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(54) 2-AZETIDINEMETHANEAMINES AND 2-PYRROLIDINEMETHANEAMINES AS TAAR-LIGANDS

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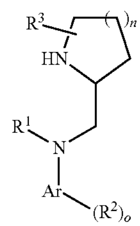
(57) **ABSTRACT**

The present invention relates to compounds of formula I



I

wherein

R^1, R^2, R^3, Ar, n and o are as defined herein and to their pharmaceutically acceptable active salts. Compounds of formula I have a good affinity to the trace amine associated receptors (TAARs), especially for TAAR1 and are useful for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

2-AZETIDINEMETHANEAMINES AND 2-PYRROLIDINEMETHANEAMINES AS TAAR-LIGANDS

PRIORITY TO RELATED APPLICATION(S)

[0001] This application is a divisional of U.S. application Ser. No. 12/176,456, filed on Jul. 21, 2008, now pending. This application claims the benefit of European Patent Application No. 07113329.2, filed Jul. 27, 2007, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The classical biogenic amines (serotonin, norepinephrine, epinephrine, dopamine, histamine) play important roles as neurotransmitters in the central and peripheral nervous system [1]. Their synthesis and storage, as well as their degradation and reuptake after release are tightly regulated. An imbalance in the levels of biogenic amines is known to be responsible for the altered brain function under many pathological conditions [2-5]. A second class of endogenous amine compounds, the so-called trace amines (TAs) significantly overlap with the classical biogenic amines regarding structure, metabolism and subcellular localization. The TAs include p-tyramine, β-phenylethylamine, tryptamine and octopamine, and they are present in the mammalian nervous system at generally lower levels than classical biogenic amines [6].

[0003] Their dysregulation has been linked to various psychiatric diseases like schizophrenia and depression [7] and for other conditions like attention deficit hyperactivity disorder, migraine headache, Parkinson's disease, substance abuse and eating disorders [8,9].

[0004] For a long time, TA-specific receptors had only been hypothesized based on anatomically discrete high-affinity TA binding sites in the CNS of humans and other mammals [10,11]. Accordingly, the pharmacological effects of TAs were believed to be mediated through the well known machinery of classical biogenic amines, by either triggering their release, inhibiting their reuptake or by "crossreacting" with their receptor systems [9,12,13]. This view changed significantly with the recent identification of several members of a novel family of GPCRs, the trace amine associated receptors (TAARs) [7,14]. There are 9 TAAR genes in human (including 3 pseudogenes) and 16 genes in mouse (including 1 pseudogene). The TAAR genes do not contain introns (with one exception, TAAR2 contains 1 intron) and are located next to each other on the same chromosomal segment. The phylogenetic relationship of the receptor genes, in agreement with an in-depth GPCR pharmacophore similarity comparison and pharmacological data suggest that these receptors form three distinct subfamilies [7,14]. TAAR1 is in the first subclass of four genes (TAAR1-4) highly conserved between human and rodents. TAs activate TAAR1 via Gαs. Dysregulation of TAs was shown to contribute to the aetiology of various diseases like depression, psychosis, attention deficit hyperactivity disorder, substance abuse, Parkinson's disease, migraine headache, eating disorders, metabolic disorders and therefore TAAR1 ligands have a high potential for the treatment of these diseases.

[0005] Therefore, there is a broad interest to increase the knowledge about trace amine associated receptors.

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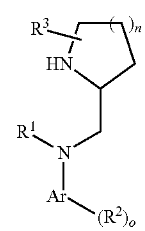
SUMMARY OF THE INVENTION

[0020] The present invention provides compounds of formula I

I



wherein

[0021] R^1 is hydrogen, lower alkyl or benzyl which is optionally substituted by halogen or lower alkoxy;

[0022] R^2 is hydrogen, halogen or OR, wherein R is lower alkyl, aryl or lower alkyl substituted by halogen;

[0023] R^3 is hydrogen or fluorine;

[0024] Ar is phenyl;

[0025] n is 0 or 1; and

[0026] o is 0, 1 or 2;

and to their pharmaceutically active salts.

[0027] The invention includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers.

[0028] The invention also provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier. The invention further provides methods for the manufacture of the compounds and compositions of the invention.

[0029] Compounds of formula I have a good affinity to the trace amine associated receptors (TAARs), especially for TAAR1.

[0030] The compounds are useful for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

[0031] The preferred indications using the compounds of the present invention are depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).

DETAILED DESCRIPTION OF THE INVENTION

[0032] The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0033] As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain hydrocarbon group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1-4 carbon atoms.

[0034] As used herein, the term "lower alkoxy" denotes the group OR where R is lower alkyl as defined above.

[0035] As used herein, the term "lower alkyl substituted by halogen" denotes a lower alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example CF_3, CHF_2, CH_2F, CH_2CF_3, $CH_2CH_2CF_3$, $CH_2CF_2CF_3$ and the like.

[0036] As used herein, the term "aryl" denotes an aromatic group, selected from phenyl or naphthalen-1-yl.

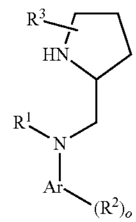
[0037] The term "halogen" denotes chlorine, iodine, fluorine and bromine.

[0038] "Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

[0039] The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

[0040] "Therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

[0041] Preferred compounds of formula I are those, wherein n is 1 (pyrrolidine):



IA

wherein

[0042] R^1 is hydrogen, lower alkyl or benzyl which is optionally substituted by halogen or lower alkoxy;

[0043] R^2 is hydrogen, halogen or OR, wherein R is lower alkyl, aryl or lower alkyl substituted by halogen;

[0044] R^3 is hydrogen or fluorine;

[0045] Ar is phenyl; and

[0046] o is 0, 1 or 2;

and their pharmaceutically active salts.

