCl₃): δ 1.30 (t, 3H), 2.57 (t, 2H), 2.70-2.76 (m, 4H), 2.83 (t, 2H), 3.17-3.23 (m, 4H), 4.19 (q, 2H), 4.90 (s, 2H), 6.18 (s, 1H), 6.98 (d, 1H), 7.17 (d, 1H), 7.19-7.33 (m, 4H).

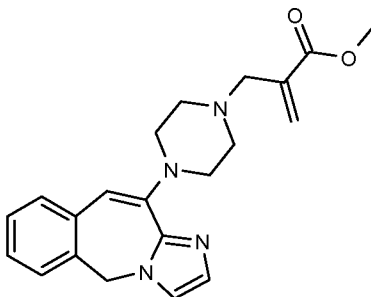
5 Intermediate 23 and Intermediate 24: Methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylate isomer 1 and Methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylate isomer 2



To a mixture of 11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 4, 40
 10 mg, 0.150 mmol) and ethyl 3-oxocyclobutanecarboxylate (29.9 mg, 0.210 mmol) in dry
 1,2-dichloroethane (2 ml) under nitrogen, a drop of AcOH was added and then the
 reaction mixture was stirred at room temperature for 30 min. Sodium
 triacetoxyborohydride (47.7 mg, 0.225 mmol) was then added and the resulting reaction
 mixture was stirred for 16 h. Partial hydrolysis of the ester was observed, so the reaction
 15 mixture was diluted with MeOH and purified by SCX column. The mixture of acid and
 ester was dissolved in MeOH/H₂O (1ml/1ml) and a 1M solution of KOH in MeOH was
 added (0.751 ml, 0.751 mmol). After 1 hour at 50°C the hydrolysis was complete and the
 reaction mixture was concentrated *in vacuo*. The crude was purified by Fraction Lynx to
 give a ~1:1 mixture of isomers of 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-
 20 piperazinyl]cyclobutanecarboxylic acid (26 mg, 0.071 mmol). 25 mg (0.069 mmol) of this
 mixture was dissolved in DCM (1 ml) and methanol (0.250 ml) and the mixture was cooled
 at 0°C. A 2M solution of trimethylsilyl diazomethane in hexane (0.069 ml, 0.137 mmol)
 was added dropwise and the temperature was allowed to rise to room temperature and
 the mixture was stirred for 2 hours. The solvent was evaporated and the residue was
 25 purified by flash chromatography on modified silica gel (10g NH₂ cartridge) eluting with a
 gradient of ethyl acetate in toluene from 10 to 30 % to afford the title compounds:
 Isomer 1: (10 mg, 0.026 mmol); HPLC Rt=2.495 min; ¹H NMR (CDCl₃): δ 2.43-2.70 (m,
 5H), 2.94-3.42 (m, 9H), 3.73 (s, 3H), 4.94 (s, 2H), 6.30 (s, 1H), 7.04 (d, 1H), 7.18-7.44 (m,
 5H)

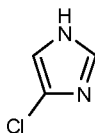
Isomer 2: (6 mg, 0.016 mmol) ; HPLC Rt=2.515 min; ^1H NMR (CDCl_3): δ 2.26-2.42 (m, 4H), 2.57-2.66 (m, 4H), 3.01-3.11 (m, 1H), 3.12-3.28 (m, 5H), 3.76, (s, 3H), 4.90 (s, 2H), 6.19 (s, 1H), 6.98 (d, 1H), 7.14 (d, 1H), 7.19-7.37 (m, 4H).

5 Intermediate 25: Methyl 2-{[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl}-2-propenoate



To a solution of 11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 4, 60 mg, 0.225 mmol) in acetonitrile (5 mL), K_2CO_3 (32.7 mg, 0.237 mmol) was added and then a solution of methyl 2-(bromomethyl)-2-propenoate (36.3 mg, 0.203 mmol) in acetonitrile (1 mL) was added slowly. The reaction mixture was left to stir at room temperature. After 2 h the mixture was partitioned between H_2O and DCM, extracted with DCM, the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (10g) eluting with a gradient of MeOH in DCM from 0 to 5%, to afford the title compound (57 mg, 0.156 mmol); UPLC/MS Rt=0.76 min; m/z (ES): 365 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3): δ 2.71-2.78 (m, 4H), 3.18-3.25 (m, 4H), 3.34 (s, 2H), 3.81 (s, 3H), 4.90 (s, 2H), 5.82-5.86 (m, 1H), 6.18 (s, 1H), 6.32-6.36 (m, 1H), 6.98 (d, 1H), 7.17 (d, 1H), 7.19-7.33 (m, 4H).

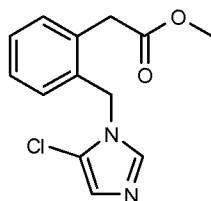
Intermediate 26: 4(5)-Chloro-1H-imidazole



To a solution of 2-[(1,1-dimethylethyl)(dimethyl)silyl]-N,N-dimethyl-1H-imidazole-1-sulfonamide (for preparation see US2005075366, 15 g, 51.8 mmol) in dry THF (100 mL), under nitrogen and at -70°C , a 1.6M solution of butyllithium in hexane (34.0 mL, 54.4 mmol) was slowly added. The temperature was allowed to reach -55°C in 1 hour then cooled down to -78°C and dimethylsulfamoyl chloride (8.33 mL, 78 mmol) was slowly added and the mixture was stirred at -78°C for 30min and at 20°C for 2 hours. The solvents were removed by evaporation and the residue was stirred with 2M HCl solution (100ml) for 12 hour at room temperature. Complete deprotection of the nitrogen was

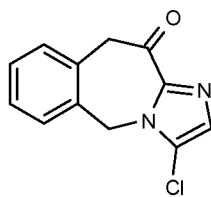
achieved while partial TBDMS deprotection was observed. The aqueous acid solution was basified with KOH pellets and the aqueous phase was extracted with EtOAc. The organic phases were dried over Na₂SO₄ and evaporated under reduced pressure. The crude residue was treated with a 1M solution of TBAF in THF (51.8 mL, 51.8 mmol) and heated to 60°C for 2 hours. The volatiles were removed under *vacuo* and the residue was chromatographed to give the title compound (3.5 g, 34.1 mmol); UPLC/MS Rt=0.33 min; m/z (ES): 103 and 105 [M+H]⁺; ¹H NMR (CDCl₃): δ 7.00 (d, 1H), 7.57 (d, 1H), 11.54 (brs, 1H).

