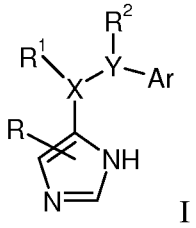
4-IMIDAZOLINES AS TAAR'S LIGANDS

The invention relates to compounds of formula



I

wherein

R is hydrogen, lower alkyl or amino;

X-R^1 is $-CH_2-$, -CH(lower alkoxy)- or –CH(OH)- and
Y-R^2 is $-CH_2$, -CH(lower alkyl)-, -CH(lower alkoxy)- -O-, -S-, -S(O)-, $-S(O)_2-$, -CH(phenyl)- or $-C(\text{lower alkyl})_2-$;
or

X-R^1 is –NH- and
Y-R^2 is $-CH_2$, -CH(lower alkyl)-, -CH(lower alkoxy)-, -CH(phenyl)- or $-C(\text{lower alkyl})_2-$;

Ar is phenyl, napthyl or benzofuranyl, which rings are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy, lower alkoxy substituted by halogen, hydroxy, amino, di-alkylamino, morpholinyl, phenyl, benzyl or by O-benzyl;

or pharmaceutically suitable acid addition salts with the exception of
5-phenethyl-1*H*-imidazole
5-(2-phenyl-propyl)-1H-imidazole
1-(1H-imidazol-4-yl)-2-phenyl-ethanol
5-(2,2-diphenyl-ethyl)-1H-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole

4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole
4-(biphenyl-2-yloxymethyl)-1H-imidazole
5-(2-methyl-2-phenyl-propyl)-1H-imidazole
4-(2-chloro-phenoxymethyl)-1H-imidazole
4-(2-fluoro-phenoxymethyl)-1H-imidazole
4-o-tolyloxymethyl-1H-imidazole
4-(3-chloro-phenoxymethyl)-1H-imidazole
4-(2,6-dimethyl-phenoxymethyl)-1H-imidazole and
5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

The known compounds are described for example in the below mentioned references, or are enclosed in public chemical libraries.

A: 5-phenethyl-1*H*-imidazole (CAS 94714-36-0)
B: 5-(2-phenyl-propyl)-1H-imidazole (CAS 86347-25-3)
C: 1-(1H-imidazol-4-yl)-2-phenyl-ethanol (CAS 79928-10-2)
D: 5-(2,2-diphenyl-ethyl)-1H-imidazole (CAS 102390-63-6)
E: 4-(2-m-tolyl-ethyl)-1H-imidazole (CAS 79928-27-1)
F: 4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole (CAS 79924-13-3)
G: 4-(biphenyl-2-yloxymethyl)-1H-imidazole (CAS 527696-96-4)
H: 5-(2-methyl-2-phenyl-propyl)-1H-imidazole (Beilstein Registry Number 4407995)
I: 4-(2-chloro-phenoxymethyl)-1H-imidazole (CAS 27325-27-5)
J: 4-(2-fluoro-phenoxymethyl)-1H-imidazole (CAS 401-45-6)
K: 4-o-tolyloxymethyl-1H-imidazole (CAS 762177-70-8)
L: 4-(3-chloro-phenoxymethyl)-1H-imidazole (CAS 802322-21-0)
M: 4-(2,6-dimethyl-phenoxymethyl)-1H-imidazole (CAS 771450-63-6)
N: 5-methyl-4-phenylsulfanylmethyl-1H-imidazole (CAS 700355-78-8)

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;

2 Wong, M.L. and Licinio, J. (2001) Research and treatment approaches to depression. *Nat. Rev. Neurosci.* 2, 343-351;

3 Carlsson, A. *et al.* (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu. Rev. Pharmacol. Toxicol.* 41, 237-260;

4 Tuite, P. and Riss, J. (2003) Recent developments in the pharmacological treatment of Parkinson's disease. *Expert Opin. Investig. Drugs* 12, 1335-1352,

5 Castellanos, F.X. and Tannock, R. (2002) Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat. Rev. Neurosci.* 3, 617-628;

6 Usdin, E. and Sandler, M. eds. (1984), *Trace Amines and the brain*, Dekker;

7 Lindemann, L. and Hoener, M. (2005) A renaissance in trace amines inspired by a novel GPCR family. *Trends in Pharmacol. Sci.* 26, 274-281;

8 Branchek, T.A. and Blackburn, T.P. (2003) Trace amine receptors as targets for novel therapeutics: legend, myth and fact. *Curr. Opin. Pharmacol.* 3, 90-97;

9 Premont, R.T. *et al.* (2001) Following the trace of elusive amines. *Proc. Natl. Acad. Sci. U. S. A.* 98, 9474-9475;

10 Mousseau, D.D. and Butterworth, R.F. (1995) A high-affinity [3H] tryptamine binding site in human brain. *Prog. Brain Res.* 106, 285-291;

11 McCormack, J.K. *et al.* (1986) Autoradiographic localization of tryptamine binding sites in the rat and dog central nervous system. *J. Neurosci.* 6, 94-101;

12 Dyck, L.E. (1989) Release of some endogenous trace amines from rat striatal slices in the presence and absence of a monoamine oxidase inhibitor. *Life Sci.* 44, 1149-1156;

13 Parker, E.M. and Cubeddu, L.X. (1988) Comparative effects of amphetamine, phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding. *J. Pharmacol. Exp. Ther.* 245, 199-210;

14 Lindemann, L. *et al.* (2005) Trace amine associated receptors form structurally and functionally distinct subfamilies of novel G protein-coupled receptors. *Genomics* 85, 372-385.

Objects of the present invention are novel compounds of formula I and the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to affinity to the trace amine associated receptors, new specific compounds falling into the scope 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-R^1 and Y-R^2 are both CH_2. Such compounds are

4-[2-(2-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(2-methoxy-phenyl)-ethyl]-1H-imidazole
4-[2-(3-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(3-fluoro-phenyl)-ethyl]-1H-imidazole
4-[2-(3-trifluoromethyl-phenyl)-ethyl]-1H-imidazole
4-[2-(3-methoxy-phenyl)-ethyl]-1H-imidazole
4-[2-(4-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(3,5-dichloro-phenyl)-ethyl]-1H-imidazole
5-phenethyl-1*H*-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole or
4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole.

Further preferred are compounds, wherein X-R^1 is CH_2 and Y-R^2 is –CH(lower alkyl), for example the following compounds:
4-(2-phenyl-butyl)-1H-imidazole or
5-(2-phenyl-propyl)-1H-imidazole.

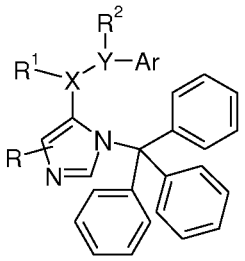
Further preferred are compounds, wherein X-R^1 is CH_2 and Y-R^2 is O, for example the following compounds:
4-(2,3-dichloro-phenoxymethyl)-1H-imidazole
4-(2,3-difluoro-phenoxymethyl)-1H-imidazole
4-(3,4-dichloro-phenoxymethyl)-1H-imidazole
4-(4-chloro-3-fluoro-phenoxymethyl)-1H-imidazole
5-(benzofuran-6-yloxymethyl)-1H-imidazole
4-o-tolyloxymethyl-1H-imidazole
4-(3-chloro-phenoxymethyl)-1H-imidazole or
4-(2-fluoro-phenoxymethyl)-1H-imidazole.