[0047] Examples of compounds of formula IA are

[0048] ethyl-(3-phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine,

[0049] ethyl-(3-phenoxy-phenyl)-(S)-1-pyrrolidin-2-ylmethyl-amine,

[0050] (3,4-dichloro-phenyl)-ethyl-(S)-1-pyrrolidin-2-ylmethyl-amine,

[0051] (4-chloro-3-methoxy-phenyl)-methyl-(S)-1-pyrrolidin-2-ylmethyl-amine,

[0052] (4-chloro-3-methoxy-phenyl)-ethyl-(S)-1-pyrrolidin-2-ylmethyl-amine,

[0053] (4-chloro-phenyl)-ethyl-(S)-1-pyrrolidin-2-ylmethyl-amine,

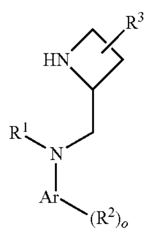
[0054] (4-chloro-3-methoxy-phenyl)-isopropyl-(S)-1-pyrrolidin-2-ylmethyl-amine,

[0055] (3,4-dichloro-phenyl)-isopropyl-(S)-1-pyrrolidin-2-ylmethyl-amine, and

[0056] (4-chloro-phenyl)-ethyl-(R)-1-pyrrolidin-2-ylmethyl-amine.

[0057] Preferred compounds are further those, wherein n is 0 (azetidine):

IB



wherein

[0058] R^1 is hydrogen, lower alkyl or benzyl which is optionally substituted by halogen or lower alkoxy;

[0059] R^2 is hydrogen, halogen or OR, wherein R is lower alkyl, aryl or lower alkyl substituted by halogen;

[0060] R^3 is hydrogen or fluorine;

[0061] Ar is phenyl; and

[0062] o is 0, 1 or 2;

and their pharmaceutically active salts.

[0063] Examples of compounds of formula IB are

[0064] (S)-1-azetidin-2-ylmethyl-(4-chloro-phenyl)-ethyl-amine,

[0065] (S)-1-azetidin-2-ylmethyl-ethyl-phenyl-amine,

[0066] (S)-1-azetidin-2-ylmethyl-ethyl-(3-methoxy-phenyl)-amine,

[0067] (S)-1-azetidin-2-ylmethyl-(3-bromo-phenyl)-ethyl-amine,

[0068] (S)-1-azetidin-2-ylmethyl-(4-chloro-phenyl)-methyl-amine,

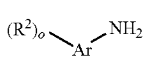
[0069] (S)-1-azetidin-2-ylmethyl-(4-chloro-phenyl)-iso-propyl-amine,

[0070] (S)-1-azetidin-2-ylmethyl-benzyl-(4-chloro-phenyl)-amine.

[0071] The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below,

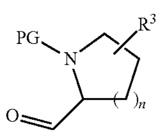
[0072] a) reacting a compound of formula

II



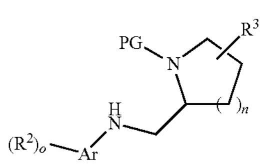
with a compound of formula

III



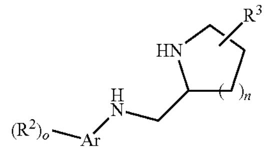
to give a compound of formula

IV



and deprotecting a compound of formula IV to give a compound of formula

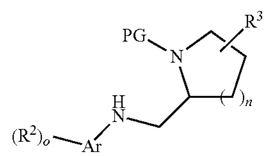
I-1



wherein the substituents are as defined above, or

[0073] b) reacting a compound of formula

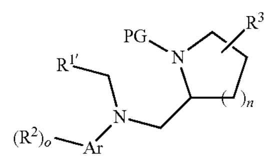
IV



with an aldehyde of formula $R^{1'}$—CHO

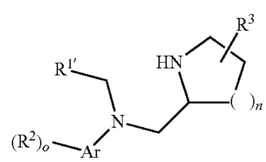
to give a compound of formula

IV-1



and deprotecting a compound of formula IV-1 to a compound of formula

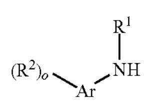
I-2



wherein $R^{1'}$ is lower alkyl or hydrogen and the other definitions are as described above, or

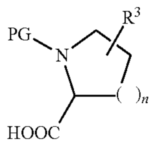
[0074] c) reacting a compound of formula

II-1



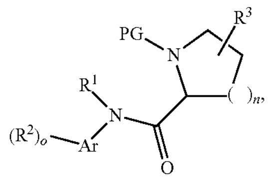
with a compound of formula

VIII



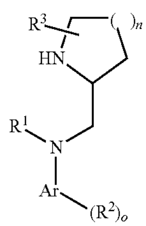
to give a compound of formula

IX



reducing the compound of formula IX and deprotecting to a compound of formula

I



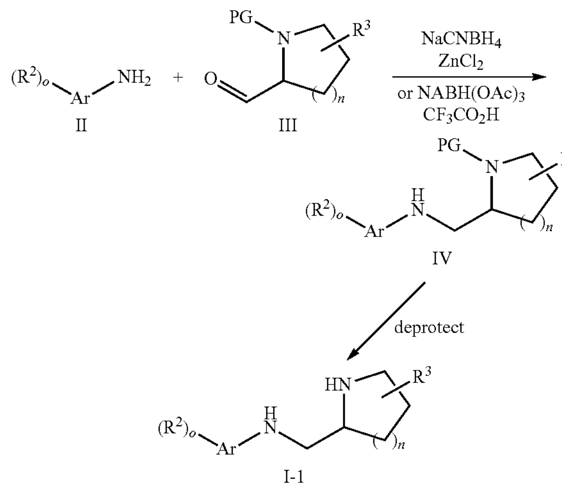
wherein the substituents are as defined above,
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

[0075] The compounds of formula I can be prepared in accordance with the process variants as described above and with the following schemes 1-3. The starting materials are either commercially available, are otherwise known in the chemical literature, or can be prepared in accordance with methods well known in the art.

