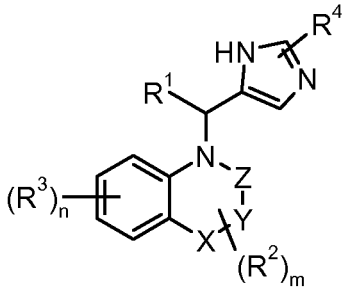
SUBSTITUTED 4-IMIDAZOLES

The present invention relates to compounds of formula I



I

wherein

R^1 is hydrogen or lower alkyl;

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen, lower alkyl, lower alkoxy, phenyloxy, benzyloxy, halogen or lower alkyl substituted by halogen;

R^4 is hydrogen or lower alkyl;

X is $-CH_2-$, -CH- or –O-;

Y is $-CH_2-$, $-CH_2CH_2-$, -CH- or a bond; when X is –O-, then Y is $-CH_2-$;

Z is $-CH_2-$ or -CH-;

m is 1 or 2; when m is 2, R^2 may be the same or not;

n is 1 or 2; when n is 2, R^3 may be the same or not;

and to pharmaceutically acceptable acid addition salts.

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

In addition, all tautomeric forms of compounds of formula I are also encompassed by the present invention.

It has been found that the compounds of formula I have a good affinity to the trace amine associated receptors (TAARs), especially for TAAR1.
The compounds may be used 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.

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].

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].

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.

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

References used:

1 Deutch, A.Y. and Roth, R.H. (1999) Neurotransmitters. In *Fundamental Neuroscience* (2nd edn) (Zigmond, M.J., Bloom, F.E., Landis, S.C., Roberts, J.L, and Squire, L.R., eds.), pp. 193-234, Academic Press;

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Objects of the present invention are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, 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.

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

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain 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.

As used herein, the term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above and which is attached via an oxygen atom.

As used herein, the term "lower alkyl substituted by halogen" denotes an 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.

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

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.

Preferred compounds of formula I are those, wherein X is CH_2 and Y is a bond. Such compounds are

(*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole
1-(3H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
5-bromo-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
5-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
(*RS*)-5-chloro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole
7-ethyl-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
4-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-5-methoxy-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-6-methoxy-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-7-methoxy-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-5-methyl-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-4-methoxy-2,3-dihydro-1H-indole
7-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-6-methyl-2,3-dihydro-1H-indole
(*RS*)-1-(1H-imidazol-4-ylmethyl)-3-methyl-2,3-dihydro-1H-indole
5-fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
6-fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
5,6-difluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
(*RS*)-5-fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-7-methyl-2,3-dihydro-1H-indole or
1-(1H-imidazol-4-ylmethyl)-4-methyl-2,3-dihydro-1H-indole.

Preferred compounds of formula I are those, wherein X is CH_2 and Y is CH_2. Such compounds are

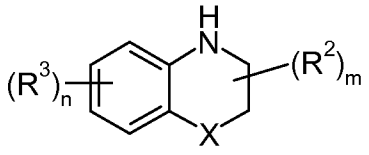
(*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
(*RS*)-6-fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
1-(3H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
6-bromo-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
(-)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
5-benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
7-benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline or
1-(1H-imidazol-4-ylmethyl)-5-phenoxy-1,2,3,4-tetrahydro-quinoline.

Preferred compounds of formula I are those, wherein X is O and Y is CH_2.
Such compounds are
4-(1H-imidazol-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]oxazine
(*RS*)-4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine or
(-)-4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine.

Preferred compounds of formula I are those, wherein X is CH_2 and Y is CH_2CH_2.
Such compounds are
1-(3H-imidazol-4-ylmethyl)-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine or
1-(3H-imidazol-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine.

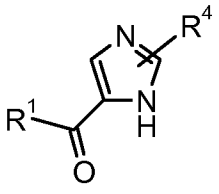
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reductively aminating a compound of formula



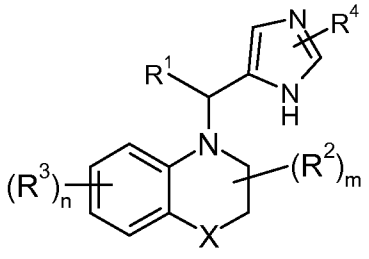
II

and a compound of formula



III

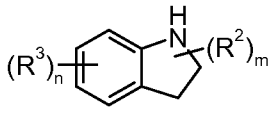
to a compound of formula



I

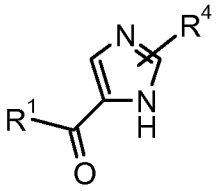
wherein R^1, R^2, R^3, R^4, X, n and m are as defined above, or

b) reductively aminating a compound of formula



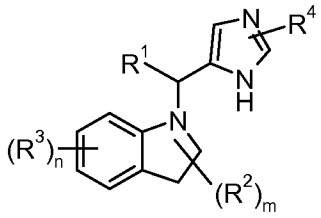
IV

and a compound of formula



III

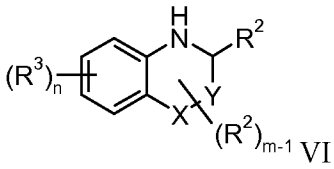
to a compound of formula



I-1

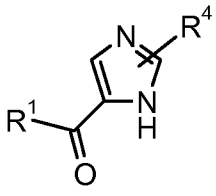
wherein R^1, R^2, R^3, R^4, m and n are as defined above, or

c) reductively aminating a compound of formula



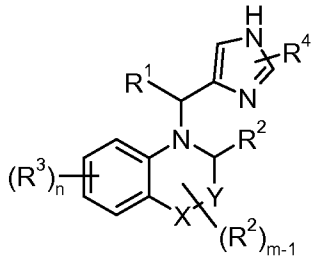
VI

and a compound of formula



III

to a compound of formula



I-2

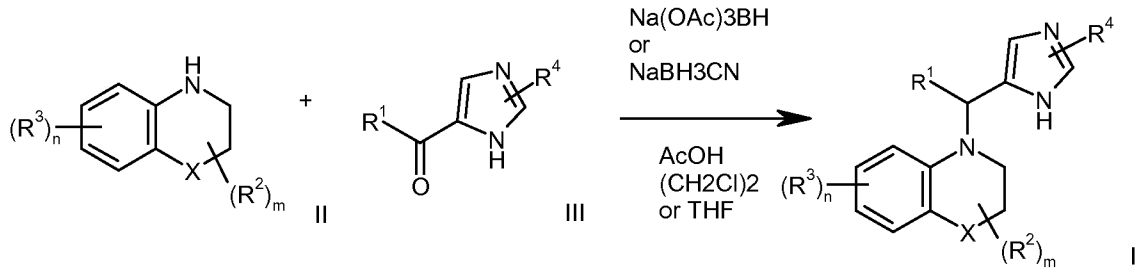
wherein R^1, R^2, R^3, R^4, X, Y, m and n are as defined above; and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with the process variants as described above and with the following schemes 1 - 4. The starting materials are either commercially available, are otherwise known in the chemical literature, or may be prepared in accordance with methods well known in the art.