A further embodiment of the invention are compounds of formula 1, wherein X-R^1 is CH_2 and Y-R^2 is S, for example the following compounds:
5-(2,3-dichloro-phenylsulfanylmethyl)-1-imidazole
4-(4-chloro-phenylsulfanylmethyl)-5-methyl-1H-imidazole

4-(naphthalen-2-ylsulfanylmethyl)-1H-imidazole or
5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

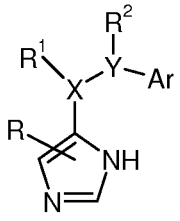
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) deprotecting a compound of formula



II

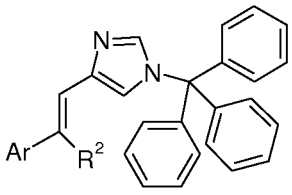
to a compound of formula



I

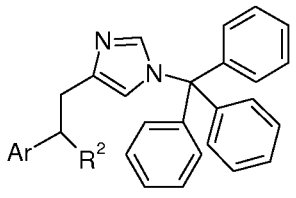
wherein the definitions are as described above, or

b) hydrogenating a compound of formula



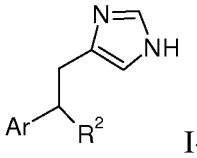
V

to a compound of formula



II-1

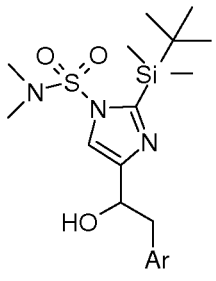
and deprotecting according to step a) to a compound of formula



I-1

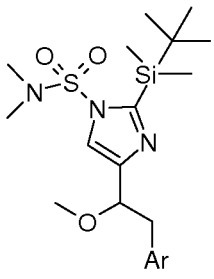
wherein Ar is as defined above and R^2 is hydrogen, lower alkyl or lower alkoxy, or

c) alkylating a compound of formula



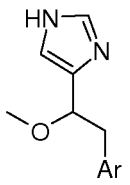
IX

to a compound of formula



II-2

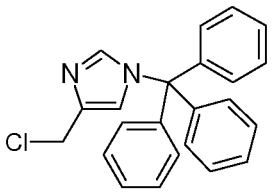
and deprotecting according to step a) to a compound of formula



I-2

wherein Ar is as defined above; or

d) reacting a compound of formula

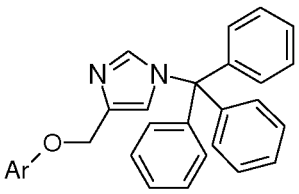


XI

and a compound of formula

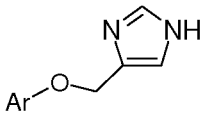
ArOH X

to a compound of formula



II-3

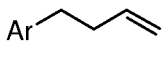
and deprotecting according to step a) to a compound of formula



I-3

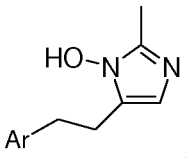
wherein the definitions are as described above, or

e) reacting a compound of formula



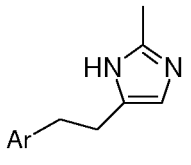
XII

with acetonitrile to a compound of formula



XIII

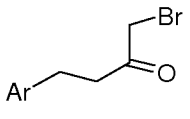
and removing the hydroxy group to a compound of formula



I-4

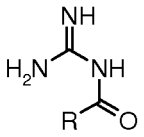
wherein Ar is as defined above, or

f) reacting a compound of formula



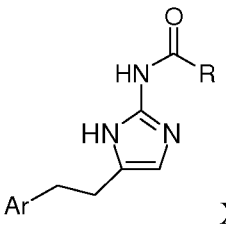
XIII

with a compound of formula



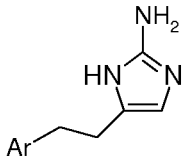
XIV

to a compound of formula



XV

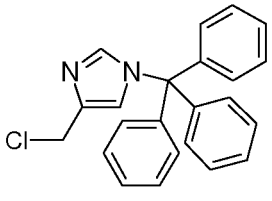
and deprotecting to a compound of formula



I-5

wherein R is lower alkyl and Ar is as described above, or

g) reacting a compound of formula

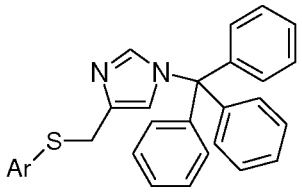


XI

and a compound of formula

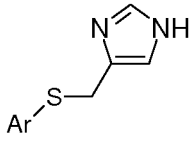
ArSH X'

to a compound of formula



II-4

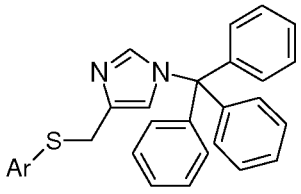
and deprotecting according to step a) to a compound of formula



I-6

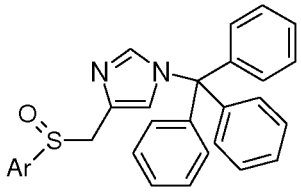
wherein Ar is as defined above, or

h) oxidizing a compound of formula

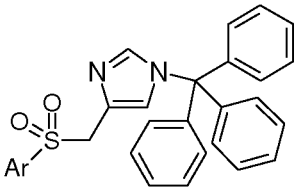


II-4

to compounds of formulas

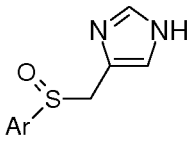


II-5 or

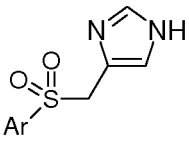


II-6

and deprotecting according to step a) to compounds of formulas



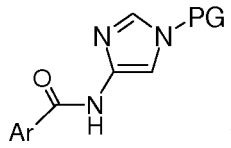
I-7 or



I-8

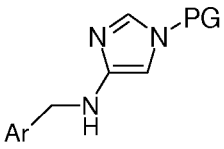
wherein Ar is as defined above; or

i) reducing a compound of formula



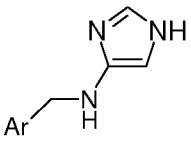
IXX

to a compound of formula



II-7

and deprotecting according to step a) to compounds of formula



I-9

wherein Ar is as described above and PG is a common N-protecting group; and

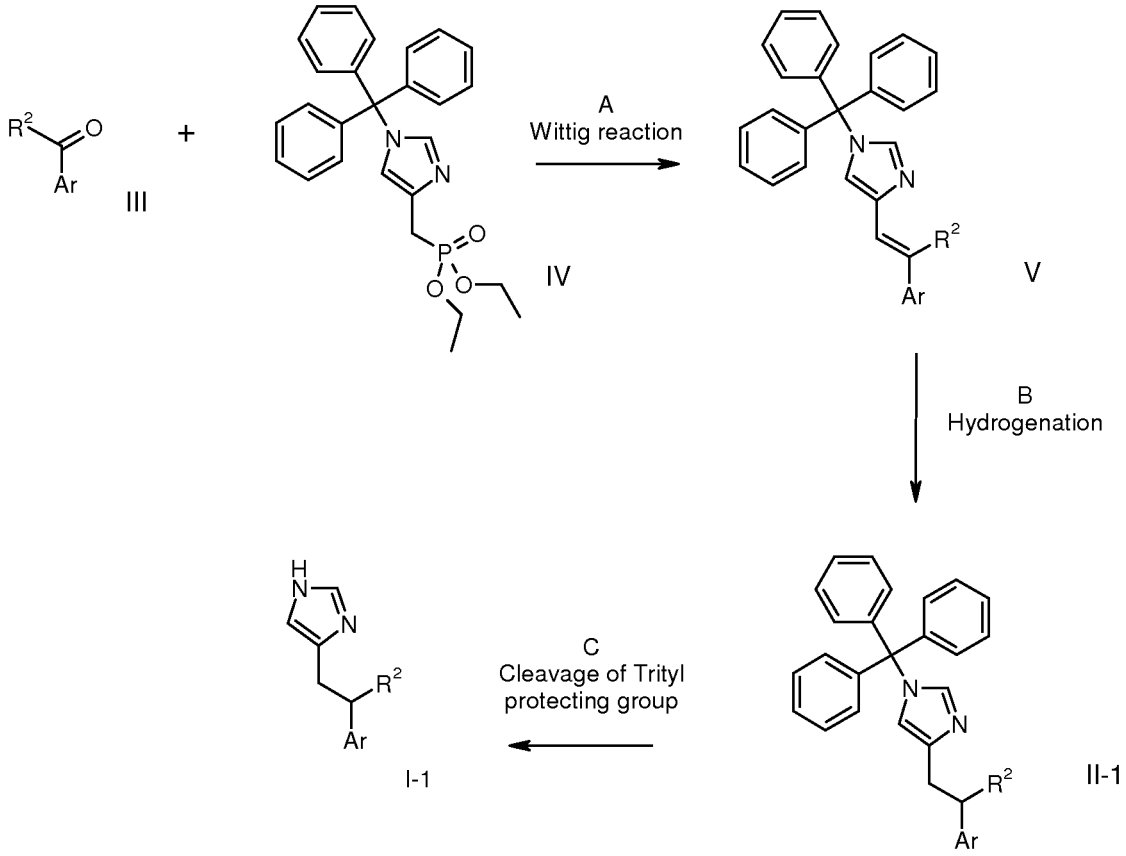
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with the process variants as described above and with the following schemes 1 - 7. 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.