Method 1

[0076]

Scheme 1

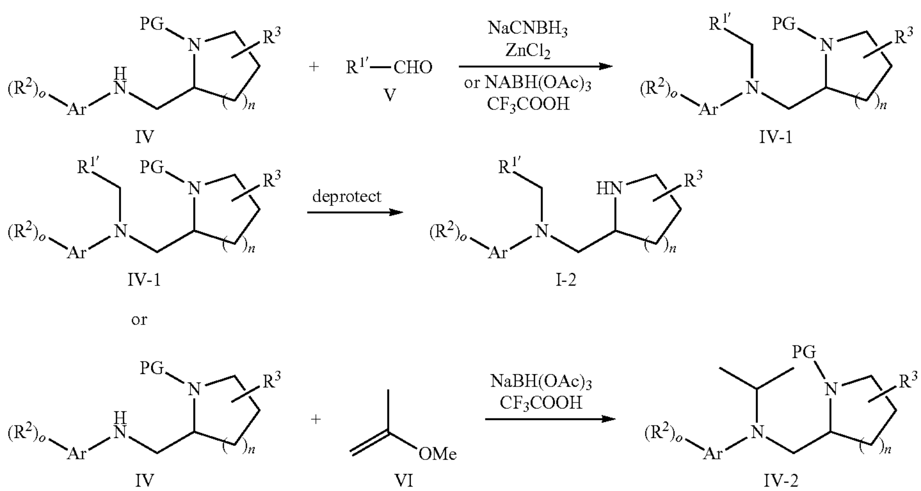


[0077] Compounds of formula I-1 can be prepared by reductive amination using an aniline of formula II and an N-protected pyrrolidine-2-carbaldehyde of formula III (n=1) or an N-protected 2-formylazetidine of formula III (n=0) in the presence of an reducing agent such as $NaCNBH_3$ or $NaBH(OAc)_3$ followed by a deprotection step on the intermediate IV in the usual matter.

Method 2

[0078]

Scheme 2



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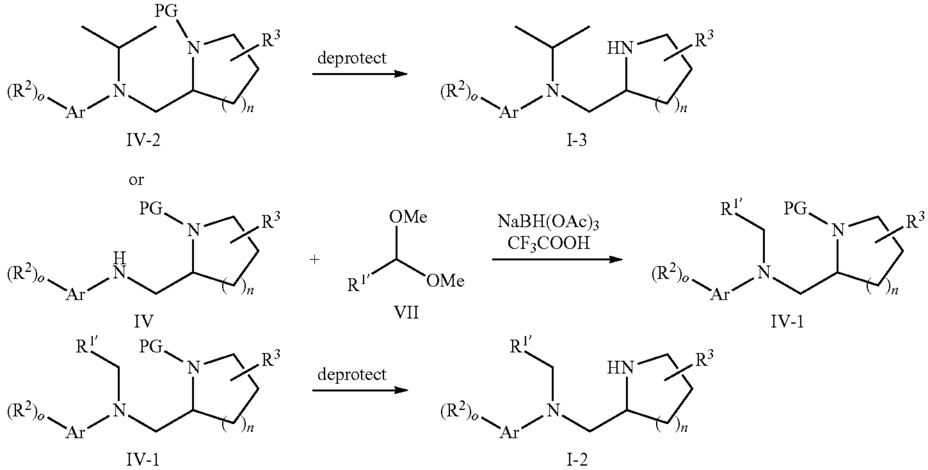
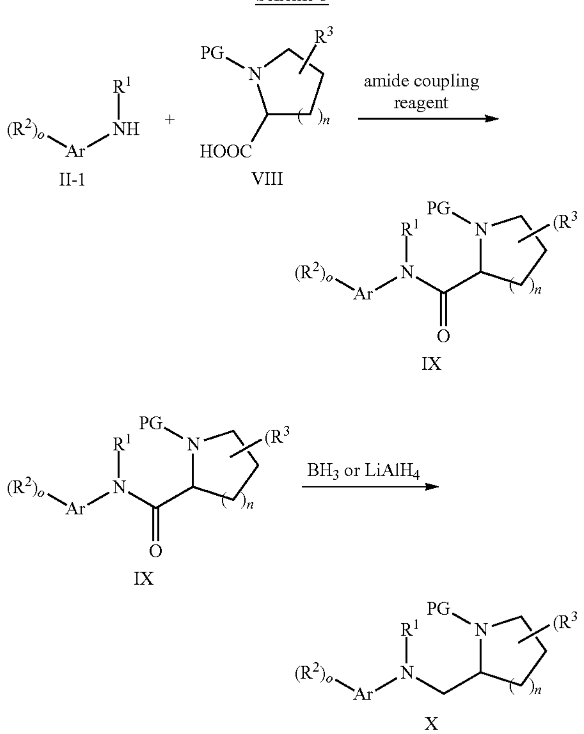


[0079] Compounds of formula I-2 and I-3 can be prepared by a second reductive amination step starting from intermediate IV using for instance reagents such as an aldehyde V, an enolether VI or an aldehyde acetal VII in presence of an reducing agent such as $NaCNBH_3$ or $NaBH(OAc)_3$ followed by N-deprotection of the pyrrolidine or azetidine in the usual matter.