Method 1

Scheme 1

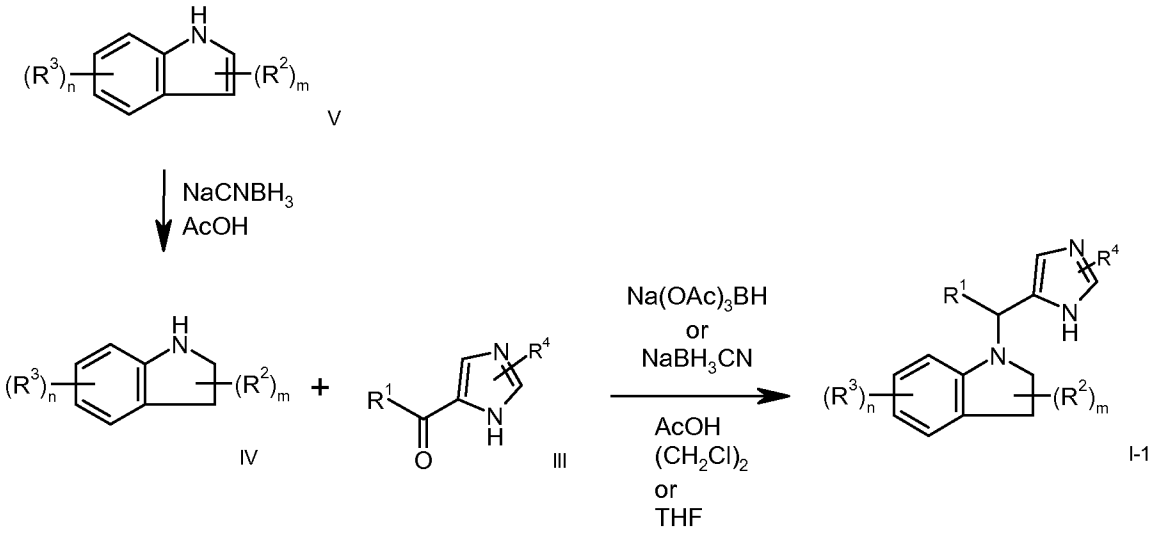


II III I

Scheme 1 describes the reductive amination using a 1,2,3,4-tetrahydroquinoline (X=CH_2) or a 3,4-dihydro-2H-benzo[1,4]oxazine (X=O) of formula II as amine component and imidazole-4-carboxaldehyde or (imidazole-4-yl)-alkyl-ketone of formula III as carbonyl component.

Method 2

Scheme 2

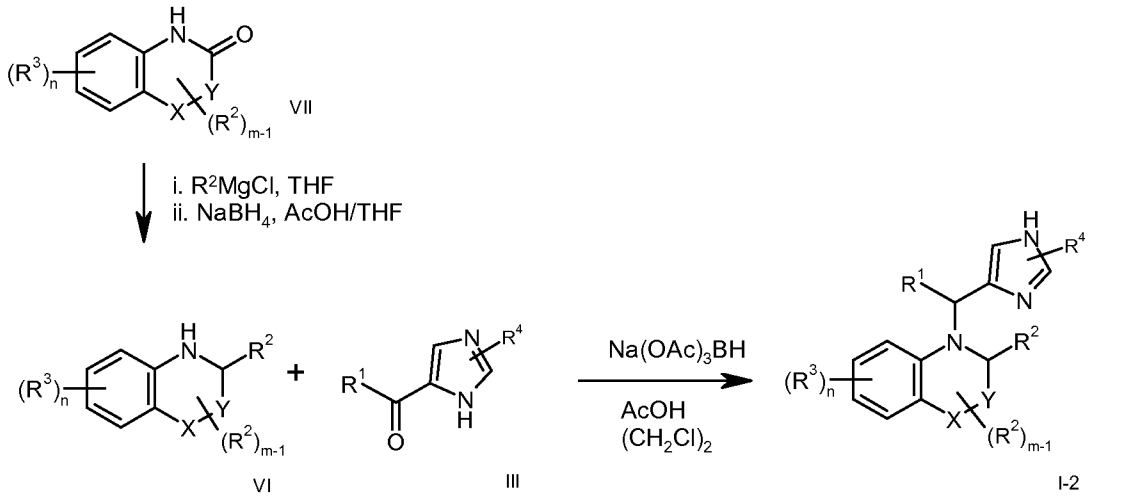


V IV III I-1

Scheme 2 describes the reductive amination using an indoline compound as amine component of formula IV and imidazole-4-carboxaldehyde or (imidazole-4-yl)-alkyl-ketone of formula III as carbonyl component. The indoline compounds may be prepared by reduction of the corresponding indole analogues of formula V.

Method 3

Scheme 3



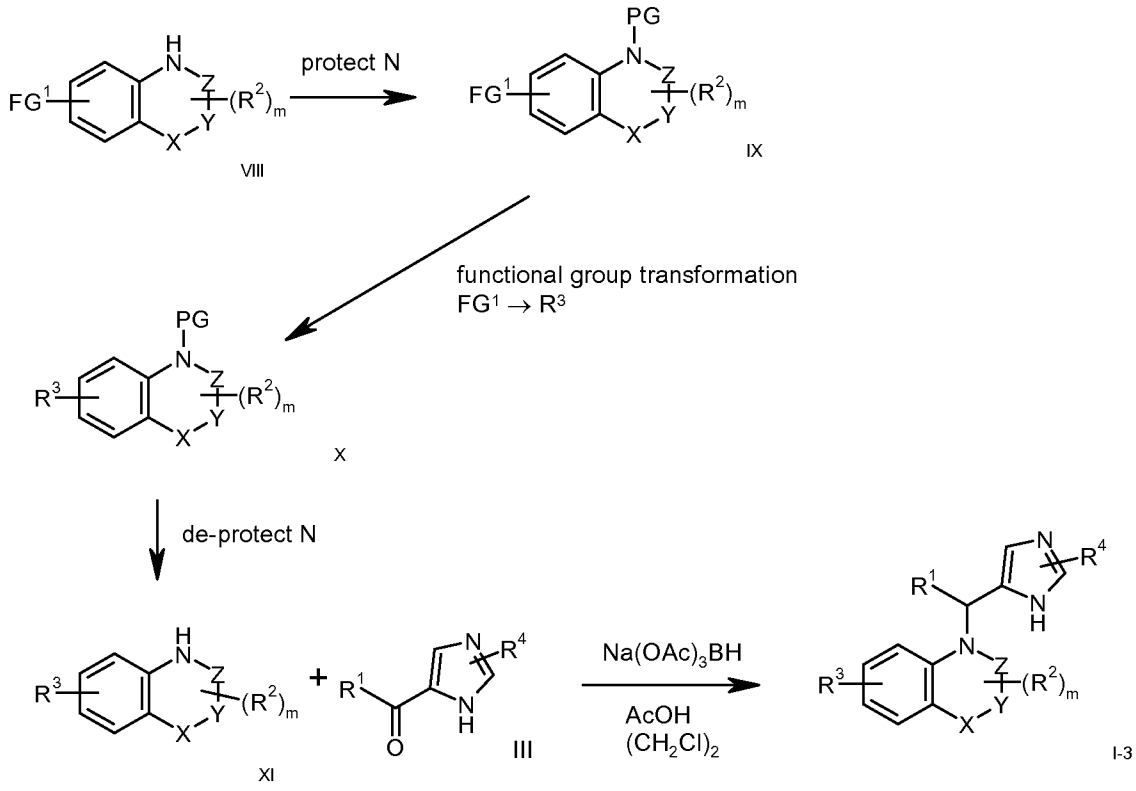
VII VI III I-2

Scheme 3 describes the reductive amination using an indoline compound (-X–Y- = -CH_2-) or a 1,2,3,4-tetrahydroquinoline compound (-X–Y- = -CH_2–CH_2-) or a 3,4-dihydro-2H-benzo[1,4]oxazine compound (-X–Y- = -O–CH_2-) of formula VI as amine component and imidazole-4-carboxaldehyde or (imidazole-4-yl)-alkyl-ketone of formula