10 Intermediate 27: Methyl {2-[(5-chloro-1H-imidazol-1-yl)methyl]phenyl}acetate



Methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 3 g, 12.34 mmol) and 4-chloro-1H-imidazole (Intermediate 26, 3.80 g, 37.0 mmol) were dissolved in dry DMF (100 ml) and stirred at room temperature for 16 hours. After dilution with water the mixture was extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (50g) eluting with a gradient of MeOH in DCM from 0 to 5% to afford the title compound (1.6 g, 6.04 mmol) contaminated with ~10% of the regioisomer methyl {2-[(4-chloro-1H-imidazol-1-yl)methyl]phenyl}acetate, which was used in the next step without further purification; UPLC/MS Rt=0.50 min; m/z (ES): 265 and 267 [M+H]⁺; ¹H NMR (CDCl₃) only signals relating to the title compound: δ 3.71 (s, 2H), 3.72 (s, 3H), 5.21 (s, 2H), 6.92 (d, 1H), 7.05 (d, 1H), 7.28-7.42 (m, 4H).

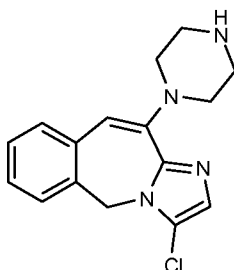
Intermediate 28: 3-Chloro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



To a solution of methyl {2-[(5-chloro-1H-imidazol-1-yl)methyl]phenyl}acetate (Intermediate 27, 1.6 g, 6.04 mmol) in THF (10 ml), at -70°C (external temperature) under nitrogen, a 1.8M solution of LDA in THF (5.04 ml, 9.07 mmol) was slowly added. The temperature was allowed to reach -10°C in 2 hours then the reaction was quenched with saturated

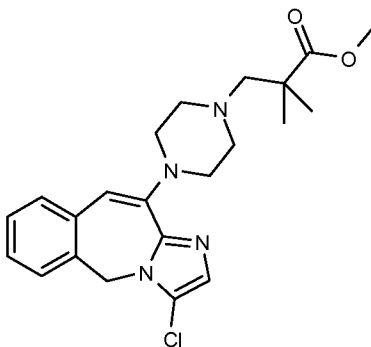
NH₄Cl solution, extracted with DCM, the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25g) eluting with a gradient of MeOH in DCM from 0 to 2%, to afford the title compound (130 mg, 0.559 mmol) contaminated with ~10% of the regioisomer 2-chloro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one; UPLC/MS Rt=0.57 min; m/z (ES): 233 and 235 [M+H]⁺; ¹H NMR (CDCl₃) only signals relating to the title compound: δ 4.22 (s, 2H), 5.38 (s, 2H), 7.25 (s, 1H), 7.27-7.46 (m, 4H).

Intermediate 29: 3-Chloro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



In a screw capped vial to 3-chloro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 28, 130 mg, 0.559 mmol) was added piperazine (241 mg, 2.79 mmol) and trimethylsilyl trifluoromethanesulfonate (303 µl, 1.676 mmol). The mixture was then heated at 130 °C for 12 hours. The mixture was then cooled at room temperature and the crude product was purified by flash chromatography on modified silica gel (25g NH₂ cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (90 mg, 0.299 mmol); UPLC/MS Rt=0.68 min; m/z (ES): 301 and 303 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.07-3.17 (m, 8H), 4.91 (s, 2H), 6.21 (s, 1H), 7.09 (s, 1H), 7.21-7.36 (m, 4H).

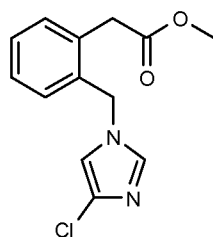
Intermediate 30: Methyl 3-[4-(3-chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



To a mixture of 3-chloro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 29, 90 mg, 0.299 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 389 mg, 1.197 mmol) in dry 1,2-dichloroethane under nitrogen, a drop of AcOH was added

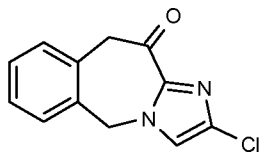
and then the mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (127 mg, 0.598 mmol) was then added and the resulting reaction mixture was stirred for 12 h, quenched with saturated aqueous NaHCO₃ solution and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20g) eluting with a gradient of MeOH in DCM from 0.5 to 1% to afford the title compound (59 mg, 0.142 mmol); UPLC/MS Rt=1.01 min; m/z (ES): 415 and 417 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.23 (s, 6H), 2.60 (s, 2H), 2.71-2.77 (m, 4H), 3.10-3.16 (m, 4H), 3.70 (s, 3H), 4.89 (s, 2H), 6.18 (s, 1H), 7.09 (s, 1H), 7.21-7.36 (m, 4H).

Intermediate 31: Methyl {2-[(4-chloro-1H-imidazol-1-yl)methyl]phenyl}acetate



4-Chloro-1H-imidazole (Intermediate 26, 1.37 g, 13.36 mmol) and 2,7,9-tris(2-methylpropyl)-2,5,7,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (4.58 g, 13.36 mmol) were dissolved in dry THF (50 mL) and after 15 min methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 3.25 g, 13.36 mmol) was added. After 2 hours the volatiles were concentrated *in vacuo*. The residue was diluted with AcOEt and filtered on a silica pad. The organic solution was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel (50g) eluting with a gradient of EtOAc in cyclohexane from 30 to 50% to afford the title compound (1.14 g, 4.31 mmol); UPLC/MS Rt=0.63 min; m/z (ES): 265 and 267 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.64 (s, 2H), 3.71 (s, 3H), 5.19 (s, 2H), 6.78 (d, 1H), 7.09-7.13 (m, 1H), 7.31-7.42 (m, 4H).

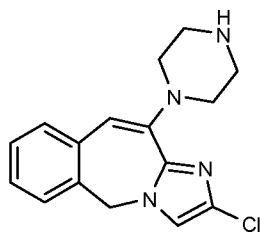
Intermediate 32: 2-Chloro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



To a solution of methyl {2-[(4-chloro-1H-imidazol-1-yl)methyl]phenyl}acetate (Intermediate 31, 1.14 g, 4.31 mmol) in THF (30 ml), at -70°C (external temperature) under nitrogen, a 1.8M solution of LDA in THF (3.59 ml, 6.46 mmol) was slowly added. The temperature was allowed to reach room temperature in 2 hours then the mixture was stirred at the

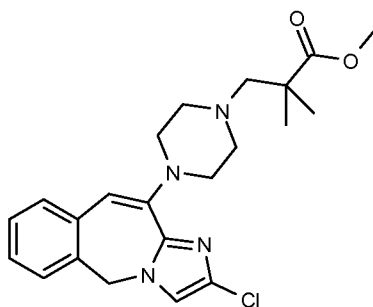
same temperature for 12 hours, then quenched with saturated NH_4Cl solution, extracted with DCM, the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (25g) eluting with a gradient of EtOAc in cyclohexane from 30 to 70%, and then by trituration with diethyl ether, to afford the title compound (327 mg, 1.405 mmol) as a white solid; UPLC/MS Rt=0.61 min; m/z (ES): 233 and 235 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3): δ 4.21 (s, 2H), 5.32 (s, 2H), 7.12 (s, 1H), 7.30-7.46 (m, 4H).