PROCEDURE A

Synthesis of C-C-linked compounds

Scheme 1



R^2 is lower alkyl or hydrogen.

Step A: The Wittig reaction between an aldehyde or a ketone of formula III and (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (IV) can be accomplished by using a base such as NaH, KOtBu, NaOMe, NaOEt, n-BuLi, LiHMDS, NaHMDS, KHMDS, LDA in a solvent such as THF, dioxane, acetonitrile, 1,2-dimethoxyethan, DMF, benzene, toluene or mixtures thereof at temperatures from -78°C – 80°C for 15 min – 8 hrs and if appropriate optional addition of a crown ether for ylide generation and then condensing the ylide with the carbonyl compound in the same solvent at temperature between 0 and 80°C for 1 – 24 hrs. Alternatively, the base, the carbonyl compound and the optional crown ether can be added to the reaction mixture at the same time without preformation of the ylide at temperatures from -78°C – 80°C. Preferred conditions for reactions with aryl ketones are ylide formation at r.t. using KOtBu as base and THF as solvent, reacting the phosphonic acid ester for 15 min at r.t., and then condensation with the carbonyl component at 80°C overnight. Preferred

conditions for benzaldehydes are ylide formation in the presence of the carbonyl compound using KOtBu as base and THF as solvent at 80°C overnight.

Step B: The reduction of the alkene of formula V can be effected by hydrogenation with hydrogen under normal or elevated pressure or by transfer hydrogenation using ammonium formiate or cyclohexadiene as hydrogen source with a catalyst such as PtO_2, Pd-C or Raney nickel in solvents such as MeOH, EtOH, H_2O, dioxane, THF, HOAc, EtOAc CH_2Cl_2, $CHCl_3$, DMF or mixtures thereof. Alternatively, the reduction of the alkene can be effected by Mg in MeOH or by $LiAlH_4$ in THF or diethylether.

The preferred procedure for trisubstituted alkenes is hydrogenation at normal pressure in MeOH/CH_2Cl_2 using 10% Pd/C as catalyst. The preferred procedure for disubstituted alkenes is hydrogenation at normal pressure in MeOH/$CHCl_3$/AcOH using 10% Pd/C as catalyst. Both conditions may lead to partial loss of the trityl protecting group. In this case the mixture of protected and unprotected products is subjected directly to conditions C.

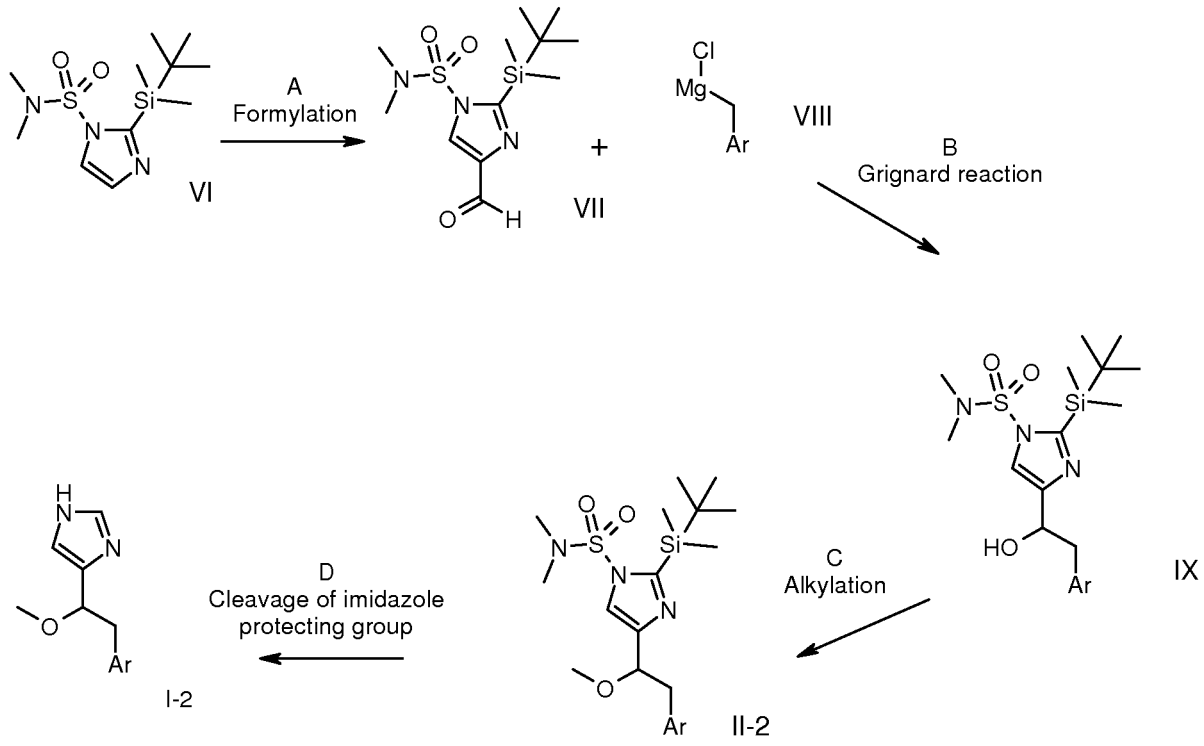
Step C: The cleavage of the trityl group can be effected with a mineral acid such as HCl, H_2SO_4 or H_3PO_4 or a organic acid such as CF_3COOH, $CHCl_2COOH$, HOAc or p-toluonesulfonic acid in a solvent such as CH_2Cl_2, $CHCl_3$, THF, MeOH, EtOH or H_2O at 0 to 60°C.

Preferred conditions are 2N HCl in EtOH at reflux for 1 -3 hrs.

PROCEDURE B

Synthesis of C-C-linked compounds with alkoxy substituent in α position to imidazoles

Scheme 2



Step A: The formylation of 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethyl-amide (VII) can be effected by deprotonation with a strong base such as n-BuLi, s-BuLi or t-BuLi and optionally an additive such as tetramethylethylene diamine or pentamethyl diethylene triamine in a solvent such as THF or diethylether at -78°C - -40°C, followed by quenching the anion with a formylating electrophile such as DMF at -78° - r.t. for 1 - 24 hrs.