III as carbonyl component. The amino compounds can be prepared from the corresponding 1,3-dihydro-indol-2-one compound (-X–Y- = -CH_2-) or a 3,4-dihydro-2(1H)-quinolinone compound (-X–Y- = -CH_2–CH_2-) or a 2H-1,4-benzoxazin-3(4H)-one compound (-X–Y- = -O–CH_2-) of formula VII by addition of a Grignard reagent followed by reduction.

Method 4

Scheme 4



PG = a nitrogen protecting group stable to conditions used to transform FG^1 into R^3, e.g. tert-butoxycarbonyl (BOC)

In cases where the starting material bears a reactive functional group (e.g. a free hydroxy group) on the aryl ring, it may be possible to perform a functional group transformation before carrying out the reductive amination step. In order to carry out the desired functional group transformation it will frequently prove advantageous to first protect the nitrogen atom which is subsequently required to participate in the reductive amination step. For instance, this nitrogen atom may be protected by conversion to a tert-butyl carbamate moiety. Examples of functional group transformations include common functional group transformations already described in the chemical literature, such as

transformation of FG^1 = hydroxy to R^3 = alkyl ether by treatment with a base such as sodium hydride and an alkylating agent such as an alkyl halide. Another possible functional group transformation is the transformation of FG^1 = hydroxy to R^3 = aryl ether by treatment with an aryl boronic acid and copper(II) acetate according to the method of Evans *et al.* (*Tetrahedron Lett.* **1998**, *39*, 2937-2940).

Isolation and purification of the compounds

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

The compounds of formula I are basic and may 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 may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may 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.

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.

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

Materials and Methods

Construction of TAAR expression plasmids and stably transfected cell lines

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, California), and expression vectors were sequence verified before introduction in cell lines.

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

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, IL). 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.

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 (10μM). 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 UniFilter-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).

The preferred compounds show a Ki value (μM) in mouse on TAAR1 in the range of
0.001 – 0.100 as shown in the table below.

Example	Ki (μM) mouse	Example	Ki	Example	Ki
1	0.0688	27	0.0389	40	0.0405
2	0.0104	28	0.0409	41	0.0104
3	0.0258	29	0.0115	43	0.0538

4	0.0091	31	0.0243	44	0.0151
6	0.0598	32	0.0403	45	0.017
7	0.0264	33	0.003	47	0.0872
14	0.0102	34	0.0133	49	0.0573
16	0.0345	35	0.0323	55	0.0046
18	0.0578	36	0.0277	57	0.0702
23	0.0042	37	0.0106	61	0.0027
25	0.0016	38	0.0144		
26	0.0834	39	0.0493		

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. 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 gelatine capsules. Suitable carriers for soft gelatine 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 gelatine 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.

The pharmaceutical preparations 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.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, 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.

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 depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).

The dosage 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 may 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)

Item	Ingredients	mg/tablet			
		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

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

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
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

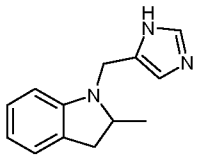
1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Experimental

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

Example 1

(*RS*)-1-(1H-Imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole

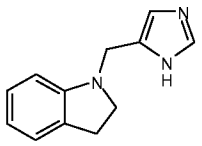


To a solution of 2-methylindoline (0.50 g, 5.20 mmol) in 1,2-dichloroethane (12 ml) were added sequentially imidazole-4-carboxaldehyde (0.75 g, 7.81 mmol), sodium triacetoxyborohydride (3.31 g, 15.6 mmol) and acetic acid (0.06 ml, 1.04 mmol). The reaction mixture was shaken at 40 °C for 16 hours, then triethylamine (0.5 ml) was added and the mixture shaken for a further 5 min. The resulting suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant: methanol/dichloromethane gradient) to yield the title compound as a white solid (0.28 g, 25%); MS (ISP): 214.1 ($[M+H]^+$).

Analogously to Example 1 there were obtained:

Example 2

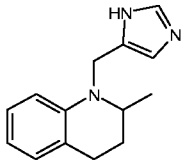
1-(3H-Imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From indoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 200.1 ($[M+H]^+$).

Example 3

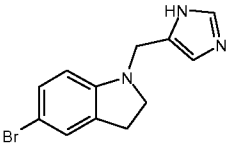
(*RS*)-1-(1H-Imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydroquinaldine, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.4 ($[M+H]^+$).

Example 4

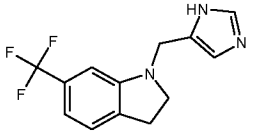
5-Bromo-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 5-bromoindoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 280.1 ($[\{^{81}Br\}M+H]^+$), 278.1 ($[\{^{79}Br\}M+H]^+$).

Example 5

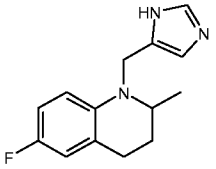
1-(1H-Imidazol-4-ylmethyl)-6-trifluoromethyl-2,3-dihydro-1H-indole



From 6-(trifluoromethyl)indoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 268.3 ($[M+H]^+$).

Example 6

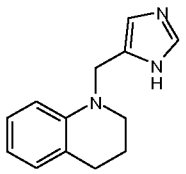
(*RS*)-6-Fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline



From 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 246.3 ($[M+H]^+$).

Example 7

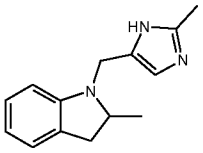
1-(3H-Imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydroquinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.4 ($[M+H]^+$).

Example 8

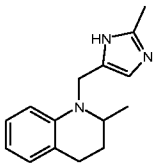
(*RS*)-2-Methyl-1-(2-methyl-1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 2-methylindoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.4 ($[M+H]^+$).

Example 9

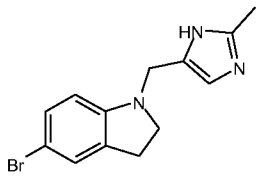
2-Methyl-1-(2-methyl-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydroquinaldine, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 242.3 ($[M+H]^+$).

Example 10

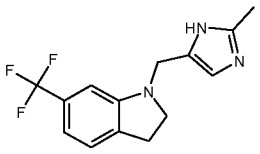
5-Bromo-1-(2-methyl-1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 5-bromoindoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 294.0 ([{^{81}Br}M+H]$^+$), 292.0 ([{^{79}Br}M+H]$^+$).