Intermediate 33: 2-Chloro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



In a screw capped vial to 2-chloro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 32, 327 mg, 1.405 mmol) was added piperazine (605 mg, 7.03 mmol) and trimethylsilyl trifluoromethanesulfonate (762 μl , 4.22 mmol). The mixture was then heated at 130 $^\circ\text{C}$ for 2 hours. The mixture was then cooled at room temperature and the mixture was partitioned between DCM and saturated NaHCO_3 solution extracted with DCM, the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on modified silica gel (110g NH_2 cartridge) eluting with a gradient of MeOH in DCM from 0 to 2% to afford the title compound (343 mg, 1.140 mmol); UPLC/MS Rt=0.65 min; m/z (ES): 301 and 303 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3): δ 3.12 (s, 8H), 4.83 (s, 2H), 6.20 (s, 1H), 6.88 (s, 1H), 7.20-7.35 (m, 4H).

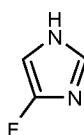
Intermediate 34: Methyl 3-[4-(2-chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



To a mixture of 2-chloro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (Intermediate 33, 300 mg, 0.997 mmol) and methyl 2,2-dimethyl-3-oxopropanoate (prepared in a similar fashion to Intermediate 5, 1298 mg, 3.99 mmol) in dry 1,2-dichloroethane under nitrogen,

a drop of AcOH was added and then the mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (423 mg, 1.995 mmol) was then added and the resulting reaction mixture was stirred for 3 h, quenched with NaHCO₃ (saturated aqueous solution) and extracted with dichloromethane. The organic layers were combined, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (20g) eluting with a gradient of MeOH in DCM from 0.5 to 1% to afford the title compound (300 mg, 0.723 mmol); UPLC/MS Rt=0.98 min; m/z (ES): 415 and 417 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.23 (s, 6H), 2.60 (s, 2H), 2.71-2.77 (m, 4H), 3.08-3.15 (m, 4H), 3.70 (s, 3H), 4.82 (s, 2H), 6.18 (s, 1H), 6.87 (s, 1H), 7.20-7.35 (m, 4H).

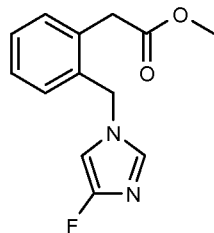
Intermediate 35: 4(5)-Fluoro-1H-imidazole



A 1.6M solution of butyllithium in hexanes (37.5 mL, 59.9 mmol) was added dropwise to a stirred solution of N,N-dimethyl-1H-imidazole-1-sulfonamide (10 g, 57.1 mmol) in THF (60 ml) at -78°C. The reaction was stirred for 20 minutes then a solution of TBDMSCl (8.60 g, 57.1 mmol) in THF (30 ml) was added dropwise at the same temperature. The reaction was allowed to warm gradually to room temperature and stirred overnight. The reaction mixture was cooled to -78°C and a 1.6M solution of butyllithium in hexanes (37.5 mL, 59.9 mmol) was added. The reaction was stirred for 1 hour then a solution of N-fluorobenzenesulfonimide (18.00 g, 57.1 mmol) in THF (50 ml) was added. The reaction was stirred at -78°C for 1 hour then allowed to warm to room temperature and stirred for another 1 hour. The reaction was quenched with 1M HCl solution (100 ml) and stirred for 1 hour. The THF was evaporated under reduced pressure then the aqueous phase was washed with EtOAc (2 x 200ml), back-extracting each EtOAc wash with HCl (2M, 100 ml). The combined acidic aqueous phases were adjusted to pH9 with NaOH pellets and the aqueous phase was extracted with EtOAc (8 x 200 ml). The organic phases were dried over Na₂SO₄ and evaporated under reduced pressure. The crude residue was treated with a 1M solution of TBAF in THF (30 mL, 30.0 mmol) and heated to 60°C for 2 hours. The reaction mixture was divided in two and each half was loaded onto a pre-conditioned SCX cartridge (70g). Each SCX cartridge was eluted with methanol and then 2M NH₃ in MeOH. The basic fractions from both columns were combined and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (340g) eluting with a gradient of EtOAc in cyclohexane from 50 to 100%, and then by treating with activated charcoal in EtOAc for 15 minutes to afford the title compound (3.16g, 36.7

mmol) as a yellow solid; UPLC/MS Rt=0.25 min; m/z (ES): 87 [M+H]⁺; ¹H NMR (CDCl₃): δ 6.56 (d, 1H), 7.26 (s, 1H), 9.55 (t, 1H); ¹⁹F NMR (CDCl₃): δ 138.0.

Intermediate 36: Methyl {2-[(4-fluoro-1H-imidazol-1-yl)methyl]phenyl}acetate

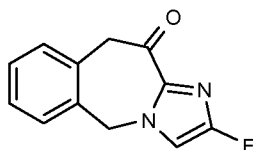


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2,7,9-Tris(2-methylpropyl)-2,5,7,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (10.84 g, 31.7 mmol) was added dropwise to a stirred solution of 4-fluoro-1H-imidazole (Intermediate 35, 2.73 g, 31.7 mmol) in THF (100 ml) at room temperature. Towards the end of the addition a precipitate formed blocking the stirring. The reaction was diluted with more THF (100 ml) to give a suspension. After 20 minutes methyl [2-(bromomethyl)phenyl]acetate (Intermediate 1, 5.4g, 21.10 mmol) was added dropwise over 20 minutes (during the addition the reaction mixture became homogeneous). The reaction was stirred for 1 hour. The reaction mixture was evaporated under reduced pressure and then taken up in EtOAc (100 ml) and filtered through a pad of SiO₂ washing with EtOAc and then 20%MeOH/EtOAc until no further 4-fluoro-1H-imidazole was eluted. The MeOH/EtOAc washings were evaporated separately under reduced pressure to give a solid residue. This residue was triturated with EtOAc (100 ml) and filtered. This filtrate was combined with the EtOAc washings from above and evaporated under reduced pressure to give a brown oil which was purified by flash chromatography on silica gel (340g) eluting with a gradient of EtOAc in cyclohexane from 30 to 100% to give the title compound (2.75 g, 11.08 mmol) as an off-white solid; UPLC/MS Rt=0.61 min; m/z (ES): 249 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.63 (s, 2H), 3.69 (s, 3H), 5.14 (s, 2H), 6.37 (dd, 1H), 7.06-7.11 (m, 2H), 7.27-7.38 (m, 3H); ¹⁹F NMR (CDCl₃): δ 133.9.

20

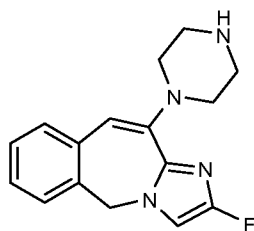
25 Intermediate 37: 2-Fluoro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one



A 1.8M solution of LDA in THF/heptane/ethylbenzene (9.50 mL, 17.10 mmol) was added dropwise to a stirred solution of methyl {2-[(4-fluoro-1H-imidazol-1-yl)methyl]phenyl}acetate (Intermediate 36, 2.83 g, 11.40 mmol) in THF (90 ml) at -78°C.