Preferred conditions are deprotonation with n-BuLi at -78°C for 10 min, then reaction with DMF at -78°C for 2 hrs.

Step B: The Grignard reaction of the protected formyl imidazole (VII) with an aryl magnesium chloride or bromide (VIII) can be effected by adding a solution of the Grignard reagent (commercially available or prepared form a benzyl chloride or bromide and Mg by standard methods) in a solvent such as diethylether, THF or benzene to a solution of the aldehyde in one of the previously mentioned solvents at -20°C – r.t. and letting the two components react at r.t. – reflux temperature for 1 – 24 hrs.

Preferred conditions addition of the Grignard reagent in diethylether to a solution of aldehyde in THF at r.t. and reaction at r.t overnight.

Step C: The alkylation of the alcohol of formula IX can be accomplished by deprotonation of the hydroxy group with a base such as NaH, KH, n-BuLi, KOtBu, KOH or aqueous NaOH and KOH in the presence of a phase transfer catalyst (tetraalkylammonium salts) in a suitable solvent such as THF, DMF, DMSO, toluene or 1,2-dimethoxyethane at -78°C – r.t. for 30 min – 2 hrs and subsequent addition of an alkyl halide.

Preferred conditions are deprotonation with NaH in THF at r.t. for 1 hr and alkylation with an alkyl iodide at r.t. overnight.

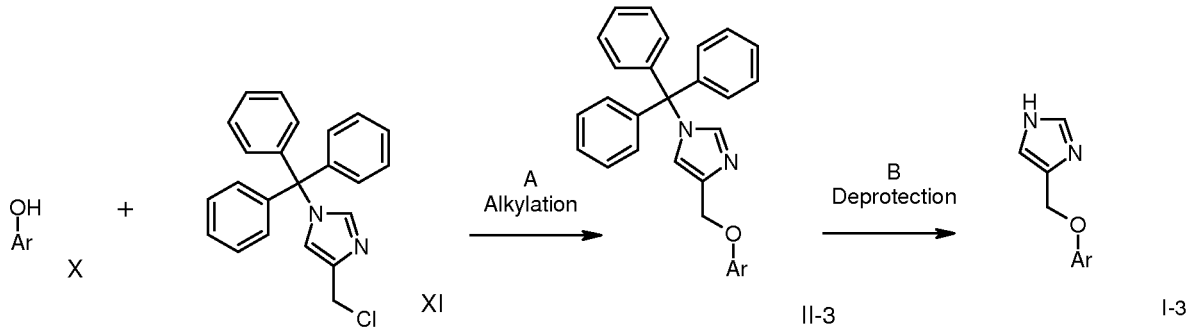
Step D: The simultaneous cleavage of both protecting groups (II-2) can be achieved in the presence of a mineral acid such as HCl, HBr or H_2SO_4 in a solvent such as EtOH, MeOH, H_2O or THF at r.t – reflux temperature for 1- 24 hrs.

Preferred conditions are 2N HCl in EtOH at reflux for 1 -3 hrs.

PROCEDURE C

Synthesis of C-O-linked compounds

Scheme 3



Step A: The alkylation of a substituted phenol with 4-chloromethyl-1-trityl-1H-imidazole (XI) can be accomplished using a base such as K_2CO_3, Cs_2CO_3, Na_2CO_3, $NaHCO_3$, aqueous NaOH, KOH, LiOH, NaH, NaOMe, NaOEt or triethylamine in a solvent such as acetone, DMF, DMSO, acetonitrile, toluene, EtOH, MeOH and optionally if appropriate a phase transfer catalyst such as tetrabutylammonium bromide or an additive such as a crown ether, tetrabutylammonium iodide or potassium iodide at r.t. – 120°C for 1 -24 hrs.

Preferred conditions are K_2CO_3 in DMF at 80°C for 5 hrs.

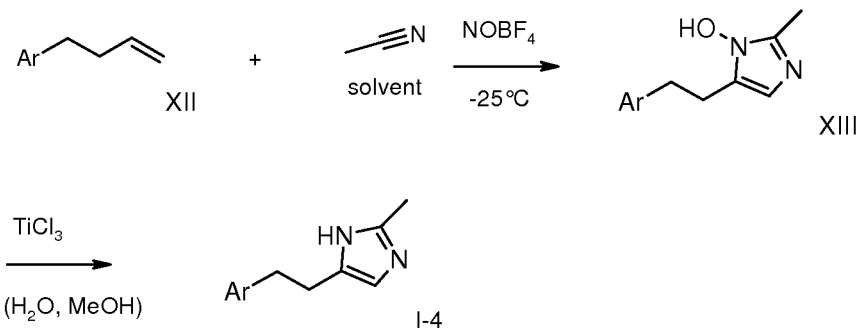
Step B: The cleavage of the trityl group can be effected with a mineral acid such as HCl, H_2SO_4 or H_3PO_4 or a organic acid such as CF_3COOH, $CHCl_2COOH$, HOAc or p-toluonesulfonic acid in a solvent such as CH_2Cl_2, $CHCl_3$, THF, MeOH, EtOH or H_2O at 0 to 60°C.

Preferred conditions are 2N HCl in EtOH at reflux for 1 -3 hrs.

PROCEDURE D

Synthesis of C-C-linked 2-methyl-4-imidazoles

Scheme 4

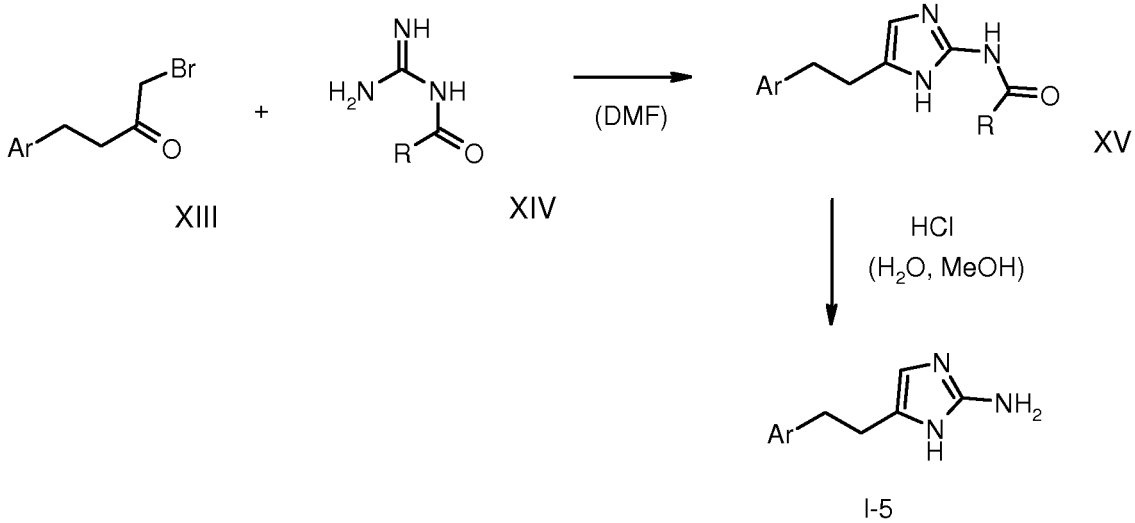


An appropriate olefin such as aryl-1-butene (XII) can be reacted at lower temperature with a nitrile such as acetonitrile and nitrosonium fluoroborate to form an imidazole-N-oxide according to Scheinbaum et al. (Tetrahedron Lett. 1971, p. 2205). To form the imidazole derivative I-4 the hydroxyfunction can be removed by various reducing agents such as Red-Al, Titanium(III)-salts, Lithiumaluminiumhydride or others as described by Lipshutz et al. in Tetrahedron Lett. 25, 1984, p. 1319.