Example 11

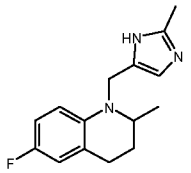
1-(2-Methyl-1H-imidazol-4-ylmethyl)-6-trifluoromethyl-2,3-dihydro-1H-indole



From 6-(trifluoromethyl)indoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 282.3 ([M+H]$^+$).

Example 12

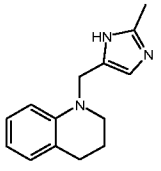
(*RS*)-6-Fluoro-2-methyl-1-(2-methyl-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 260.3 ([M+H]$^+$).

Example 13

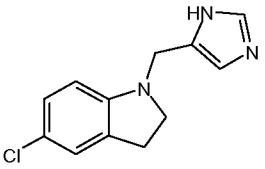
1-(2-Methyl-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydroquinoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.6 ($[M+H]^+$).

Example 14

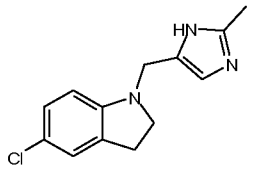
5-Chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 5-chloroindoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 236.2 ($[\{^{37}Cl\}M+H]^+$), 234.2 ($[\{^{35}Cl\}M+H]^+$).

Example 15

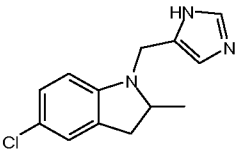
5-Chloro-1-(2-methyl-1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



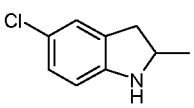
From 5-chloroindoline, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 250.1 ($[\{^{37}Cl\}M+H]^+$), 248.2 ($[\{^{35}Cl\}M+H]^+$).

Example 16

(*RS*)-5-Chloro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole



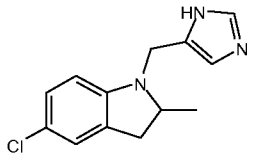
(a) (*RS*)-5-Chloro-2-methyl-2,3-dihydro-1H-indole



To a solution of 5-chloro-2-methylindole (1.00 g, 6.04 mmol) in acetic acid (7 ml) was added portionwise sodium cyanoborohydride (0.76 g, 12.1 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The resulting solution was diluted with ethyl acetate and washed sequentially with water and with 5 N aq. sodium hydroxide solution. The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant:

heptane/ethyl acetate gradient) to yield the title compound as a colourless oil (1.00 g, 100%); MS (ISP): 170.2 ([{^{37}Cl}M+H]$^+$), 168.3 ([{^{35}Cl}M+H]$^+$).

(b) (*RS*)-5-Chloro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole

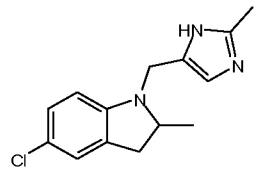


Prepared analogously to Example 1, from (*RS*)-5-chloro-2-methyl-2,3-dihydro-1H-indole, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 250.2 ([{^{37}Cl}M+H]$^+$), 248.3 ([{^{35}Cl}M+H]$^+$).

Analogously to Example 16 there was obtained:

Example 17

(*RS*)-5-Chloro-2-methyl-1-(2-methyl-1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

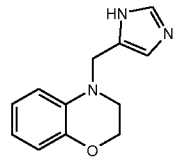


From (*RS*)-5-chloro-2-methyl-2,3-dihydro-1H-indole, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 264.2 ([{^{37}Cl}M+H]$^+$), 262.2 ([{^{35}Cl}M+H]$^+$).

Analogously to Example 1 there were obtained:

Example 18

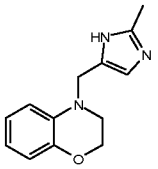
4-(1H-Imidazol-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]oxazine



From 3,4-dihydro-2H-benzo[]1,4]oxazine, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 216.4 ([M+H]$^+$).

Example 19

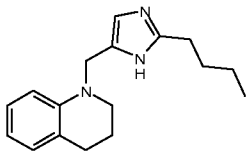
4-(2-Methyl-1H-imidazol-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]oxazine



From 3,4-dihydro-2H-benzo[]1,4]oxazine, 2-methyl-imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 20

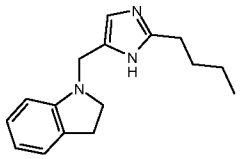
1-(2-Butyl-3H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydroquinoline, 2-*n*-butyl-imidazole-4-carboxaldehyde, sodium cyanoborohydride and acetic acid in THF. MS (ISP): 270.4 ($[M+H]^+$).

Example 21

1-(2-Butyl-3H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

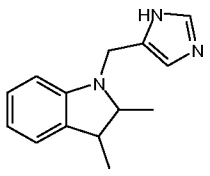


From indoline, 2-*n*-butyl-imidazole-4-carboxaldehyde, sodium cyanoborohydride and acetic acid in THF. MS (ISP): 256.4 ($[M+H]^+$).

Analogously to Example 16 there were obtained:

Example 22

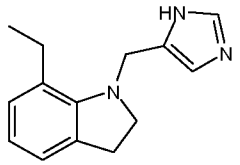
(2*RS*,3*RS*)-1-(1H-Imidazol-4-ylmethyl)-2,3-dimethyl-2,3-dihydro-1H-indole



From 2,3-dimethylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.6 ($[M+H]^+$).

Example 23

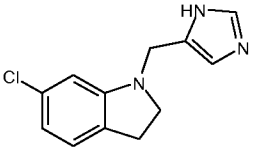
7-Ethyl-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 7-ethylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.6 ($[M+H]^+$).

Example 24

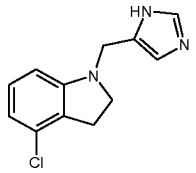
6-Chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 6-chloroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 236.2 ($[\{^{37}Cl\}M+H]^+$), 234.1 ($[\{^{35}Cl\}M+H]^+$).

Example 25

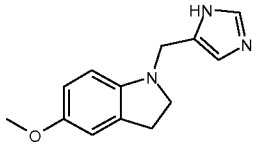
4-Chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 4-chloroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 236.2 ($[\{^{37}Cl\}M+H]^+$), 234.1 ($[\{^{35}Cl\}M+H]^+$).

Example 26

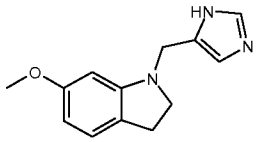
1-(1H-Imidazol-4-ylmethyl)-5-methoxy-2,3-dihydro-1H-indole



From 5-methoxyindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 27

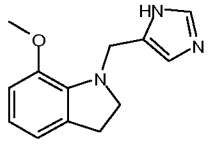
1-(1H-Imidazol-4-ylmethyl)-6-methoxy-2,3-dihydro-1H-indole



From 6-methoxyindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 28

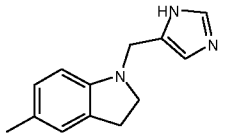
1-(1H-Imidazol-4-ylmethyl)-7-methoxy-2,3-dihydro-1H-indole



From 7-methoxyindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 29

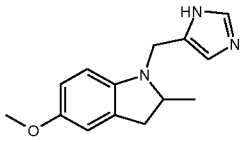
1-(1H-Imidazol-4-ylmethyl)-5-methyl-2,3-dihydro-1H-indole



From 5-methylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.3 ($[M+H]^+$).