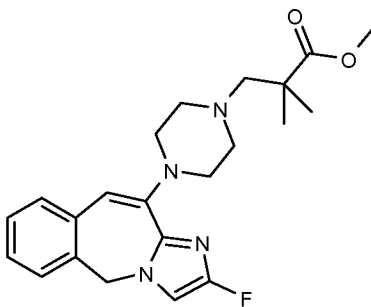
The mixture was allowed to stir and warm to -20°C over a period of 2 hours. The mixture was allowed to stir and warm to room temperature overnight. The reaction mixture was quenched with saturated NH₄Cl solution (50 ml), diluted with brine (100 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phases were dried (Na₂SO₄) and
5 evaporated under reduced pressure to give a yellow solid. The crude was triturated with EtOAc (10 ml) and EtOAc/cyclohexane (1:1, 3 x 10 ml). The supernatants were loaded sequentially onto a preconditioned silica gel column (100g), which was then eluted with 30-70% EtOAc in cyclohexane. Fractions containing the desired product were combined with the solids from the trituration and evaporated under reduced pressure to give a pale
10 yellow solid which was further triturated with diethyl ether (20 ml), filtered and washed with diethyl ether (20 ml). The resulting solid was collected and dried under reduced pressure to give the title compound (985 mg, 4.56 mmol) as an off-white solid; UPLC/MS Rt=0.58 min; m/z (ES): 217 [M+H]⁺; ¹H NMR (CDCl₃): δ 4.17 (s, 2H), 5.28 (s, 2H), 6.75 (d, 1H), 7.29-7.43 (m, 4H); ¹⁹F NMR (CDCl₃): δ 130.1.

15 Intermediate 38: 2-Fluoro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine



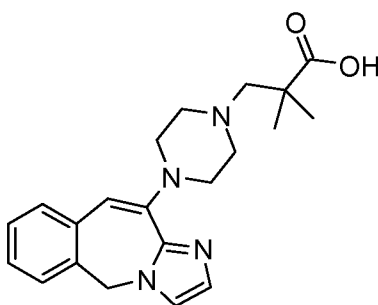
Trimethylsilyl trifluoromethanesulfonate (2467 µl, 13.65 mmol) was added to a mixture of 2-fluoro-5,10-dihydro-11H-imidazo[1,2-b][2]benzazepin-11-one (Intermediate 37, 984 mg, 4.55 mmol) and piperazine (1960 mg, 22.76 mmol) in a screw-topped vial at room
20 temperature. The mixture was heated to 130°C with shaking in a PLS reaction station for 17 hours. The mixture was cooled and partitioned between dichloromethane (100 ml) and saturated Na₂CO₃ solution (50 ml). The phases were separated and the aqueous phase was extracted with dichloromethane (50 ml). The combined organic phases were washed
25 with brine (100 ml), dried (Na₂SO₄) and evaporated under reduced pressure to give a tan foam which was purified twice by flash chromatography on modified silica gel (110g NH cartridge) eluting with a gradient of MeOH in EtOAc from 5 to 10% for the first chromatography and with a gradient of MeOH in DCM from 0 to 4% for the second chromatography to give the title compound (854 mg, 3.00 mmol) as a pale orange foam;
30 UPLC/MS Rt=0.63 min; m/z (ES): 285 [M+H]⁺; ¹H NMR (CDCl₃): δ 3.09-3.18 (m, 8H), 4.79 (s, 2H), 6.20 (s, 1H), 6.49 (d, 1H), 7.21-7.34 (m, 4H); ¹⁹F NMR (CDCl₃): δ 133.1.

Intermediate 39: Methyl 3-[4-(2-fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate



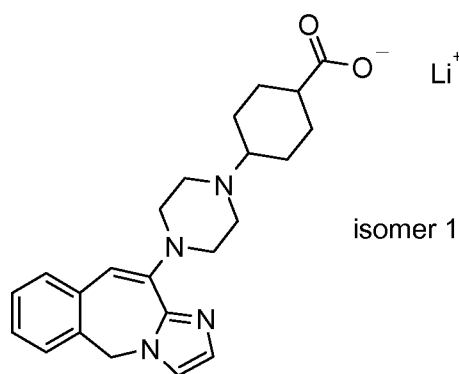
2 Drops of acetic acid were added to a stirred solution of methyl 2,2-dimethyl-3-oxopropanoate (Intermediate 5, 2289 mg, 7.03 mmol) and 2-fluoro-11-(1-piperazinyl)-5H-imidazo[1,2-b][2]benzazepine (500 mg, 1.759 mmol) in 1,2-dichloroethane (15 ml) at room temperature. The resulting mixture was stirred for 30 minutes then sodium triacetoxymethylborohydride (745 mg, 3.52 mmol) was added and stirring was continued overnight (16 hours). The mixture was quenched with saturated NaHCO₃ solution (50 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried (Na₂SO₄) and evaporated under reduced pressure to give a crude which was purified by flash chromatography on silica gel (100g) eluting with a gradient of 99/1 EtOAc/MeOH in DCM from 0 to 20% to give the title compound in a mixture with methyl 3-hydroxy-2,2-dimethylpropanoate (620 mg). This mixture was dissolved in MeOH and loaded onto a preconditioned SCX cartridge (10 g). The cartridge was eluted with MeOH and then 2M NH₃ in MeOH. The basic fractions were evaporated under reduced pressure to give the title compound (570 mg, 1.43 mmol) as a colourless glass; UPLC/MS Rt=0.96 min; m/z (ES): 399 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.20 (s, 6H), 2.58 (s, 2H), 2.68-2.73 (m, 4H), 3.06-3.12 (m, 4H), 3.68 (s, 3H), 4.77 (s, 2H), 6.16 (s, 1H), 6.48 (s, 1H), 7.19-7.33 (m, 4H); ¹⁹F NMR (CDCl₃): δ 133.1.

Compound 1: 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid



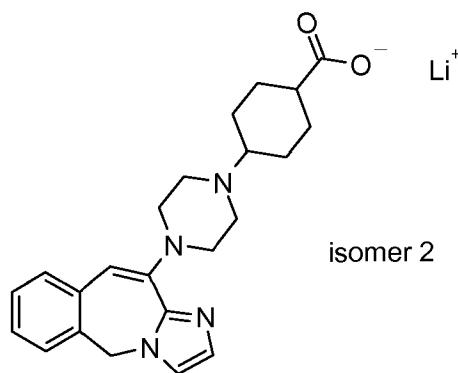
To a solution of methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 6, 36 mg, 0.095 mmol) in THF (3 ml) and water (1 ml) was added a 1M solution of KOH in MeOH (1 ml, 1 mmol) and the mixture was refluxed for 4 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (10g) to give the title compound (30 mg, 0.082 mmol) as white solid; HPLC Rt=2.73 min; MS m/z (ES): 367.0 [M+H]⁺, 389.2 [M+Na]⁺ and 184.0 [M+2H]²⁺; ¹H NMR (CDCl₃): δ 1.30 (s, 6H), 2.67 (s, 2H), 3.02-3.10 (m, 4H), 3.13-3.42 (brs, 4H), 4.91 (s, 2H), 6.21 (s, 1H), 7.00 (d, 1H), 7.17 (d, 1H), 7.22-7.35 (m, 4H).