Method 3

[0080]

Scheme 3



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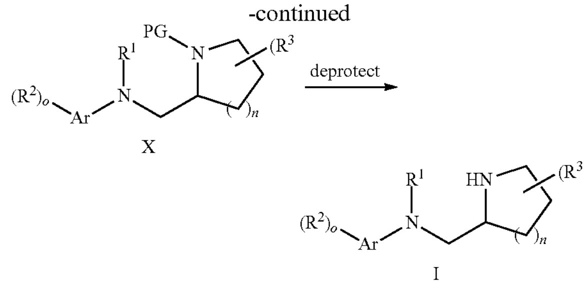


[0081] Scheme 3 describes the preparation of a compound of formula I by formation of an amide IX followed by reduction of the amide bond by a reducing agent such as borane or lithium aluminumhydride and protecting group removal in the usual matter.

Isolation and Purification of the Compounds

[0082] Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

Salts of Compounds of Formula I

[0083] The compounds of formula I are basic and can be converted to a corresponding acid addition salt. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0° C. and 50° C. The resulting salt precipitates spontaneously or can be brought out of solution with a less polar solvent.

[0084] The acid addition salts of the basic compounds of formula I can be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

[0085] The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention have a good affinity to the trace amine associated receptors (TAARs), especially TAAR1.

[0086] The compounds were investigated in accordance with the test given hereinafter.

Materials and Methods

Construction of TAAR Expression Plasmids and Stably Transfected Cell Lines

[0087] For the construction of expression plasmids the coding sequences of human, rat and mouse TAAR 1 were amplified from genomic DNA essentially as described by Lindemann et al. [14]. The Expand High Fidelity PCR System (Roche Diagnostics) was used with 1.5 mM Mg^{2+} and purified PCR products were cloned into pCR2.1-TOPO cloning vector (Invitrogen) following the instructions of the manufacturer. PCR products were subcloned into the pIRESneo2 vector (BD Clontech, Palo Alto, Calif.), and expression vectors were sequence verified before introduction in cell lines.

[0088] HEK293 cells (ATCC #CRL-1573) were cultured essentially as described Lindemann et al. (2005). For the generation of stably transfected cell lines HEK293 cells were transfected with the pIRESneo2 expression plasmids containing the TAAR coding sequences (described above) with Lipofectamine 2000 (Invitrogen) according to the instructions of the manufacturer, and 24 hrs post transfection the culture medium was supplemented with 1 mg/ml G418 (Sigma, Buchs, Switzerland). After a culture period of about 10 d clones were isolated, expanded and tested for responsiveness to trace amines (all compounds purchased from Sigma) with the cAMP Biotrak Enzyme immunoassay (EIA) System (Amersham) following the non-acetylation EIA procedure provided by the manufacturer. Monoclonal cell lines which displayed a stable EC_{50} for a culture period of 15 passages were used for all subsequent studies.

Membrane Preparation and Radioligand Binding

[0089] Cells at confluence were rinsed with ice-cold phosphate buffered saline without Ca^{2+} and Mg^{2+} containing 10 mM EDTA and pelleted by centrifugation at 1000 rpm for 5 min at 4° C. The pellet was then washed twice with ice-cold phosphate buffered saline and cell pellet was frozen immediately by immersion in liquid nitrogen and stored until use at −80° C. Cell pellet was then suspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing 10 mM EDTA, and homogenized with a Polytron (PT 3000, Kinematica) at 10,000 rpm for 10 s. The homogenate was centrifuged at 48,000×g for 30 min at 4° C. and the pellet resuspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing 0.1 mM EDTA (buffer A), and homogenized with a Polytron at 10,000 rpm for 10 s. The homogenate was then centrifuged at 48,000×g for 30 min at 4° C. and the pellet resuspended in 20 ml buffer A, and homogenized with a Polytron at 10,000 rpm for 10 s. Protein concentration was determined by the method of Pierce (Rockford, Ill.). The homogenate was then centrifuged at 48,000×g for 10 min at 4° C., resuspended in HEPES-NaOH (20 mM), pH 7.0 including $MgCl_2$ (10 mM) and $CaCl_2$ g protein per ml and (2 mM) (buffer B) at 200 homogenized with a Polytron at 10,000 rpm for 10 s.

[0090] Binding assay was performed at 4° C. in a final volume of 1 ml, and with an incubation time of 30 min. The radioligand [^{3}H]-rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline was used at a concentration equal to the calculated K_d value of 60 nM to give a bound at around 0.1% of the total added radioligand concentration, and a specific binding which represented approximately 70-80% of the total binding. Non-specific binding was defined as the amount of [^{3}H]-rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline bound in the presence of the appropriate unlabelled ligand (10 μM). Competing ligands were tested in a wide range of concentrations (10 pM-30 μM). The final dimethylsulphoxide concentration in the assay was 2%, and it did not affect radioligand binding. Each experiment was performed in duplicate. All incubations were terminated by rapid filtration through Uni-Filter-96 plates (Packard Instrument Company) and glass filter GF/C, pre-soaked for at least 2 h in polyethylenimine 0.3%, and using a Filtermate 96 Cell Harvester (Packard Instrument Company). The tubes and filters were then washed 3 times with 1 ml aliquots of cold buffer B. Filters were not dried and soaked in Ultima gold (45 μl/well, Packard Instrument Company) and bound radioactivity was counted by a TopCount Microplate Scintillation Counter (Packard Instrument Company).

[0091] The preferred compounds show a Ki value (μM) in mouse on TAAR1 in the range of <0.1 μM. Representative compounds are shown in the table below.

Example	Ki (μM) mouse	Example	Ki (μM) mouse	Example	Ki
3	0.0044	12	0.0213	19	0.0137
4	0.0172	13	0.005	20	0.0047
6	0.0028	16	0.0056	21	0.021
8	0.0859	17	00024	22	0.041
9	0.0092	18	0.0092	23	0.0107
11	0.0131				

[0092] The present invention also provides pharmaceutical compositions containing compounds of the invention, for example compounds of formula I and their pharmaceutically suitable acid addition salts, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. The pharmaceutical compositions also can be in the form of suppositories or injectable solutions.