Example 30

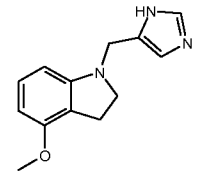
(*RS*)-1-(1H-Imidazol-4-ylmethyl)-5-methoxy-2-methyl-2,3-dihydro-1H-indole



From 5-methoxy-2-methylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 244.4 ($[M+H]^+$).

Example 31

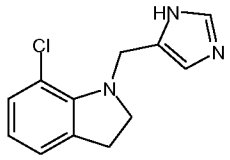
1-(1H-Imidazol-4-ylmethyl)-4-methoxy-2,3-dihydro-1H-indole



From 4-methoxyindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 32

7-Chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

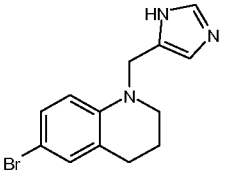


From 7-chloroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 236.2 ($[\{^{37}Cl\}M+H]^+$), 234.1 ($[\{^{35}Cl\}M+H]^+$).

Analogously to Example 1 there was obtained:

Example 33

6-Bromo-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline

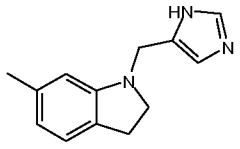


From 6-bromo-1,2,3,4-tetrahydro-quinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 294.1 ($[\{^{81}Br\}M+H]^+$), 292.1 ($[\{^{79}Br\}M+H]^+$).

Analogously to Example 16 there were obtained:

Example 34

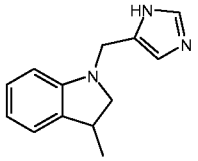
1-(1H-Imidazol-4-ylmethyl)-6-methyl-2,3-dihydro-1H-indole



From 6-methylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.1 ($[M+H]^+$).

Example 35

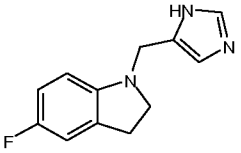
(*RS*)-1-(1H-Imidazol-4-ylmethyl)-3-methyl-2,3-dihydro-1H-indole



From 3-methylindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.1 ($[M+H]^+$).

Example 36

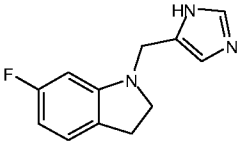
5-Fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 5-fluoroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 218.3 ($[M+H]^+$).

Example 37

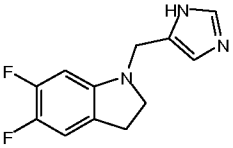
6-Fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 6-fluoroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 218.3 ($[M+H]^+$).

Example 38

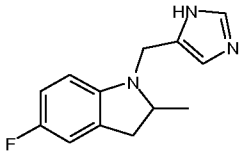
5,6-Difluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole



From 5,6-difluoroindole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 236.4 ($[M+H]^+$).

Example 39

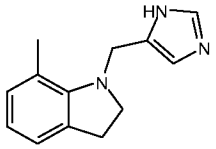
(*RS*)-5-Fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole



From 5-fluoro-2-methyl-indole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 232.1 ($[M+H]^+$).

Example 40

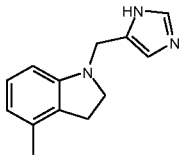
1-(1H-Imidazol-4-ylmethyl)-7-methyl-2,3-dihydro-1H-indole



From 7-methyl-indole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.1 ($[M+H]^+$).

Example 41

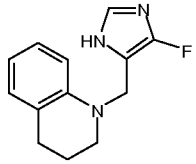
1-(1H-Imidazol-4-ylmethyl)-4-methyl-2,3-dihydro-1H-indole



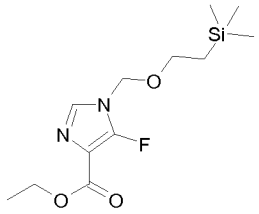
From 4-methyl-indole and sodium cyanoborohydride in acetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 214.1 ($[M+H]^+$).

Example 42

1-(5-Fluoro-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline

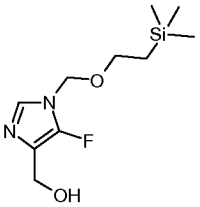


(a) 5-Fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid ethyl ester



To a stirred suspension of NaH (276 mg; 55% dispersion in mineral oil) at 0 °C in DMF (15 ml) under an argon atmosphere was added portionwise 5-fluoro-3H-imidazole-4-carboxylic acid ethyl ester (1.0 g) over a period of 10 min (strong bubbling!). The ice bath was removed and the mixture (almost clear light brown solution) was stirred at r.t. for 1 h 30 min. The mixture was cooled again in an ice bath and 2-(trimethylsilyl)-ethoxymethylchloride (1.24 ml) was added over a period of 5 min. The mixture (slowly warming up to r.t.) was then stirred for 16 h. The off-white slurry was diluted with EtOAc and washed with H_2O. The aqueous phase was back extracted with EtOAc (25 ml). The combined organics were washed with H_2O and brine, dried over MgSO4, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 3:2) to give 5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid ethyl ester (1.57 g) as light yellow oil. MS (ISP): 288.9 ($[M+H]^+$).

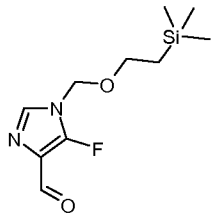
(b) [5-Fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-methanol



To a stirred solution of 5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carboxylic acid ethyl ester (400 mg) in toluene (10 ml) at -78°C under an argon atmosphere was added dropwise DIBAL (1.72 ml; 20 wt % solution in toluene) for 10 min (temperature below -75°C) during the addition. After 2 h stirring at -78°C conversion of the ester was found to be incomplete. More DIBAL solution (1.17 ml.) was added over a period of 5 min and stirring at -78°C was continued for 1 h 30. The mixture was quenched by the addition of 10 ml potassium-sodium tartrate concentrated aqueous solution. The aqueous phase was back extracted with EtOAc. The combined organics were washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated to leave [5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-methanol as (346 mg)

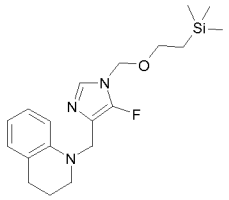
as off-white solid. The crude product was used in the next reaction step without further purification. MS (ISP): 247.3 ($[M+H]^+$).

(c) 5-Fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbaldehyde



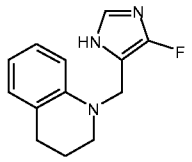
To a stirred solution of [5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-yl]-methanol (339 mg) at r.t. in dichloromethane (15 ml) under an argon atmosphere was added MnO_2 (1.20 g). The black suspension was heated to reflux and stirring at that temperature was continued for 18 h, then was cooled to r.t., filtered and the cake was washed with dichloromethane. The filtrate was concentrated to leave 5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbaldehyde (262 mg) as light yellow viscous oil. The crude product was used in the next reaction step without further purification. MS (EI): 171.1 ($[M - Si(Me)_3]$).