Compound 2: Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1



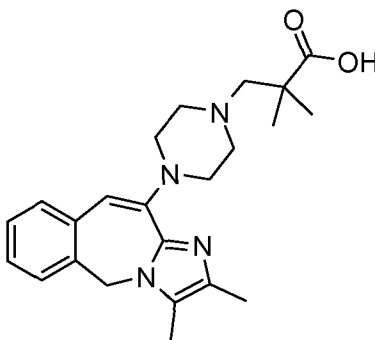
Methyl 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1 (Intermediate 7, 15.0 mg, 0.037 mmol) was dissolved in methanol (1 ml) and water (1 ml) and lithium hydroxide (5 mg, 0.209 mmol) was added to the reaction. The mixture was heated at 40 °C for 4 hours. Then MeOH was evaporated and the water phase was purified by C18 cartridge (5g) by using water and then MeOH as eluant to obtain, after solvent evaporation, the title compound (10.0 mg, 0.025 mmol); UPLC/MS Rt=0.40 min; m/z (ES): 393 [M-Li+2H]⁺ and 197 [M-Li+3H]²⁺; ¹H NMR (CDCl₃): δ 1.30-1.60 (m, 4H), 1.90-2.03 (m, 2H), 2.15-2.65 (m, 8H), 3.05 (brs, 4H), 4.95 (s, 2H), 6.14 (s, 1H), 6.99 (d, 1H), 7.15-7.37 (m, 5H).

Compound 3: Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2



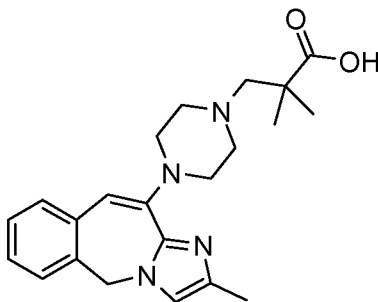
Methyl 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2 (Intermediate 8, 7.0 mg, 0.017 mmol) was dissolved in methanol (1 ml) and water (1ml) and lithium hydroxide (5 mg, 0.209 mmol) was added to the reaction. The mixture was heated at 40 °C for 4 hours. Then MeOH was evaporated and the water phase was purified by C18 cartridge (5g) by using water and then MeOH as eluant to obtain, after solvent evaporation, the title compound (5.4 mg, 0.014 mmol); MS m/z (ES): 393.3 [M-Li+2H]⁺ and 197.2 [M-Li+3H]²⁺; ¹H NMR (CDCl₃): 1.07-1.28 (m, 4H), 1.58-1.89 (m, 4H), 2.12-2.23 (m, 1H), 2.45-2.65 (m, 5H), 3.04 (brs, 4H), 4.94 (s, 2H), 6.13 (s, 1H), 6.99 (d, 1H), 7.15-7.37 (m, 5H).

Compound 4: 3-[4-(2,3-Dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid



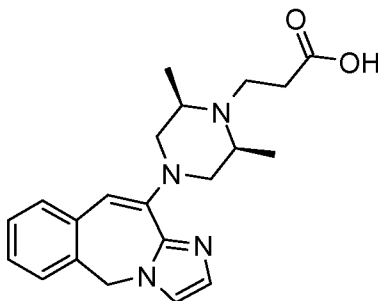
To a solution of methyl 3-[4-(2,3-Dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 12, 28 mg, 0.069 mmol) in methanol (3 ml) and water (1 ml), LiOH (8.21 mg, 0.343 mmol) was added and the mixture was refluxed for 4 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (5g) to give the title compound (18 mg, 0.046 mmol); HPLC/MS Rt=1.19 min; m/z (ES): 395.1 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.29 (s, 6H), 2.35 (s, 3H), 2.38 (brs, 3H), 2.75 (s, 2H), 3.00-3.50 (brs, 8H), 4.84 (s, 2H), 6.38 (brs, 1H), 7.23-7.40 (m, 4H).

Compound 5: 2,2-Dimethyl-3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid



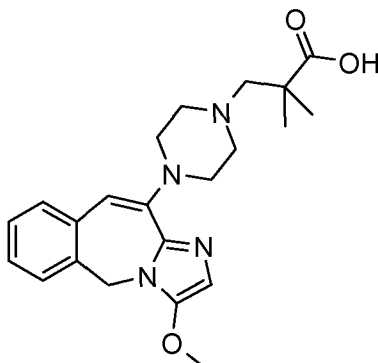
To a solution of methyl 3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 16, 18 mg, 0.046 mmol) in methanol (4 ml) and water (1 ml), LiOH (5.46 mg, 0.228 mmol) was added and the mixture was refluxed for 4 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (5g) to give the title compound (14 mg, 0.037 mmol) as a white solid; HPLC Rt=3.54 min; MS m/z (ES): 381.2 [M+H]⁺ and 191.2 [M+2H]²⁺; ¹H NMR (CDCl₃): δ 1.30 (s, 6H), 2.33 (brs, 3H), 2.71 (s, 2H), 3.05-3.45 (two overlapping brs, 8H), 4.87 (s, 2H), 6.28 (brs, 1H), 6.77 (s, 1H), 7.25-7.39 (m, 4H).

Compound 6: 3-[(2R,6S)-4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-2,6-dimethyl-1-piperazinyl]propanoic acid



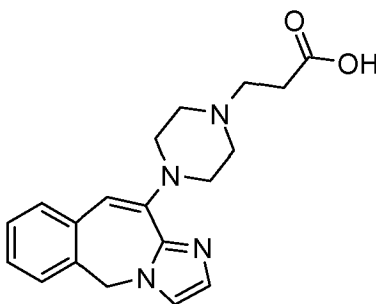
In a screw capped vial to 11-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-5H-imidazo[1,2-b][2]benzazepine (Intermediate 17, 27 mg, 0.092 mmol) in methanol (2 ml) and water (1 ml), ethyl acrylate (0.039 ml, 0.367 mmol) was added. The reaction mixture was heated at 130°C for 16 hours. A 1M solution of KOH in MeOH (0.367 ml, 0.367 mmol) was then added and the mixture was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure and the crude was purified by Fraction Lynx to give the title compound (1.7 mg, 4.64 μmol); MS m/z (ES): 367.3 [M+H]⁺ and 184.2 [M+2H]²⁺; ¹H NMR (CDCl₃): δ 1.31 (d, 6H), 2.64 (t, 2H), 2.76 (t, 2H), 3.22-3.31 (m, 2H), 3.36 (t, 2H), 3.43 (d, 2H), 4.91 (s, 2H), 6.22 (s, 1H), 7.01 (d, 1H), 7.23-7.35 (m, 5H).