[0093] The pharmaceutical compounds of the invention, in addition to one or more compounds of the invention, contain a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include pharmaceutically inert, inorganic and organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatin capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

[0094] The pharmaceutical compositions can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

[0095] The invention also provides a method for preparing compositions of the invention which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

[0096] The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of schizophrenia, depression, cognitive impairment and Alzheimer's disease.

[0097] The dosage at which compounds of the invention can be administered can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage can be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation

Wet Granulation

[0098]

		mg/tablet			
Item	Ingredients	5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

[0099] 1. Mix items 1, 2, 3 and 4 and granulate with purified water.

2. Dry the granules at 50° C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

[0100]

		mg/capsule			
Item	Ingredients	5 mg	25 mg	100 mg	500mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	—
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

[0101] 1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

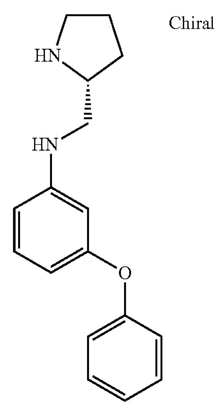
EXPERIMENTAL

[0102] The following examples illustrate the invention but are not intended to limit its scope.

Example 1

(3-Phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine

[0103]

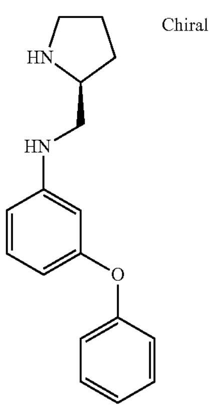


[0104] To a solution of 3-phenoxyaniline (0.3 g, 1.62 mmol) in 1,2-dichloroethane (4 ml) were added N-(tert-butoxycarbonyl)-D-prolinal (0.322 g, 1.62 mmol) and sodium triacetoxyborohydride (0.480 g, 2.26 mmol). The resulting suspension was stirred overnight at 50° C. The mixture was then cooled to room temperature, water (8 ml) was added and extracted with ethyl acetate (3×20 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2: heptane/ethyl acetate=70:30) to yield a light yellow oil that was dissolved in dichloromethane (4 ml). Trifluoroacetic acid (1 ml) was added and the mixture was stirred for 3 h at room temperature. Aqueous sodium hydroxide solution (4N) was added until basic pH and the mixture was extracted with ethyl acetate (2 times 30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate) to yield a colourless oil, (0.256 g, 59%); MS (ISP): 269.1 ((M+H)$^+$.).

Example 2

(3-Phenoxy-phenyl)-(8)-1-pyrrolidin-2-ylmethyl-amine

[0105]

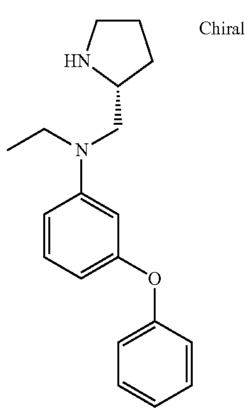


[0106] The title compound, MS (ISP): 269.1 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 1 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal.

Example 3

Ethyl-(3-phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine

[0107]



a) (R)-2-{[Ethyl-(3-phenoxy-phenyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

[0108] To a solution of 3-phenoxyaniline (0.3 g, 1.62 mmol) in 1,2-dichloroethane (4 ml) were added N-(tert-butoxycarbonyl)-D-prolinal (0.322 g, 1.62 mmol) and sodium triacetoxyborohydride (0.480 g, 2.26 mmol). The resulting suspension was stirred overnight at 50° C. The mixture was then cooled to room temperature, water (8 ml) was added and extracted with ethyl acetate (3×20 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2: heptane/ethyl acetate=70:30) to yield a light yellow oil that was dissolved in methanol (8 ml). Acetaldehyde (0.134 g, 3.05 mmol), zinc chloride (0.333 g, 2.44 mmol) and sodium cyanoborohydride (0.115 g, 1.83 mmol) were added and the mixture was stirred overnight at 40° C. Saturated ammonium acetate solution (10 ml) was added and extracted with ethyl acetate (3×30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2: heptane/ethyl acetate=70:30) to yield 0.43 g (67%) of a colourless oil; MS (ISP): 397.0 ((M+H)$^+$.).

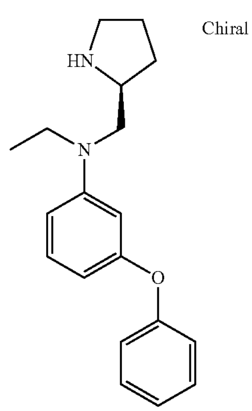
b) Ethyl-(3-phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine

[0109] To a solution of (R)-2-{[ethyl-(3-phenoxy-phenyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (0.162 g, 0.41 mmol) in dichloromethane (3 ml) was added trifluoroacetic acid (1 ml) and the mixture was stirred for 3 h at room temperature. Aqueous sodium hydroxide solution (4N) was added until basic pH and the mixture was extracted with ethyl acetate (2 times 30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate) to yield a colourless oil, (0.043 g, 36%); MS (ISP): 297.5 ((M+H)$^+$.).

Example 4

Ethyl-(3-phenoxy-phenyl)-(S)-1-pyrrolidin-2-ylmethyl-amine

[0110]

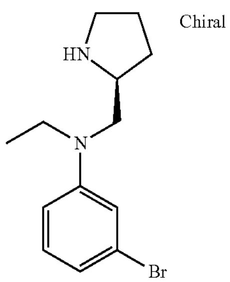


[0111] The title compound, MS (ISP): 297.5 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal in step a).