(d) 1-[5-Fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-ylmethyl]-1,2,3,4-tetrahydro-quinoline



To a stirred solution of 5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-4-carbaldehyde (202 mg) at r.t. in methanol (10 ml) under an argon atmosphere were added zinc chloride (409 mg) and 1,2,3,4-tetrahydroquinoline (100 mg). The clear light yellow solution was stirred for 4 h 30 min. Then, $NaBH_3CN$ (141 mg) was then added in one portion. The mixture was heated to 60°C and stirring at that temperature was continued for 22 h. The reaction was directly adsorbed on silica gel. The crude product was isolated by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 65:35) to give 1-[5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-ylmethyl]-1,2,3,4-tetrahydroquinoline (238 mg) as colorless viscous oil. MS (ISP): 362.3 ($[M+H]^+$).

(e) 1-(5-Fluoro-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydroquinoline

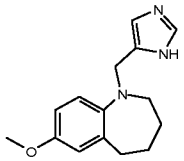


To a stirred solution of 1-[5-fluoro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-4-ylmethyl]-1,2,3,4-tetrahydroquinoline (103 mg) at r.t. in THF (5 ml) under an argon atmosphere was added TBAF (1.1 ml; 1 M solution in THF). The mixture was heated to 60 °C and stirring at that temperature was continued for 20 min, then the mixture was adsorbed directly on silica gel. The crude product was isolated by column chromatography (silica gel; gradient: cyclohexane -> EtOAc) to give 1-(5-fluoro-1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline (32 mg) as light yellow solid. (MS (ISP): 232.1 ($[M+H]^+$).

Analogously to Example 1 there were obtained:

Example 43

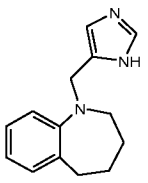
1-(3H-Imidazol-4-ylmethyl)-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine



From 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine hydrochloride (CAS: 23561-82-2), imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 258.3 ($[M+H]^+$).

Example 44

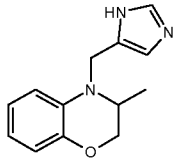
1-(3H-Imidazol-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine



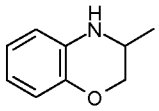
From 2,3,4,5-tetrahydro-1H-benzo[b]azepine, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 228.1 ($[M+H]^+$).

Example 45

(*RS*)-4-(1H-Imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

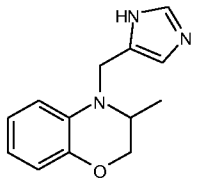


(a) (*RS*)-3-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine



To a solution of 2H-1,4-benzoxazin-3(4H)-one (2.00 g, 13.4 mmol) in tetrahydrofuran (20 ml) was added dropwise at 5 °C a THF solution of methylmagnesium chloride (17.9 ml, 3 M, 53.7 mmol) and the reaction mixture was then stirred at 50 °C for 90 min. The reaction mixture was then cooled to 5 °C and quenched by dropwise addition of 20 ml acetic acid. Sodium borohydride (1.27 g, 33.5 mmol) was then added portionwise and the mixture was stirred at room temperature overnight. The resulting suspension was then cooled to 0 °C and 3 N aq. sodium hydroxide solution was added dropwise until the mixture was pH 10. Ethyl acetate was then added, the phases separated, and the organic phase dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant: heptane/ethyl acetate gradient) to yield the title compound as a colourless oil (0.92 g, 46%); MS (ISP): 150.3 ($[M+H]^+$).

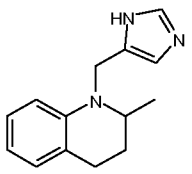
(b) (*RS*)-4-(1H-Imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine



Prepared analogously to Example 1, from (*RS*)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 230.4 ($[M+H]^+$).

Example 46

(+)-1-(1H-Imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline

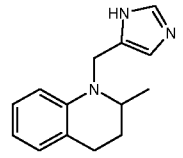


Separation of the enantiomers of (*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline (Example 3) with chiral HPLC (Chiracel OD

column; eluant isopropanol/heptane 10:90; flow-rate 35 ml min^{-1}; pressure 15 bar; retention time 65 min). MS (ISP): 228.4 ($[M+H]^+$). $[\alpha]_D^{20}$ = +6.54° (c = 0.52, MeOH).

Example 47

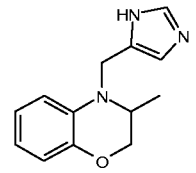
(-)-1-(1H-Imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline



Separation of the enantiomers of (*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline (Example 3) with chiral HPLC (Chiracel OD column; eluant isopropanol/heptane 10:90; flow-rate 35 ml min^{-1}; pressure 15 bar; retention time 87 min). MS (ISP): 228.4 ($[M+H]^+$). $[\alpha]_D^{20}$ = -6.28° (c = 0.52, MeOH). 96% ee.

Example 48

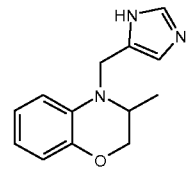
(+)-4-(1H-Imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine



Separation of the enantiomers of (*RS*)-4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (Example 45) with chiral HPLC (Chiracel OD column; eluant isopropanol/heptane 10:90; flow-rate 35 ml min^{-1}; pressure 15 bar; retention time 59 min). MS (ISP): 228.4 ($[M+H]^+$). $[\alpha]_D^{20}$ = + 31.8° (c = 0.60, MeOH).

Example 49

(-)-4-(1H-Imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

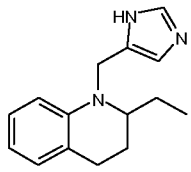


Separation of the enantiomers of (*RS*)- 4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (Example 45) with chiral HPLC (Chiracel OD column; eluant isopropanol/heptane 10:90; flow-rate 35 ml min^{-1}; pressure 15 bar; retention time 67 min). MS (ISP): 228.4 ($[M+H]^+$). $[\alpha]_D^{20}$ = - 24.4° (c = 0.58, MeOH). 76% ee.

Analogously to Example 45 there was obtained:

Example 50

(*RS*)-2-Ethyl-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline

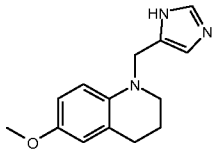


From 3,4-dihydro-2(1H)-quinolinone and ethylmagnesium chloride in tetrahydrofuran, then treatment with sodium borohydride in acetic acid and tetrahydrofuran, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 242.3 ($[M+H]^+$).

Analogously to Example 1 there was obtained:

Example 51

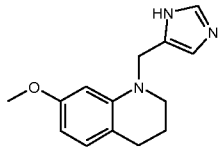
1-(3H-Imidazol-4-ylmethyl)-6-methoxy-1,2,3,4-tetrahydro-quinoline



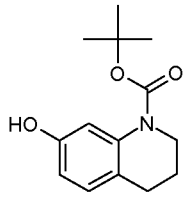
From 6-methoxy-1,2,3,4-tetrahydro-quinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 244.4 ($[M+H]^+$).