Compound 7: 2,2-Dimethyl-3-{4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl}propanoic acid



- 5 To a solution of methyl 2,2-dimethyl-3-{4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl}propanoate (Intermediate 21, 30 mg, 0.073 mmol) in methanol (1.5 mL) and water (1.5 mL), a 1M solution of KOH in MeOH (0.731 mL, 0.731 mmol) was added and the mixture was refluxed for 2 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl
- 10 solution. This mixture was purified by C18 column (10g) to give the title compound (22 mg, 0.055 mmol); UPLC/MS Rt=0.58 min; m/z (ES): 397 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.31 (s, 6H), 2.72 (s, 2H), 3.11 (brs, 4H), 3.30 (brs, 4H), 3.95 (s, 3H), 4.81 (s, 2H), 6.19 (s, 1H), 6.59 (s, 1H), 7.23-7.40 (m, 4H).

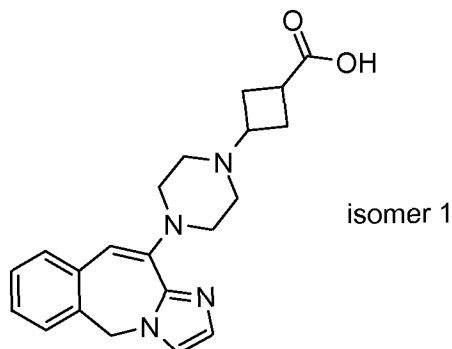
15 Compound 8: 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid



- To a solution of ethyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoate (Intermediate 22, 40 mg, 0.109 mmol) in methanol (1 mL) and water (1 mL), a 1M solution of KOH in MeOH (1.092 mL, 1.092 mmol) was added and the
- 20 mixture was refluxed for 1 hour. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (5g) to give the title compound (35 mg, 0.103 mmol) as white solid; UPLC/MS Rt=0.47 min; m/z (ES): 339 [M+H]⁺; ¹H NMR (CDCl₃): δ 2.62 (t, 2H), 2.90

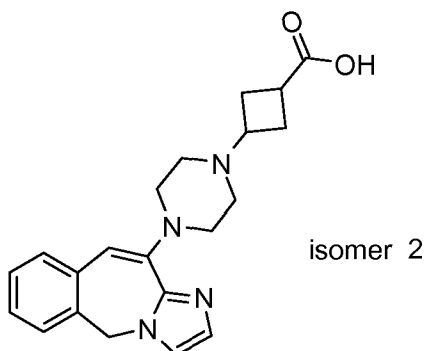
(t, 2H), 2.99 (brs, 4H), 3.30 (brs, 4H), 4.92 (s, 2H), 6.22 (s, 1H), 7.01 (d, 1H), 7.18 (d, 1H), 7.23-7.37 (m, 4H).

Compound 9: 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 1



To a solution of methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylate isomer 1 (Intermediate 23, 10 mg, 0.026 mmol) in methanol (0.5 mL) and water (0.5 mL), a 1M solution of KOH in MeOH (0.106 mL, 0.106 mmol) was added and the mixture was refluxed for 1 hour. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (10g) to give the title compound (7 mg, 0.019 mmol); UPLC/MS Rt=0.33 min; m/z (ES): 365 [M+H]⁺ and 183 [M+2H]²⁺; ¹H NMR (d6-DMSO): δ 1.76-1.89 (m, 2H), 1.96-2.05 (m, 2H), 2.17-2.27 (m, 1H), 2.31-2.40 (m, 4H), 2.44-2.49 (m, 1H), 2.99-3.12 (m, 4H), 4.97 (s, 2H), 6.17 (s, 1H), 6.99 (d, 1H), 7.17-7.40 (m, 5H).

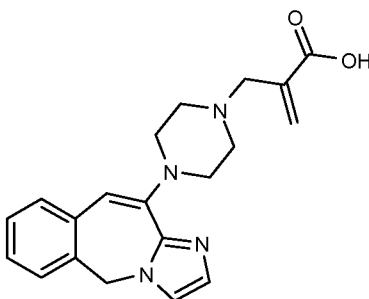
Compound 10: 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 2



To a solution of methyl 3-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylate isomer 2 (Intermediate 24, 6 mg, 0.016 mmol) in methanol (0.5 mL) and water (0.5 mL), a 1M solution of KOH in MeOH (0.063 mL, 0.063

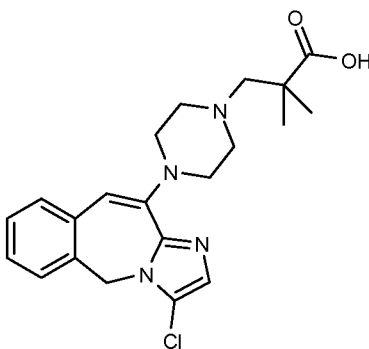
mmol) was added and the mixture was refluxed for 1 hour. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (10g) to the title compound (4 mg, 0.011 mmol); UPLC/MS Rt=0.33 min; m/z (ES): 365 [M+H]⁺ and 183 [M+2H]²⁺; ¹H NMR (d6-DMSO): δ 1.74-1.87 (m, 2H), 1.89-2.03 (m, 1H), 2.04-2.13 (m, 2H), 2.30-2.39 (m, 4H), 2.72-2.82 (m, 1H), 3.01-3.10 (m, 4H), 4.95 (s, 2H), 6.14 (s, 1H), 6.99 (d, 1H), 7.15-7.38 (m, 5H).

Compound 11: 2-{[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl}-2-propenoic acid



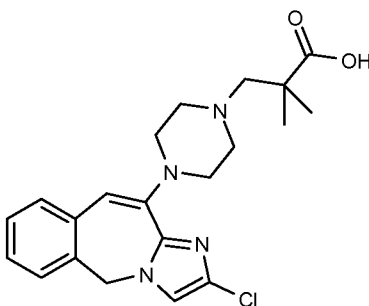
To a solution of methyl 2-{[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl}-2-propenoate (Intermediate 25, 57 mg, 0.156 mmol) in THF (3 ml) and water (1 ml), LiOH (18.73 mg, 0.782 mmol) was added and the mixture was stirred at room temperature for 12 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (5g) to give the title compound (50 mg, 0.143 mmol) as white solid; UPLC/MS Rt=0.47 min; m/z (ES): 351 [M+H]⁺; ¹H NMR (d6-DMSO): δ 2.89 (brs, 4H), 3.23 (brs, 4H), 3.56 (brs, 2H), 5.05 (s, 2H), 5.99 (s, 1H), 6.34 (s, 2H), 7.17 (s, 1H), 7.24-7.47 (m, 5H).