Example 5

(3-Bromo-phenyl)-ethyl-(S)-1-pyrrolidin-2-ylmethyl-amine

[0112]

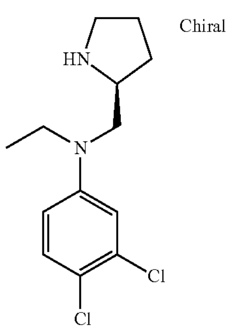


[0113] The title compound, MS (ISP): 283.1; 285.1 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal and 3-bromoaniline instead of 3-phenoxyaniline in step a).

Example 6

(3,4-Dichloro-phenyl)-ethyl-(S)-1-pyrrolidin-2-ylmethyl-amine

[0114]

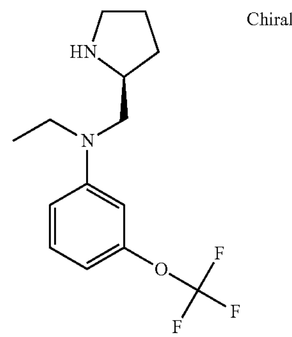


[0115] The title compound, MS (ISP): 273.2; 275.1 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal and 3,4-dichloroaniline instead of 3-phenoxyaniline in step a).

Example 7

Ethyl-(S)-1-pyrrolidin-2-ylmethyl-(3-trifluoromethoxy-phenyl)-amine

[0116]

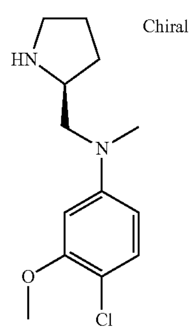


[0117] The title compound, MS (ISP): 289.0 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal and 3-trifluoromethoxy-aniline instead of 3-phenoxyaniline in step a).

Example 8

(4-Chloro-3-methoxy-phenyl)-methyl-(8)-1-pyrrolidin-2-ylmethyl-amine

[0118]

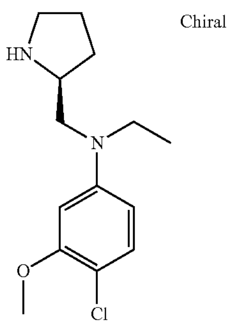


[0119] The title compound, MS (ISP): 255.3 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal, 4-chloro-3-methoxy-aniline instead of 3-phenoxyaniline and paraformaldehyde instead of acetaldehyde in step a).

Example 9

(4-Chloro-3-methoxy-phenyl)-ethyl-(8)-1-pyrrolidin-2-ylmethyl-amine

[0120]

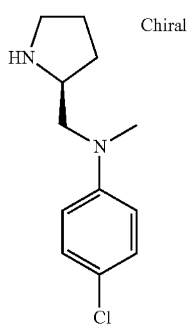


[0121] The title compound, MS (ISP): 269.4 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal and 4-chloro-3-methoxy-aniline instead of 3-phenoxyaniline in step a).

Example 10

(4-Chloro-phenyl)-methyl-(8)-1-pyrrolidin-2-ylmethyl-amine

[0122]

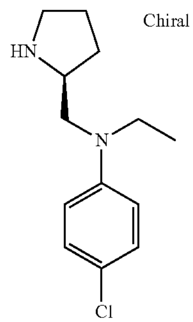


[0123] The title compound, MS (ISP): 225.3 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal, 4-chloroaniline instead of 3-phenoxyaniline and paraformaldehyde instead of acetaldehyde in step a).

Example 11

(4-Chloro-phenyl)-ethyl-(8)-1-pyrrolidin-2-ylmethyl-amine

[0124]

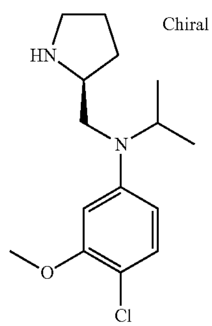


[0125] The title compound, MS (ISP): 239.3 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 3 using N-(tert-butoxycarbonyl)-L-prolinal instead of N-(tert-butoxycarbonyl)-D-prolinal and 4-chloroaniline instead of 3-phenoxyaniline in step a).

Example 12

(4-Chloro-3-methoxy-phenyl)-isopropyl-(S)-1-pyrrolidin-2-ylmethyl-amine

[0126]



a) (S)-2-[(4-Chloro-3-methoxy-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

[0127] To a solution of 4-chloro-3-methoxyaniline (1.57 g, 10.0 mmol) in methanol (27 ml) were added acetic acid (3 ml), N-(tert-butoxycarbonyl)-L-prolinal (2.40 g, 12.05 mmol) and sodium cyanoborohydride (1.56 g, 24.1 mmol). The resulting suspension was stirred for 2 hours at room temperature. Aqueous sodium bicarbonate solution (30 ml) was added and the mixture was extracted with ethyl acetate (3×20 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2: heptane/ethyl acetate=70:30) to yield a light yellow oil (2.31 g, 68%); MS (ISP): 341.0, 342.9 ((M+H)$^+$.).

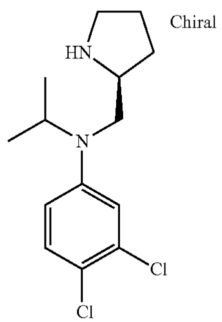
b) (4-Chloro-3-methoxy-phenyl)-isopropyl-(S)-1-pyrrolidin-2-ylmethyl-amine

[0128] To a solution of (S)-2-[(4-chloro-3-methoxy-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.68 g, 2.0 mmol) were added 2-methoxypropene (0.216 g, 3.0 mmol), trifluoracetic acid (0.228 g, 2.0 mmol) and sodium triacetoxyborohydride (0.64 g, 3.0 mmol). The mixture was stirred overnight at 60° C. Saturated sodium bicarbonate solution (10 ml) was added and the mixture was extracted with ethyl acetate (3×30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (3 ml) and trifluoroacetic acid (3 ml) was added. Solvent and access trifluoroacetic acid was evaporated, diisopropylethylamine (1 ml) was added to liberate the free base and the mixture was purified by flash chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate/heptane 1:1) to yield a light yellow oil, (0.185 g, 33%); MS (ISP): 283.5, 285.2 ($(M+H)^+$.).