Example 52

1-(3H-Imidazol-4-ylmethyl)-7-methoxy-1,2,3,4-tetrahydro-quinoline



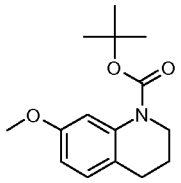
(a) 7-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester



To a suspension of 1,2,3,4-tetrahydro-quinolin-7-ol (0.50 g, 3.35 mmol) in dichloromethane (40 ml) were added di-tert-butyldicarbonate (1.54 g, 7.04 mmol) and triethylamine (1.86 ml, 13.4 mmol) and the reaction mixture was stirred at 45 °C for 48 h. The mixture was then acidified to pH 6 by addition of 10% aq. citric acid solution and extracted with dichloromethane. The combined organic phases were washed with

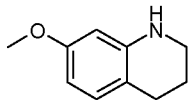
saturated brine, dried over sodium sulphate, and concentrated *in vacuo*. The residue was dissolved in methanol (40 ml) and aq. sodium hydroxide solution (6.70 ml, 13.4 mmol, 2 M) was added. After stirring for 16 h at 60 °C, the mixture was cooled to room temperature and acidified to pH 6 by addition of 10% aq. citric acid solution and extracted with dichloromethane. The combined organic phases were dried over sodium sulphate and concentrated *in vacuo* to yield the title compound as a colourless oil which was used in the next step without further purification (0.33 g, 40%); MS (ISP): 250.3 ($[M+H]^+$), 194.4 ($[M+H\text{-}Me_2C{=}CH_2]^+$).

(b) 7-Methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester



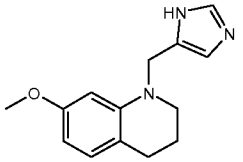
To a solution of 7-hydroxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (120 mg, 0.48 mmol) in N,N-dimethylformamide (6 ml) was added sodium hydride (23 mg, 0.57 mmol, 60% dispersion in oil) and the reaction mixture was stirred at room temperature for 10 min. The mixture was then cooled to 0 °C and methyl iodide 0.04 ml, 0.64 mmol) was added dropwise. After stirring for 16 h at room temperature, the mixture was quenched by addition of water (10 ml) and extracted three times with ethyl acetate. The combined organic phases were washed with saturated brine, dried over sodium sulphate, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant: heptane/ethyl acetate gradient) to yield the title compound as a colourless oil (52 mg, 41%); MS (ISP): 264.0 ($[M+H]^+$), 208.1 ($[M+H\text{-}Me_2C{=}CH_2]^+$).

(c) 7-Methoxy-1,2,3,4-tetrahydro-quinoline



To a solution of 7-methoxy-3,4-dihydro-2H-quinoline-1-carboxylic acid tert-butyl ester (52 mg, 0.20 mmol) in dichloromethane (7 ml) at 0 °C was added dropwise trifluoroacetic acid (0.23 ml, 3.01 mmol) and the reaction mixture was then stirred at room temperature for 24 h. The mixture was then made basic to pH 9 by dropwise addition of saturated aq. sodium carbonate solution. The mixture was extracted three times with a 1:1 mixture of ethyl acetate and tetrahydrofuran, the phases separated, and the organic phase dried over sodium sulphate and concentrated *in vacuo* to yield the title compound as a light brown oil (37 mg, 92%); MS (ISP): 164.4 ($[M+H]^+$).

(d) 1-(3H-Imidazol-4-ylmethyl)-7-methoxy-1,2,3,4-tetrahydro-quinoline

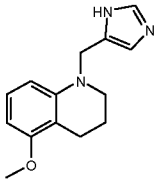


Prepared analogously to Example 1, from 7-methoxy-1,2,3,4-tetrahydro-quinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 244.4 ($[M+H]^+$).

Analogously to Example 52 there were obtained:

Example 53

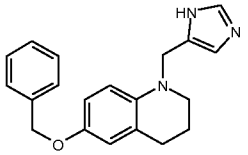
1-(1H-Imidazol-4-ylmethyl)-5-methoxy-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-5-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with methyl iodide and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 244.4 ($[M+H]^+$).

Example 54

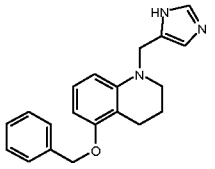
6-Benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-6-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with benzyl bromide and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 320.3 ($[M+H]^+$).

Example 55

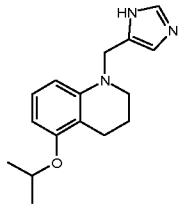
5-Benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-5-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with benzyl bromide and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 320.3 ($[M+H]^+$).

Example 56

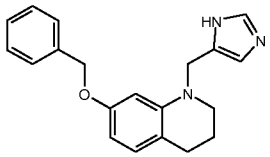
1-(1H-Imidazol-4-ylmethyl)-5-isopropoxy-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-5-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with isopropyl bromide and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 272.3 ($[M+H]^+$).

Example 57

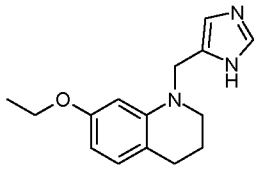
7-Benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-7-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with benzyl bromide and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 320.3 ($[M+H]^+$).

Example 58

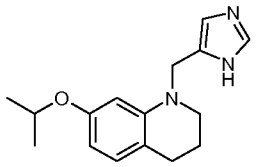
7-Ethoxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-7-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with iodoethane and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 258.0 ($[M+H]^+$).

Example 59

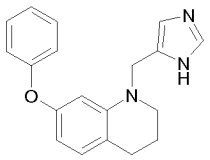
1-(1H-Imidazol-4-ylmethyl)-7-isopropoxy-1,2,3,4-tetrahydro-quinoline



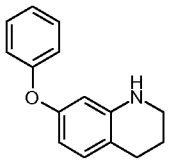
From 1,2,3,4-tetrahydro-quinolin-7-ol, di-tert-butyldicarbonate and triethylamine in dichloromethane, then treatment with sodium hydroxide in methanol, then treatment with 2-bromopropane and sodium hydride in N,N-dimethylformamide, then treatment with trifluoroacetic acid, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 272.5 ($[M+H]^+$).

Example 60

1-(1H-Imidazol-4-ylmethyl)-7-phenoxy-1,2,3,4-tetrahydro-quinoline



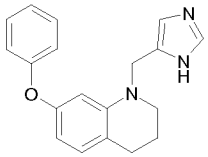
(a) 7-Phenoxy-1,2,3,4-tetrahydro-quinoline



To a solution of 0.15 g (1.01 mmol) 1,2,3,4-tetrahydro-quinolin-7-ol in 10 ml dichloromethane were added 0.19 g (1.56 mmol) phenylboronic acid, 0.27 g (1.49 mmol) copper(II) acetate, a spatula end of 4Å molecular sieves and 0.64 ml (5.03 mmol) triethylamine. The reaction mixture was stirred at room temperature for 72 h and then filtered through celite, washing with dicloromethane. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel, ethyl

acetate/heptane gradient) to afford 15 mg (7%) of the title compound as a light yellow oil. MS (ISP): 226.3 ($[M+H]^+$).

(b) 1-(1H-Imidazol-4-ylmethyl)-7-phenoxy-1,2,3,4-tetrahydro-quinoline

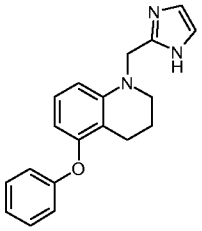


Prepared analogously to Example 1, from 7-phenoxy-1,2,3,4-tetrahydro-quinoline, imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 306.4 ($[M+H]^+$).