PROCEDURE E

Synthesis of C-C-linked 2-amino-4-imidazoles

Scheme 5

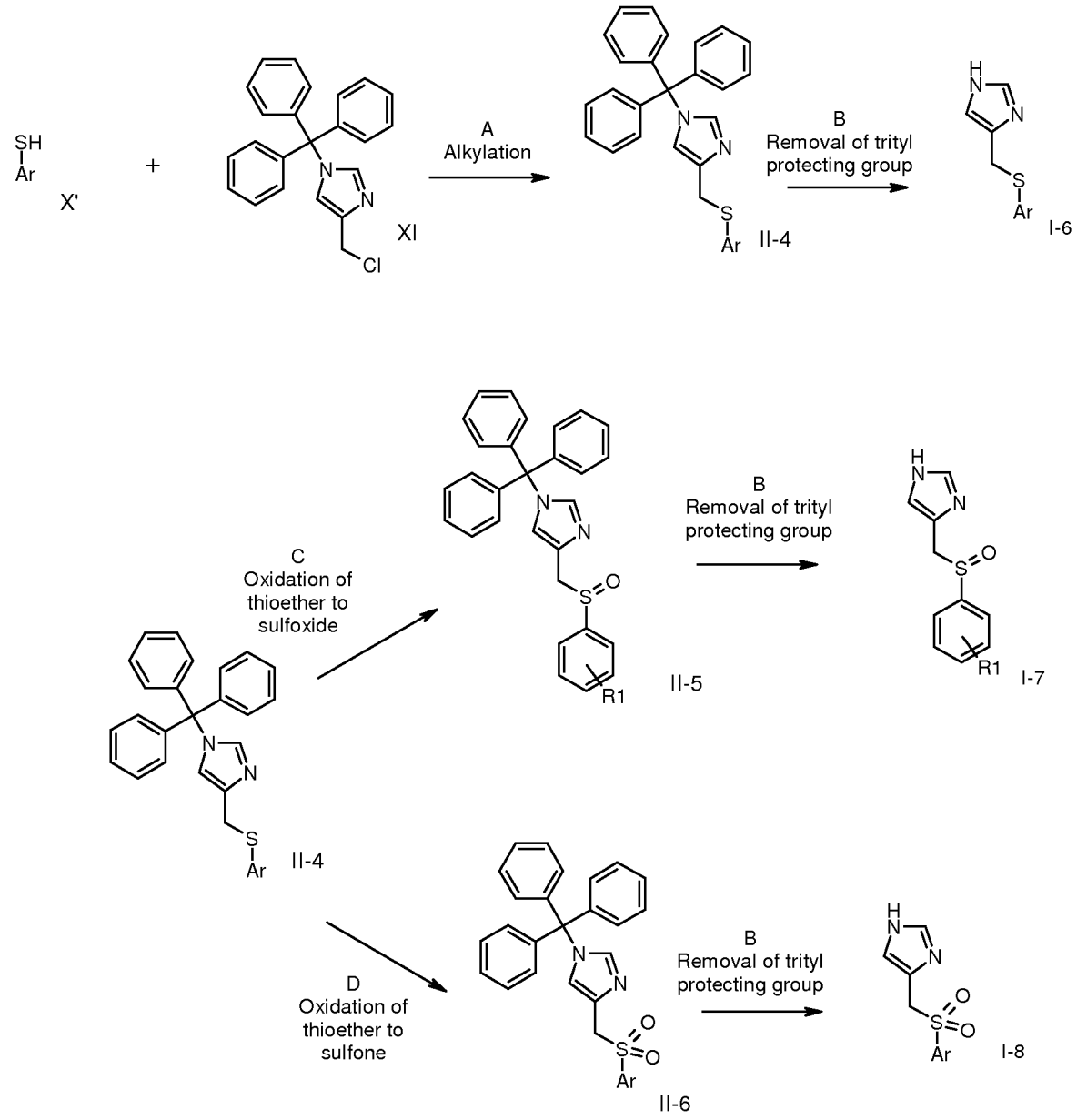


An alpha-bromoketone of formula XIII is reacted with an protected guanidine such as acetylguanidine (XIV) in a solvent such as dimethylformamide followed by deprotection of the amino group to form 2-aminoimidazole I-5. This deprotection can be achieved for instance by acid or base catalysed hydrolysis, in case of the acetyl group most favourable by treatment with hydrochloric acid in a polar solvent such as water, alkohols or mixtures of water and alkohols.

PROCEDURE F

Synthesis of C-S-linked compounds

Scheme 6



Step A: The alkylation of a substituted phenol (X) with 4-chloromethyl-1-trityl-1H-imidazole (XI) can be accomplished using a base such as K_2CO_3, Cs_2CO_3, Na_2CO_3, $NaHCO_3$, aqueous NaOH, KOH, LiOH, NaH, NaOMe, NaOEt or triethylamine in a solvent such as acetone, DMF, DMSO, acetonitrile, toluene, EtOH or MeOH and optionally if appropriate a phase transfer catalyst such as tetrabutylammonium bromide or an additive such as a crown ether, tetrabutylammonium iodide or potassium iodide at r.t. – 120°C for 1 -24 hrs.

Preferred conditions are K_2CO_3 in DMF at 80°C for 5 hrs.

Step B: The cleavage of the trityl group can be effected with a mineral acid such as HCl, H_2SO_4 or H_3PO_4 or a organic acid such as CF_3COOH, $CHCl_2COOH$, HOAc or p-

toluonesulfonic acid in a solvent such as CH_2Cl_2, $CHCl_3$, THF, MeOH, EtOH or H_2O at 0 to 60°C.

Preferred conditions are 2N HCl in EtOH at reflux for 1 -3 hrs.

Step C: The oxidation of the thioether (II-4) to the corresponding sulfoxide (II-5) can be accomplished by oxidants such as mCPBA, isopropyl 2-iodoxybenzoate, oxone or natriumperiodate in a solvent such as CH_2Cl_2, dichloroethane, toluene, acetonitrile, MeOH at temperatures from 0°C – reflux.

Preferred conditions are 1 equivalent of mCPBA in CH_2Cl_2 at 0°C – rt. for 1 – 5 hrs.