Compound 12: 3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid



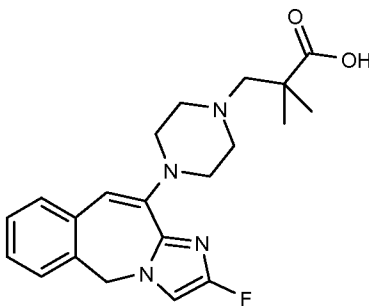
To a solution of methyl 3-[4-(3-chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 30, 59 mg, 0.142 mmol) in methanol (1 mL) and water (1 mL), a 1M solution of KOH in MeOH (0.995 mL, 0.995 mmol) was added and the mixture was refluxed for 4 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (10g) to give the title compound (50 mg, 0.125 mmol) as a white solid; UPLC/MS Rt=0.57 min; m/z (ES): 401 and 403 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.29 (s, 6H), 2.66 (s, 2H), 3.04 (brs, 4H), 3.26 (brs, 4H), 4.90 (s, 2H), 6.23 (s, 1H), 7.09 (s, 1H), 7.23-7.36 (m, 4H).

Compound 13: 3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid



To a solution of methyl 3-[4-(2-chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 34, 300 mg, 0.723 mmol) in methanol (4 mL) and water (4 mL), a 1M solution of KOH in MeOH (3.62 mL, 3.62 mmol) was added and the mixture was refluxed for 4 hours. The solvent was concentrated under reduced pressure, the residue was dissolved in water and neutralized with 1M HCl solution. This mixture was purified by C18 column (25g) to give the title compound (250 mg, 0.624 mmol) as a white solid; UPLC/MS Rt=0.54 min; m/z (ES): 401 and 403 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.29 (s, 6H), 2.66 (s, 2H), 3.05 (brs, 4H), 3.25 (brs, 4H), 4.83 (s, 2H), 6.21 (s, 1H), 6.90 (s, 1H), 7.22-7.36 (m, 4H).

Compound 14: 3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid



1M Potassium hydroxide in MeOH (4269 μ l, 4.27 mmol) was added to a suspension of methyl 3-[4-(2-fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoate (Intermediate 39, 567 mg, 1.423 mmol) in methanol/water (1:1, 10ml) at room temperature. The resulting mixture was stirred overnight and became a homogeneous solution. The mixture was heated to reflux for 5 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was twice dissolved in water (10 ml) and then evaporated to dryness under reduced pressure to remove all traces of methanol. The residue was dissolved in water (10 ml) and the pH was adjusted to pH6 by addition of 1M HCl (~4.5 ml required). The reaction mixture was loaded onto a pre-conditioned C18 column and eluted with water to remove salts and then with MeOH to elute the product. Product containing fractions were combined and evaporated under reduced pressure to give the title compound (494 mg, 1.285 mmol) as a white solid; UPLC/MS Rt=0.52 min; m/z (ES): 385 [M+H]⁺; ¹H NMR (CDCl₃): δ 1.28 (s, 6H), 2.65 (s, 2H), 3.03 (brs, 4H), 3.25 (brs, 4H), 4.80 (s, 2H), 6.22 (s, 1H), 6.52 (d, 1H), 7.22-7.36 (m, 4H); ¹⁹F NMR (CDCl₃): δ 132.8.

Biological Assays

1. H₁ Antagonist Assay

a) 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-based 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 resulted 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. The media was removed by aspiration 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.

Supporting compounds 1-6 were tested and gave a pK_i against H₁ in the range 6.9-7.7. Compound 1 gave a pK_i against H₁ of 7.6

b) Frozen Chinese Hamster Ovary (CHO) cells stably expressing the human H₁ histamine receptor and aequorin apo-protein were thawed and added drop wise to an appropriate volume of warm DMEM media (Gibco Invitrogen 41965-039) containing 10% dialysed foetal bovine serum (FBS) (Invitrogen; 05-4011DK). Cells were then spun down at 1000rpm for 5 minutes at room temperature. The supernatant was poured off and the pellet re-suspended in HBSS buffer (Sigma kit H1387) supplemented with HEPES (Sigma H0887), NaHCO₃ (Sigma S8761)) containing 0.1% Pluronic Acid F68 solution (Sigma; P5556) and 0.1% Bovine Serum Albumin (CalBiochem; 126609)). A sample was taken and a cell count performed. Cells were diluted down to 2.5e6 cells/ml in loading buffer, Coelenterazine [5uM] (DiscoverX; 90-0084L) was added to the cell suspension and cell vessel wrapped in foil. Cell vessel was put on windmill rotator (Bibby Stuart) and left overnight at room temperature. Before assay, a sample was taken and a cell count performed. Cells were diluted to an appropriate final density immediately prior to assay. Plates containing compounds (0.5ul) were placed in a Lumilux, where they were diluted in buffer (20ul), before additions of cells (10ul) and a pre-determined sub-maximal concentration of histamine (10ul) whilst luminescence was monitored. Data was analysed using area under curve for the entire timecourse, normalised to in-plate nominal high and low controls and fitted to a four parameter logistic equation.

Supporting compounds 1-14 were tested and gave a pK_i against H₁ in the range 6.5-7.9. Compound 1 gave a pK_i against H₁ of 7.

2. 5HT_{2A} Antagonist Assay

a) Adherent SH-SY5Y cells stably expressing 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 cells are neuroblastoma and are commercially available from the American Type Culture Collection (ATCC). The SH-SY5Y cells, expressing 5-HT_{2A} receptors, were seeded into black-walled clear-based 384-well plates at a density of 16,000 cells per well and cultured overnight at 37°C under 5% CO₂. The media was removed by aspiration 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 cytoplasmic calcium indicator, Fluo-4 in the acetylmethyl form (4 mM), 2.5mM Probenecid and 250µM 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.

Supporting compounds 1 and 8-14 were tested and gave a pK_i against 5HT_{2A} in the range 5.0-9.0. Compound 1 gave a pK_i against 5HT_{2A} of 6.6.

b) Frozen Human Embryonic Kidney (HEK) cells stably expressing the human 5-HT_{2A} serotonin receptor and aequorin apo-protein were thawed and added drop wise to an appropriate volume of warm DMEM media (Gibco Invitrogen 41965-039) containing 10% dialysed foetal bovine serum (FBS) (Invitrogen; 05-4011DK). Cells were then spun down at 1000rpm for 5 minutes at room temperature. The supernatant was poured off and the pellet re-suspended in HBSS buffer (Sigma kit H1387) supplemented with HEPES (Sigma H0887), NaHCO₃ (Sigma S8761)) containing 0.1% Pluronic Acid F68 solution (Gibco Invitrogen; 24040-032) and 0.1% Bovine Serum Albumin (CalBiochem; 126609)). A sample was taken and a cell count performed. Cells were diluted down to 2.5e6 cells/ml in loading buffer, Coelenterazine [5µM] (Invitrogen; C6780) was added to the cell suspension and cell vessel wrapped in foil. Cell vessel was put on windmill rotator (Bibby Stuart) and left overnight at room temperature. Before assay, a sample was taken and a cell count performed. Cells were diluted to an appropriate final density immediately prior to assay. Plates containing compounds (0.5ul) were placed in a Lumilux, where they were diluted in buffer (20ul), before additions of cells (10ul) and a pre-determined sub-maximal concentration of 5-HT (10ul) whilst luminescence was monitored. Data was analysed using area under curve for the entire timecourse, normalised to in-plate nominal high and low controls and fitted to a four parameter logistic equation.