Analogously to Example 60 there was obtained:

Example 61

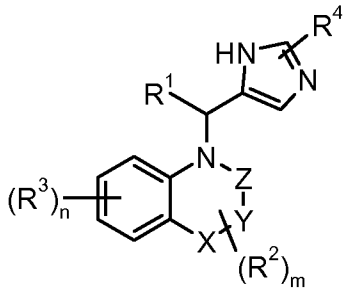
1-(1H-Imidazol-4-ylmethyl)-5-phenoxy-1,2,3,4-tetrahydro-quinoline



From 1,2,3,4-tetrahydro-quinolin-5-ol, phenylboronic acid, copper(II) acetate and triethylamine in dichloromethane, then treatment with imidazole-4-carboxaldehyde, sodium triacetoxyborohydride and acetic acid in 1,2-dichloroethane. MS (ISP): 306.1 ($[M+H]^+$).

Claims

1. A compound of formula



I

wherein

R^1 is hydrogen or lower alkyl;

R^2 is hydrogen or lower alkyl;

R^3 is hydrogen, lower alkyl, lower alkoxy, phenyloxy, benzyloxy, halogen or lower alkyl substituted by halogen;

R^4 is hydrogen or lower alkyl;

X is $-CH_2-$, -CH- or –O-;

Y is $-CH_2-$, $-CH_2CH_2-$, -CH- or a bond; when X is –O-, then Y is $-CH_2-$;

Z is $-CH_2-$ or -CH-;

m is 1 or 2; when m is 2, R^2 may be the same or not;

n is 1 or 2; when n is 2, R^3 may be the same or not;

and to pharmaceutically acceptable acid addition salts.

2. A compound of formula I according to claim 1, wherein X is CH_2 and Y is a bond.

3. A compound of formula I according to claim 2, which compounds are

(*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole

1-(3H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

5-bromo-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

5-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

(*RS*)-5-chloro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole

7-ethyl-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

4-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole

1-(1H-imidazol-4-ylmethyl)-5-methoxy-2,3-dihydro-1H-indole

1-(1H-imidazol-4-ylmethyl)-6-methoxy-2,3-dihydro-1H-indole

1-(1H-imidazol-4-ylmethyl)-7-methoxy-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-5-methyl-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-4-methoxy-2,3-dihydro-1H-indole
7-chloro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-6-methyl-2,3-dihydro-1H-indole
(*RS*)-1-(1H-imidazol-4-ylmethyl)-3-methyl-2,3-dihydro-1H-indole
5-fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
6-fluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
5,6-difluoro-1-(1H-imidazol-4-ylmethyl)-2,3-dihydro-1H-indole
(*RS*)-5-fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-2,3-dihydro-1H-indole
1-(1H-imidazol-4-ylmethyl)-7-methyl-2,3-dihydro-1H-indole or
1-(1H-imidazol-4-ylmethyl)-4-methyl-2,3-dihydro-1H-indole.

4. A compound of formula I according to claim 1, wherein X is CH_2 and Y is CH_2.

5. A compound of formula I according to claim 4, which compounds are
(*RS*)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
(*RS*)-6-fluoro-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
1-(3H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
6-bromo-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
(-)-1-(1H-imidazol-4-ylmethyl)-2-methyl-1,2,3,4-tetrahydro-quinoline
5-benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline
7-benzyloxy-1-(1H-imidazol-4-ylmethyl)-1,2,3,4-tetrahydro-quinoline or
1-(1H-imidazol-4-ylmethyl)-5-phenoxy-1,2,3,4-tetrahydro-quinoline.

6. A compound of formula I according to claim 1, wherein X is O and Y is CH_2.

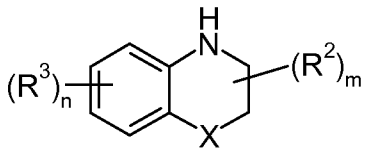
7. A compound of formula I according to claim 6, which compounds are
4-(1H-imidazol-4-ylmethyl)-3,4-dihydro-2H-benzo[1,4]oxazine
(*RS*)-4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine or
(-)-4-(1H-imidazol-4-ylmethyl)-3-methyl-3,4-dihydro-2H-benzo[1,4]oxazine.

8. A compound of formula I according to claim 1, wherein X is CH_2 and Y is CH_2CH_2.

9. A compound of formula I according to claim 6, which compounds are
1-(3H-imidazol-4-ylmethyl)-7-methoxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine or
1-(3H-imidazol-4-ylmethyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine.

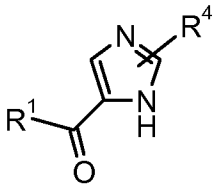
10. A process for preparation of compounds of formula I, which process comprises

a) reductively aminating a compound of formula



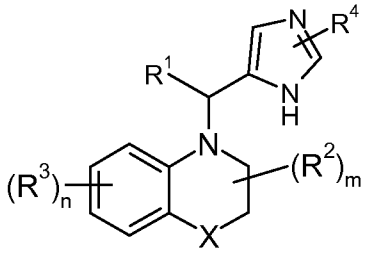
II

and a compound of formula



III

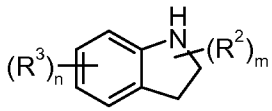
to a compound of formula



I

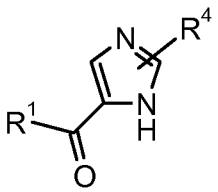
wherein R^1, R^2, R^3, R^4, X, n and m are as defined in claim 1, or

b) reductively aminating a compound of formula



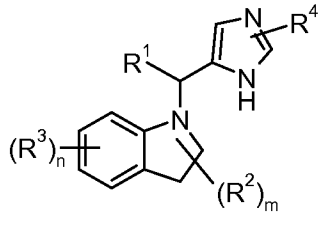
IV

and a compound of formula



III

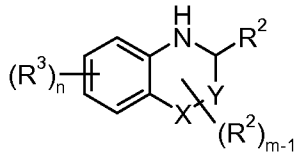
to a compound of formula



I-1

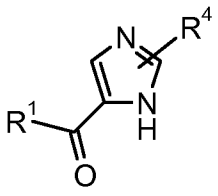
wherein R^1, R^2, R^3, R^4, m and n are as defined in claim 1, or

c) reductively aminating a compound of formula



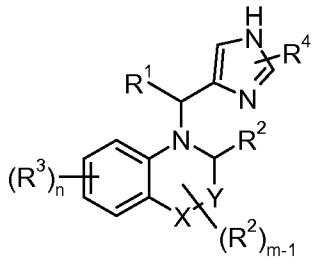
VI

and a compound of formula



III

to a compound of formula



I-2

wherein R^1, R^2, R^3, R^4, X, Y, m and n are as defined in claim 1; and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound of formula I according to claim 1, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

12. A medicament containing one or more compounds of formula I in accordance with claim 1 and pharmaceutically acceptable excipients.

13. A medicament as claimed in claim 12 for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders, 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.

14. A medicament according to claim 13 containing one or more compounds as claimed in claims 1- 9 for the treatment of depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).

15. The use of a compound of formula I according to claim 1 for the preparation of a medicament for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders, 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.

16. The invention as herein before described.

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