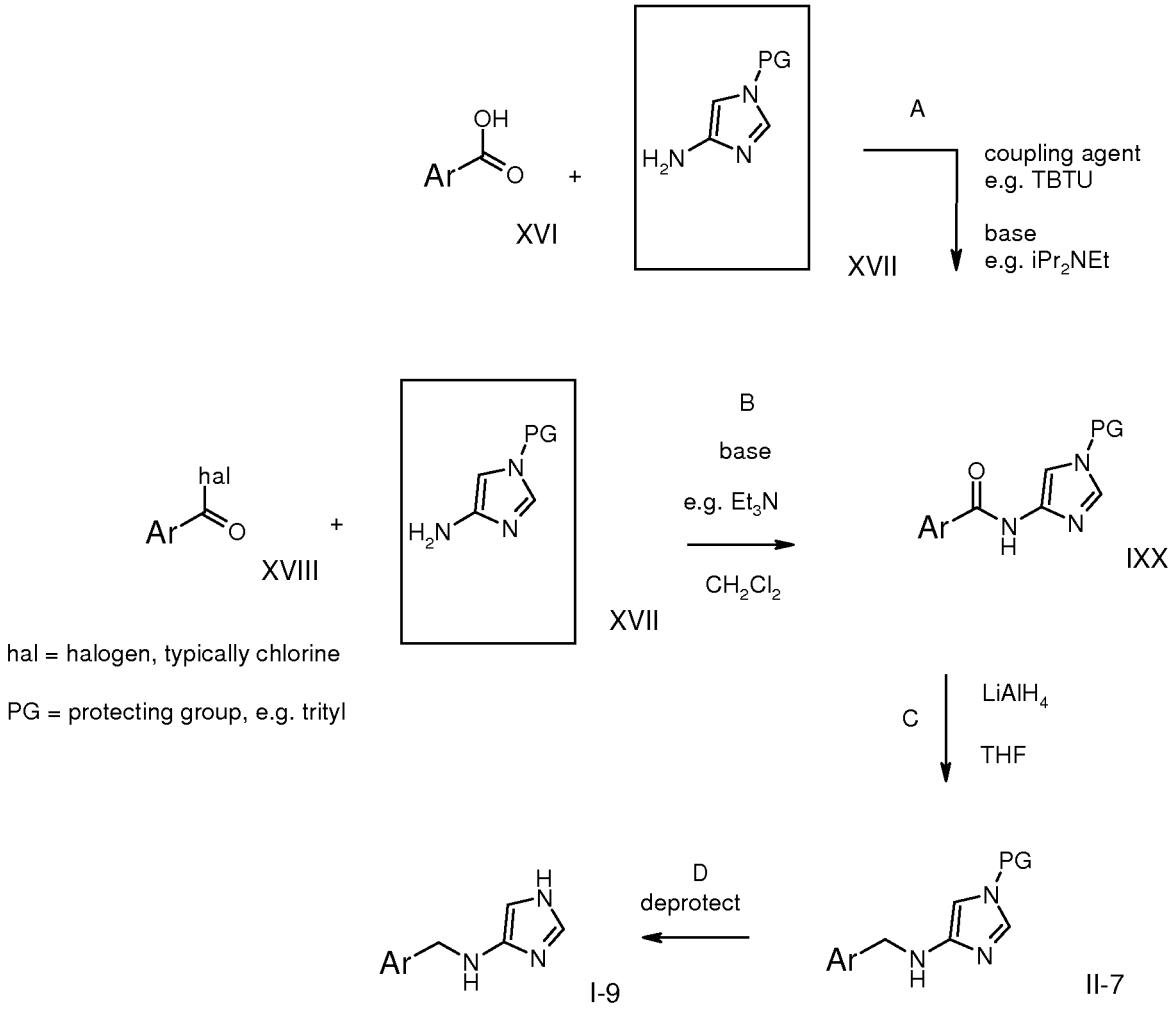
Step D: The oxidation of the thioether (II-4) to the corresponding sulfoxide (II-6) can be accomplished by oxidants such as mCPBA, H_2O_2, oxone or sodium wolframate in a solvent such as CH_2Cl_2, dichloroethane, toluene, acetonitrile, THF, acetone, MeOH at temperatures from 0°C – reflux.

Preferred conditions are 2 equivalent of mCPBA in CH_2Cl_2 at 0°C – r.t. for 1 – 5 hrs.

PROCEDURE E

Synthesis of C-N-linked compounds

Scheme 7



Step A: The coupling of a substituted arylcarboxylic acid (XVI) with a suitably protected 4-amino-imidazole compound (XVII) to afford an amide compound (IXX) can be accomplished using a coupling agent such as 2-(1h-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or 2-(1h-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or o-(7-azabenzotriazol-1-yl)-n,n,n',n'-tetramethyluronium hexafluorophosphate (HATU) and a base such as triethylamine or ethyldiisopropylamine in a solvent such as THF, DMF, or dichloromethane. Suitable nitrogen protecting groups include tert-butoxycarbamate (BOC), trityl, dimethylaminosulfonyl and trimethylsilyl-ethyl (SEM).

Preferred conditions are TBTU and ethyldiisopropylamine in DMF at 40 °C for 16 hrs, and a preferred protecting group is trityl.

Step B: The coupling of a substituted arylcarboxylic acid chloride (XVIII) with a suitably protected 4-amino-imidazole compound (XVII) to afford an amide compound (IXX) can be accomplished using a base such as pyridine, triethylamine or ethyldiisopropylamine in a solvent such as THF, DMF or dichloromethane and optionally using a catalyst such as N,N-dimethylformamide or 4-N,N-dimethylaminopyridine (DMAP)

Preferred conditions are triethylamine in dichloromethane at room temperature for 1 hr, and a preferred protecting group is trityl.

Step C: The reduction of an amide (IXX) to an amine (II-7) can be accomplished using a metal hydride reducing agent such as lithium aluminium hydride or a borane reagent such as borane-tetrahydrofuran complex in a solvent such as dioxane, ether or tetrahydrofuran at elevated temperature.

Preferred conditions are lithium aluminium hydride in tetrahydrofuran at reflux temperature for 16 hrs.

Step D: The deprotection conditions depend on the nature of the protecting group employed and many methods are well known in the art.

In the case of the trityl protecting group, preferred deprotection conditions are 4 M aqueous hydrochloric acid in dioxane at room temperature for 1-2 hours.

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

<0.1 μM as shown in the table below.

Example	Ki (μM) mouse	Example	Ki
1	0.0609	39	0.0684
5	0.0059	42	0.0041
8	0.0843	46	0.0146
11	0.0025	47	0.0103
12	0.0097	A	0.017
13	0.0106	B	0.0728
14	0.0606	E	0.0036
16	0.0172	F	0.0693
17	0.0019	J	0.0536
20	0.043	K	0.0762
35	0.0889	L	0.044
36	0.0227	N	0.0638
37	0.0802		

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.

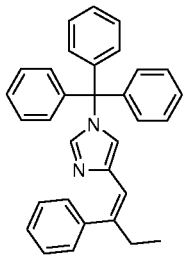
Experimental

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

Example 1

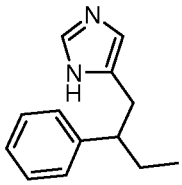
4-(2-Phenyl-butyl)-1H-imidazole

a) 4-(2-Phenyl-but-1-enyl)-1-trityl-1H-imidazole



To a stirred solution of (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (1.24 g; CAS 473659-21-1) at r.t. in THF (20 ml) under an argon atmosphere was added potassium tert-butylate (301 mg). After 15 min stirring at r.t., propiophenone (0.3 ml) was added in one portion. The mixture was heated to 80°C and stirring at that temperature was continued for 2 days. The compact suspension was cooled to r.t. and the solid was filtered off and washed with THF. The filtrate was concentrated to leave a dark violet viscous oil. This was taken up in EtOAc and washed with brine. The aqueous phase was back extracted with EtOAc. The combined organics were washed with 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 4-(2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (269 mg; not completely pure) as off-white solid. MS (ISP): 243.2 ($[Trt]^+$)

b) 4-(2-Phenyl-butyl)-1H-imidazole

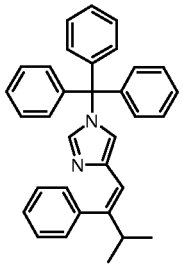


To a stirred solution of 4-(2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (260 mg) at r.t. in methanol (5 ml) and dichloromethane (2 ml) under an argon atmosphere was added 10% Pd/C (26 mg). The mixture was then stirred at r.t. under a hydrogen atmosphere for 17 h. The catalyst was filtered off and washed with methanol. The filtrate was concentrated. The crude product was purified by column chromatogrphy (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1 to give 4-(2-phenyl-butyl)-1H-imidazole (18 mg) as colorless gum. MS (ISP): 201.3 ($[M+H]^+$)