Example 13

(3,4-Dichloro-phenyl)-isopropyl-(S)-1-pyrrolidin-2-ylmethyl-amine

[0129]

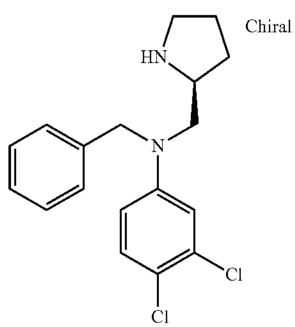


[0130] The title compound, MS (ISP): 287.1, 289.1 ($[M+H]^+$.) was obtained in comparable yield analogous to the procedure described for Example 12 using 3,4-dichloroaniline instead of 4-chloro-3-methoxyaniline in step a).

Example 14

Benzyl-(3,4-dichloro-phenyl)-(S)-1-pyrrolidin-2-ylmethyl-amine

[0131]

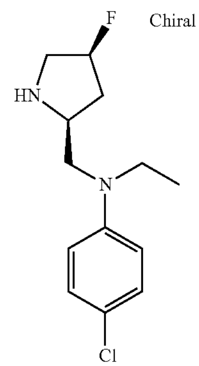


[0132] The title compound, MS (ISP): 335.3, 337.2 ($[M+H]^+$.) was obtained in comparable yield analogous to the procedure described for Example 12 using 3,4-dichloroaniline instead of 4-chloro-3-methoxyaniline in step a) and benzaldehyde dimethylacetal instead of 2-methoxypropene in step b).

Example 15

(4-Chloro-phenyl)-ethyl-((2S,4S)-4-fluoro-pyrrolidin-2-ylmethyl)-amine

[0133]

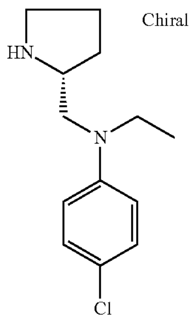


[0134] To a solution of N-ethyl-4-chloro-aniline (0.31 g, 2.0 mmol) in dichloromethane (8 ml) were added (2S,4S)-tert-butyloxycarbonyl-4-fluoro-pyrrolidine-2-carboxylic acid (0.47 g, 2.0 mmol), bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.76 g, 3.0 mmol) and diisopropylethylamine (0.39 g, 3.0 mmol). The mixture was stirred for 3 days at room temperature. Aqueous sodium bicarbonate solution (20 ml) was added and the mixture was extracted with dichloromethane (3×20 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO2: heptane/ethyl acetate=2:1) to yield a light yellow oil (0.55 g), that was dissolved in tetrahydrofurane (15 ml). Borane-tetrahydrofurane-complex (7.4 ml, 1M, 7.4 mmol) was added and the mixture was heated at 60° C. overnight. After cooling 5 drops of aqueous hydrochloric acid (4N) were added and the solvent was evaporated. The white residue was dissolved in aqueous hydrochloric acid (4N, 10 ml) and heated at 60° C. for 1 hour. After cooling aqueous sodium hydroxide solution was added until basic pH and the mixture was extracted with dichloromethane (2×30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate/heptane 1:1) to yield a light yellow oil, (0.137 g, 27%); MS (ISP): 257.1 ($(M+H)^+$.).

Example 16

(4-Chloro-phenyl)-ethyl-(R)-1-pyrrolidin-2-ylm-ethyl-amine

[0135]

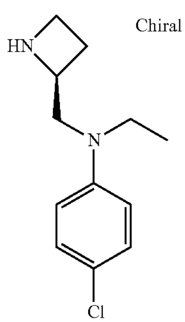


[0136] The title compound, MS (ISP): 239.0, 241.1 ([M+H]$^{+}$.) was obtained in comparable yield analogous to the procedure described for Example 3 using 4-chloroaniline instead of 3-phenoxyaniline in step a).

Example 17

(S)-1-Azetidin-2-ylmethyl-(4-chloro-phenyl)-ethyl-amine

[0137]



a) (S)-2-[(4-Chloro-phenylamino)-methyl]-azetidine-1-carboxylic acid tert-butyl ester

[0138] To a solution of 4-chloro-aniline (0.57 g, 4.5 mmol) in methanol (18 ml) were added acetic acid (2 ml), (S)-2-formyl-azetidine-1-carboxylic acid tert.butyl ester (1.74 g, 9.4 mmol) and after 15 min stirring sodium cyanoborohydride (0.57 g, 9.0 mmol). The resulting suspension was stirred for 2 hours at room temperature. Aqueous sodium bicarbonate solution (20 ml) was added and the mixture was extracted with ethyl acetate (3×20 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO2: heptane/ethyl acetate=9:1) to yield a colourless oil (0.99 g, 74%); MS (ISP): 297.1 ((M+H)$^{+}$.); 241.3 ((M−C(CH$_{3}$)$_{3}$+H)$^{+}$.).