Supporting compounds 1-14 were tested and gave a pKi against 5HT_{2A} in the range 6.0-7.4. Compound 1 gave a pKi against 5HT_{2A} of 7.1.

The results of the assays are set out in Table 1 below:

5

Table 1

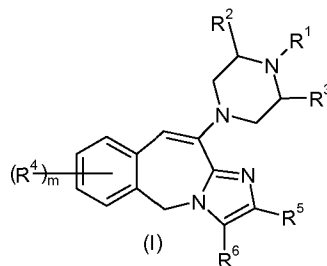
Ex No.	Name	Assay			
		1a H1 Antag pKi	1b H1 Antag Lum pKi	2a 5HT _{2A} Antag pKi	2b 5HT _{2A} Antag Lum pKi
1	3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid	****	***	**	***
2	Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1	**	**		*
3	Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2	***	**		*
4	3-[4-(2,3-Dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid	***	**		*
5	2,2-Dimethyl-3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid	***	**		**
6	3-[(2R,6S)-4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-2,6-dimethyl-1-piperazinyl]propanoic acid	****	****		***
7	2,2-Dimethyl-3-[4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl]propanoic acid		**		**
8	3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid		***	*	**
9	3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 1		****	*	*
10	3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 2		****	< 5.7	*
11	2-[[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl]-2-propenoic acid		****	*	**
12	3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid		***	***	***
13	3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid		***	9	***
14	3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid		***	****	***

Key to Table 1

	*	indicates a pKi of 6.0 to 6.4;
	**	indicates a pKi of 6.5 to 6.9;
	***	indicates a pKi of 7.0 to 7.4; and
5	****	indicates a pKi of 7.5 to 7.9.

CLAIMS

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



wherein

R^1 is carboxyC₃₋₆cycloalkyl, carboxyC₃₋₆cycloalkylmethyl, carboxymethylC₃₋₆cycloalkyl, $-(CR^{1a}R^{1b})_{2-6}CO_2H$ or $-(CR^{1a}R^{1b})_x(CR^{1c}R^{1d})(CR^{1a}R^{1b})_yCO_2H$; R^{1a} and R^{1b} which may be the same or different are H or C₁₋₄alkyl or R^{1a} and R^{1b} can together form methylene ($=CH_2$);

R^{1c} and R^{1d} together with the C atom to which they are attached form a ring independently selected from C₃₋₄cycloalkane, oxirane and oxetane;

R^2 and R^3 are each independently selected from H, C₁₋₃alkyl and C₁₋₃haloalkyl;

each R^4 is independently selected from halo, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃haloalkyl and C₁₋₃haloalkoxy, cyano;

R^5 and R^6 are each independently selected from H, F, Cl, C₁₋₃alkyl, C₁₋₃alkoxy, cyano, trifluoromethyl and trifluoromethoxy;

x is 0-6;

y is 0-6 provided that $x+y$ is 1-6; and

m is 0, 1 or 2.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is carboxyC₃₋₆cycloalkyl or $-(CR^{1a}R^{1b})_{2-6}CO_2H$.
3. The compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} which may be the same or different are H or methyl.
4. The compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are each independently selected from H and C₁₋₃alkyl.

5. The compound according to any preceding claim or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are each independently selected from H, Cl and F.
6. The compound according to claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1.
7. A compound according to claim 1 wherein, the compound of formula (I) is selected from the list consisting of:
 - 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
 - Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 1;
 - Lithium 4-[4-(5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclohexanecarboxylate isomer 2;
 - 3-[4-(2,3-Dimethyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
 - 2,2-Dimethyl-3-[4-(2-methyl-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid;
 - 3-[(2R,6S)-4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-2,6-dimethyl-1-piperazinyl]propanoic acid;
 - 2,2-Dimethyl-3-{4-[3-(methyloxy)-5H-imidazo[1,2-b][2]benzazepin-11-yl]-1-piperazinyl}propanoic acid;
 - 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]propanoic acid;
 - 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 1;
 - 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]cyclobutanecarboxylic acid isomer 2;
 - 2-{[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]methyl}-2-propenoic acid;
 - 3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
 - 3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid; and
 - 3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1, wherein the compound of formula (I) is selected from the list consisting of:
3-[4-(3-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
3-[4-(2-Chloro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid; and
3-[4-(2-Fluoro-5H-imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid;
or a pharmaceutically acceptable salt thereof.
9. 3-[4-(5H-Imidazo[1,2-b][2]benzazepin-11-yl)-1-piperazinyl]-2,2-dimethylpropanoic acid or a pharmaceutically acceptable salt thereof.
10. A compound according to any one of claims 1-9 or a pharmaceutically acceptable salt thereof, for use in therapy.
11. A compound according to any one of claims 1-9 or a pharmaceutically acceptable salt thereof, for use in the treatment of diseases or conditions mediated by antagonism of the H₁ receptor.
12. 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 compound or a pharmaceutically acceptable salt thereof, as claimed in claim 1.
13. Use of a compound according to any one of claims 1-8 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a disease or condition mediated by antagonism of the H₁ receptor.
14. The compound according to claim 11, the method as claimed in claim 12 or the use according to claim 13, wherein the disease or condition is a sleep disorder.
15. A pharmaceutical composition comprising a compound as defined in any one of claims 1-9 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

16. The pharmaceutical composition according to claim 15, further comprising an additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/057948

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/55 A61P25/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 357 043 A2 (HOFFMANN LA ROCHE [CH]) 7 March 1990 (1990-03-07) claims	1-16
A	HINO KATSUHIKO ET AL: "Agents acting on the central nervous system. Synthesis of 3-phenyl-2-piperazinyl-1-benzazocines, 3-substituted-2-piperazinyl-1- benzazepines and related compounds" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 36, 1 January 1988 (1988-01-01), pages 2386-2400, XP002217345 ISSN: 0009-2363 table 1	1-16

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

7 July 2010

Date of mailing of the international search report

19/07/2010

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/057948

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KHANNA J M ET AL: "Agents acting on the central nervous system. X. 1-Substituted 3-phenyl-2,3,4,5-tetrahydro-1H-1benzazepines" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US LNKD-DOI:10.1021/JM00317A043, vol. 395, no. 10, 1 January 1967 (1967-01-01), pages 944-945, XP002968897 ISSN: 0022-2623 the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/057948

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