Example 2

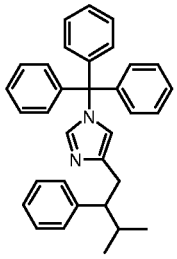
4-(3-Methyl-2-phenyl-butyl)-1H-imidazole

a) 4-(3-Methyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole



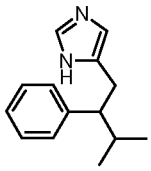
To a stirred suspension of (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (921 mg; CAS 473659-21-1) at r.t. in THF (20 ml) under an argon atmosphere was added potassium tert-butylate (241 mg). The mixture was then stirred at r.t. for 15 min, and isobutyrophenone (0.25 ml) was added in one portion. The mixture (clear brown orange solution) was heated to 80°C for 21 h. The reaction mixture was filtered and the cake was washed with EtOAc. The filtrate was concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 1:1) to give 4-(3-methyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (91 mg; not completely pure) as orange sticky solid. MS (ISP): 243.2 ($[Trt]^+$)

b) 4-(3-Methyl-2-phenyl-butyl)-1-trityl-1H-imidazole



To a stirred solution of 4-(3-methyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (87 mg) at r.t. in methanol (4 ml) and CH_2Cl_2 (1 ml) under an argon atmosphere was added the 10% Pd/C (10 mg). The mixture was then stirred at r.t. under a hydrogen atmosphere for 38 h. The catalyst was filtered off and washed with MeOH. The filtrate was concentrated to leave 4-(3-methyl-2-phenyl-butyl)-1-trityl-1H-imidazole (82 mg) of an off-white sticky solid which was used in the next step without further purification. MS (ISP): 243.2 ($[Trt]^+$)

c) 4-(3-Methyl-2-phenyl-butyl)-1H-imidazole

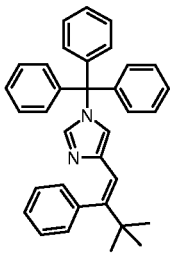


To a stirred suspension of 4-(3-methyl-2-phenyl-butyl)-1-trityl-1H-imidazole (80 mg) at r.t. in ethanol (2 ml) under an argon atmosphere was added 2 N HCl (3 ml). The mixture (suspension) was heated to reflux (turning to a clear light yellow solution when reaching 90 °C) and stirred for 2 h 30, then cooled to r.t. and concentrated to leave a light brown sticky solid. This was taken up in H_2O and basified to pH > 12 by the addition of 4 N NaOH. The product was extracted with CH_2Cl_2/MeOH 9:1. The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2-> CH_2Cl_2/MeOH 85:15) to give 4-(3-methyl-2-phenyl-butyl)-1H-imidazole (8 mg) as colorless gum. MS (ISP): 215.4 ($[M+H]^+$)

Example 3

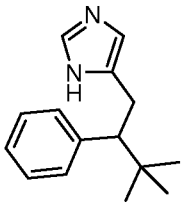
4-(3,3-Dimethyl-2-phenyl-butyl)-1H-imidazole

a) 4-(3,3-Dimethyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole



To a stirred suspension of (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (341 mg; CAS 473659-21-1) at r.t. in THF (7.5 ml) under an argon atmosphere was added potassium tert-butylate (83 mg). The mixture was then stirred at r.t. for 15 min, and 2,2-dimethylpropiophenone (0.1 ml) was added in one portion. The mixture (clear brown orange solution) was heated to 80°C and stirring at that temperature was continued for 24 h. The reaction mixture was directly adsorbed on silica gel. The product was isolated by chromatography (gradient: cyclohexane -> cyclohexane/EtOAc 65:35) to give 4-(3,3-dimethyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (135 mg; not completely pure) as light yellow solid. MS (ISP): 243.2 ($[Trt]^+$)

b) 4-(3,3-Dimethyl-2-phenyl-butyl)-1H-imidazole

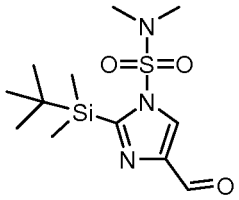


To a stirred solution of 4-(3,3-dimethyl-2-phenyl-but-1-enyl)-1-trityl-1H-imidazole (121 mg) at r.t. in methanol (5 ml) and dichloromethane (1 ml) under an argon atmosphere was added 10% Pd/C (12 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 17 h. The catalyst was filtered off and washed with methanol. The filtrate was concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give 4-(3,3-dimethyl-2-phenyl-butyl)-1H-imidazole (25 mg) as colorless gum. MS (ISP): 229.4 ($[M+H]^+$)

Example 4

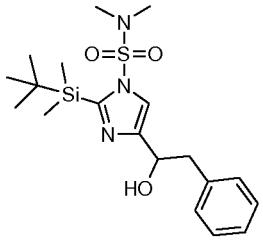
4-(1-Methoxy-2-phenyl-ethyl)-1H-imidazole

a) 2-(tert-Butyl-dimethyl-silanyl)-4-formyl-imidazole-1-sulfonic acid dimethylamide



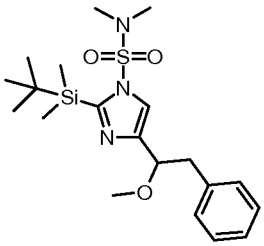
To a stirred, cooled (-78°C) solution of 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide (1.02 g; CAS 129378-52-5) in THF (20 ml) under an argon atmosphere was added dropwise butyl lithium (3.3 ml; 1.6 M solution in hexanes) over a period of 10 min. After 30 min stirring, DMF (1.3 ml) was added over a period of 5 min and the mixture (clear light yellow solution) was stirred at -78°C for another 2 h. The mixture was quenched with sat. aq. NH_4Cl and diluted with EtOAc. 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 give 2-(tert-butyl-dimethyl-silanyl)-4-formyl-imidazole-1-sulfonic acid dimethylamide (1.22 g) as viscous orange oil which was used in the next reaction step without further purification. MS (ISP): 318.3 ($[M+H]^+$)

b) 2-(tert-Butyl-dimethyl-silanyl)-4-(1-hydroxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide



Benzyl bromide (4.1 ml) was added dropwise to a stirred suspension of magnesium (1.01 g) in diethyl ether (10 ml). When the vigourously exothermic reaction was complete, the supernatant solution was decanted from the solid and kept in the fridge, ready for use. An aliquot of this solution (1 ml) was added dropwise (exothermic!) to a cooled (0°C, ice bath) stirred solution of 2-(tert-butyl-dimethyl-silanyl)-4-formyl-imidazole-1-sulfonic acid dimethylamide (725 mg) at r.t. in THF (5 ml) under an argon atmosphere. When addition was complete, stirring at r.t. was continued overnight. The mixture was quenched by the addition of sat. aq. NH_4Cl and extracted with EtOAc. 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. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 25:75) to give 2-(tert-butyl-dimethyl-silanyl)-4-(1-hydroxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide (168 mg) as light yellow solid. MS (ISP): 410.1 ($[M+H]^+$)

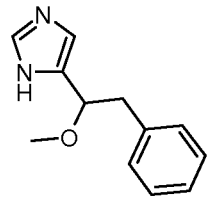
c) 2-(tert-Butyl-dimethyl-silanyl)-4-(1-methoxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide



To a stirred solution of 2-(tert-butyl-dimethyl-silanyl)-4-(1-hydroxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide (160 mg) at r.t. in THF (5 ml) under an argon atmosphere was added NaH (18 mg; 55 % dispersion in mineral oil) in one portion. After 1 h stirring at r.t., MeI (0.04 ml) was added and stirring at r.t. was continued overnight. The mixture was diluted with EtOAc and washed with H_2O. 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. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 65:35) to give 2-