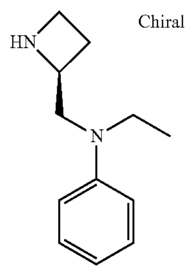
b) (S)-1-Azetidin-2-ylmethyl-(4-chloro-phenyl)-ethyl-amine

[0139] (S)-2-[(4-Chloro-phenylamino)-methyl]-azetidine-1-carboxylic acid tert-butyl ester (0.08 g, 0.27 mmol) was dissolved in methanol (3 ml), then acetaldehyde (0.059 g, 1.35 mmol), zinc chloride (0.147 g, 1.1 mmol) and sodium cyanoborohydride (0.51 g, 0.81 mmol) were added and the mixture was stirred overnight at 40° C. Saturated ammonium acetate solution (10 ml) was added and extracted with ethyl acetate (3×30 ml). The combined organic layers were dried with magnesium sulphate, filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (3 ml) and trifluoroacetic acid (3 ml) was added. Solvent and access trifluoroacetic acid was evaporated, diisopropylethylamine (0.3 ml) was added to liberate the free base and the mixture was purified by flash chromatography (column: Isolute® Flash-NH$_{2}$ from Separtis; eluent: ethyl acetate/heptane 1:1) to yield a light yellow gum, (0.022 g, 38%); MS (ISP): 225.1 ((M+H)$^{+}$.).

Example 18

(S)-1-Azetidin-2-ylmethyl-ethyl-phenyl-amine

[0140]

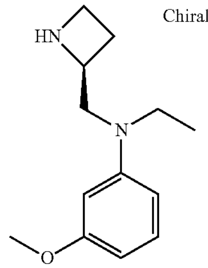


[0141] The title compound, MS (ISP): 191.4 ([M+H]$^{+}$.) was obtained in comparable yield analogous to the procedure described for Example 17 using aniline instead of 4-chloroaniline in step a).

Example 19

(S)-1-Azetidin-2-ylmethyl-ethyl-(3-methoxy-phenyl)-amine

[0142]

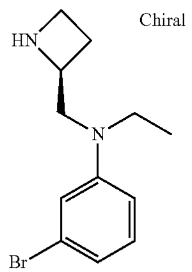


[0143] The title compound, MS (ISP): 221.4 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 17 using 3-methoxyaniline instead of 4-chloroaniline in step a).

Example 20

(S)-1-Azetidin-2-ylmethyl-(3-bromo-phenyl)-ethyl-amine

[0144]

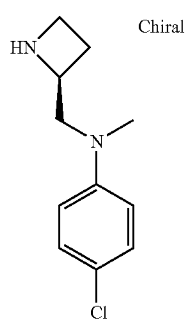


[0145] The title compound, MS (ISP): 269.4; 271.4 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 17 using 3-bromoaniline instead of 4-chloroaniline in step a).

Example 21

(S)-1-Azetidin-2-ylmethyl-(4-chloro-phenyl)-methyl-amine

[0146]

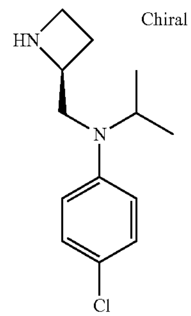


[0147] The title compound, MS (ISP): 211.1 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 17 using paraformaldehyde instead of acetaldehyde in step b).

Example 22

(S)-1-Azetidin-2-ylmethyl-(4-chloro-phenyl)-isopropyl-amine

[0148]

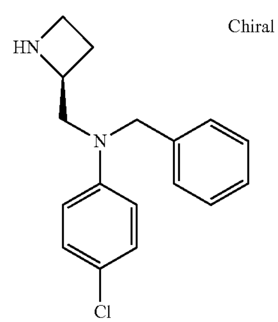


[0149] The title compound, MS (ISP): 239.3 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 12 using 4-chloroaniline instead of 4-chloro-3-methoxyaniline and (S)-2-formyl-azetidine-1-carboxylic acid tert.butyl ester instead of N-(tert-butoxycarbonyl)-L-prolinal in step a).

Example 23

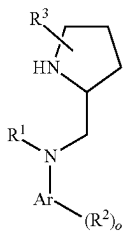
(S)-1-Azetidin-2-ylmethyl-benzyl-(4-chloro-phenyl)-amine

[0150]



[0151] The title compound, MS (ISP): 287.3 ([M+H]$^+$.) was obtained in comparable yield analogous to the procedure described for Example 12 using 4-dichloroaniline instead of 4-chloro-3-methoxyaniline and (S)-2-formyl-azetidine-1-carboxylic acid tert.butyl ester instead of N-(tert-butoxycarbonyl)-L-prolinal in step a) and benzaldehyd dimethylacetal instead of 2-methoxypropene in step b).

1. A compound of formula IA



IA

wherein

R^1 is hydrogen, lower alkyl or benzyl which is optionally substituted by halogen or lower alkoxy;

R^2 is OR, wherein R is aryl or lower alkyl substituted by halogen;

R^3 is hydrogen or fluorine;

Ar is phenyl; and

o is 1 or 2;

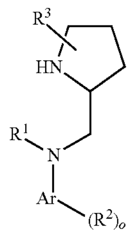
or a pharmaceutically acceptable salt thereof.

2. The compound of claim **1**, selected from the group consisting of

ethyl-(3-phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine, and

ethyl-(3-phenoxy-phenyl)-(S)-1-pyrrolidin-2-ylmethyl-amine.

3. A pharmaceutical composition comprising a compound of formula IA



IA

wherein

R^1 is hydrogen, lower alkyl or benzyl which is optionally substituted by halogen or lower alkoxy;

R^2 is OR, wherein R is aryl or lower alkyl substituted by halogen;

R^3 is hydrogen or fluorine;

Ar is phenyl; and

o is 1 or 2.

4. The composition of claim **3**, wherein the compound of formula IA is selected from the group consisting of

ethyl-(3-phenoxy-phenyl)-(R)-1-pyrrolidin-2-ylmethyl-amine, and

ethyl-(3-phenoxy-phenyl)-(S)-1-pyrrolidin-2-ylmethyl-amine.

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