(tert-butyl-dimethyl-silanyl)-4-(1-methoxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide (111 mg) as light yellow viscous oil. MS (ISP): 424.3 ($[M+H]^+$)

d) 4-(1-Methoxy-2-phenyl-ethyl)-1H-imidazole

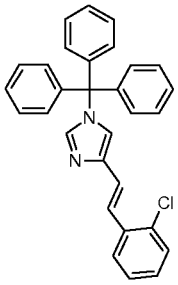


To a stirred suspension of 2-(tert-butyl-dimethyl-silanyl)-4-(1-methoxy-2-phenyl-ethyl)-imidazole-1-sulfonic acid dimethylamide (105 mg) at r.t. in ethanol (3 ml) under an argon atmosphere was added 2 N HCl (3 ml). The mixture was heated to reflux for 3 h. The mixture was cooled to r.t. and concentrated to leave a light yellow solid which was taken up in H2O and brought to pH 12 by the addition of 4 N NaOH. The product was extracted with CH_2Cl_2/MeOH 4:1. The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give 4-(1-methoxy-2-phenyl-ethyl)-1H-imidazole (38 mg) as white solid. MS (ISP): 203.4 ($[M+H]^+$)

Example 5

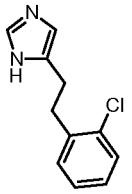
4-[2-(2-Chloro-phenyl)-ethyl]-1H-imidazole

a) 4-[2-(2-Chloro-phenyl)-vinyl]-1-trityl-1H-imidazole



To a stirred suspension of (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (448 mg; CAS 473659-21-1) at r.t. in THF (7 ml) under an argon atmosphere were added potassium tert-butylate (109 mg) and 2-chlorobenzaldehyde (114 mg). The mixture (clear brown orange solution) was heated to 80°C over night. The reaction mixture was cooled to r.t and concentrated. The crude product was purified by column chormatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 3:2) to give 4-[2-(2-chloro-phenyl)-vinyl]-1-trityl-1H-imidazole (329 mg) as off-white solid . MS (ISP): 243.3 ($[Trt]^+$)

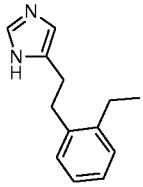
b) 4-[2-(2-Chloro-phenyl)-ethyl]-1H-imidazole



To a stirred mixture of 4-[2-(2-chloro-phenyl)-vinyl]-1-trityl-1H-imidazole (329 mg) at r.t. in ethanol (7 ml) and chloroform (3 ml) under an argon atmosphere were added acetic acid (0.2 ml) and 10% Pd/C (30 mg). The mixture was hydrogenated (ambient pressure) over night. The catalyst was filtered off and washed with ethanol. The mixture was concentrated to leave a light brown gum. This material was taken up in ethanol (3 ml) and 2 N HCl (3 ml) and heated to reflux for 3 h. Then, the mixture was cooled to r.t., concentrated. The residual solid was taken up in 1 N NaOH (10 ml) and extracted with CH_2Cl_2/MeOH 4:1. The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give 4-[2-(2-chloro-phenyl)-ethyl]-1H-imidazole (44 mg) as light brown gum. MS (ISP): 207.1 ($[M+H]^+$)

Example 6

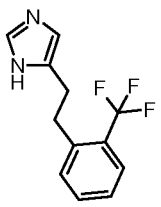
4-[2-(2-Ethyl-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 2-ethylbenzaldehyde and then converted to 4-[2-(2-ethyl-phenyl)-ethyl]-1H-imidazole. Colorless viscous oil. MS (ISP): 201.3 ($[M+H]^+$)

Example 7

4-[2-(2-Trifluoromethyl-phenyl)-ethyl]-1H-imidazole

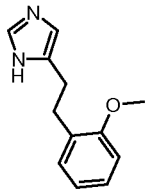


In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 2-(trifluormethyl)benzaldehyde and then converted

to 4-[2-(2-trifluoromethyl-phenyl)-ethyl]-1H-imidazole. Colorless viscous oil. MS (ISP): 241.3 ($[M+H]^+$)

Example 8

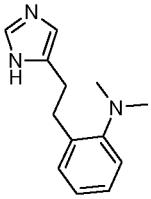
4-[2-(2-Methoxy-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 2-methoxybenzaldehyde and then converted to 4-[2-(2-methoxy-phenyl)-ethyl]-1H-imidazole. Colorless viscous oil. MS (ISP): 203.1 ($[M+H]^+$)

Example 9

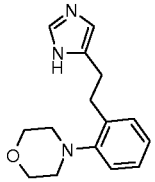
{2-[2-(1H-Imidazol-4-yl)-ethyl]-phenyl}-dimethyl-amine



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 2-(N,N-dimethylamino)benzaldehyde and then converted to {2-[2-(1H-Imidazol-4-yl)-ethyl]-phenyl}-dimethyl-amine. Light yellow viscous oil. MS (ISP): 216.3 ($[M+H]^+$)

Example 10

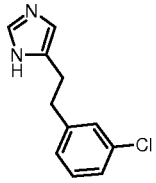
4-{2-[2-(1H-Imidazol-4-yl)-ethyl]-phenyl}-morpholine



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 2-morpholinobenzaldehyde and then converted to 4-{2-[2-(1H-imidazol-4-yl)-ethyl]-phenyl}-morpholine. Light yellow viscous oil. MS (ISP): 258.3 ($[M+H]^+$)

Example 11

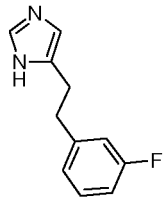
4-[2-(3-Chloro-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3-chlorobenzaldehyde and then converted to 4-[2-(3-chloro-phenyl)-ethyl]-1H-imidazole. Off-white solid. MS (ISP): 207.1 ($[M+H]^+$)

Example 12

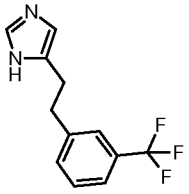
4-[2-(3-Fluoro-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3-fluorobenzaldehyde and then converted to 4-[2-(3-fluoro-phenyl)-ethyl]-1H-imidazole. Off-white solid. MS (ISP): 191.1 ($[M+H]^+$)

Example 13

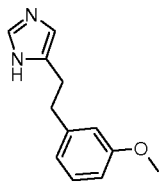
4-[2-(3-Trifluoromethyl-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3-(trifluoromethyl)benzaldehyde and then converted to 4-[2-(3-trifluoromethyl-phenyl)-ethyl]-1H-imidazole. Off-white viscous oil. MS (ISP): 241.1 ($[M+H]^+$)

Example 14

4-[2-(3-Methoxy-phenyl)-ethyl]-1H-imidazole

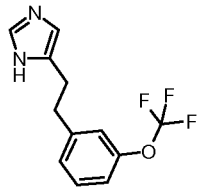


In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3-methoxybenzaldehyde and then converted to 4-

[2-(3-methoxy-phenyl)-ethyl]-1H-imidazole. Off-white solid. MS (ISP): 203.3 ($[M+H]^+$)

Example 15

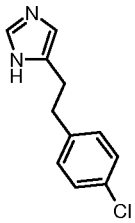
4-[2-(3-Trifluoromethoxy-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3-(trifluoromethoxy)benzaldehyde and then converted to 4-[2-(3-trifluoromethoxy-phenyl)-ethyl]-1H-imidazole. Light yellow viscous oil. MS (ISP): 257.3 ($[M+H]^+$)

Example 16

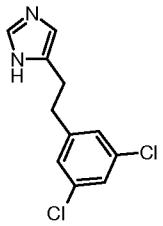
4-[2-(4-Chloro-phenyl)-ethyl]-1H-imidazole



In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 4-chlorobenzaldehyde and then converted to 4-[2-(4-chloro-phenyl)-ethyl]-1H-imidazole. Off-white solid. MS (ISP): 207.1 ($[M+H]^+$)

Example 17

4-[2-(3,5-Dichloro-phenyl)-ethyl]-1H-imidazole

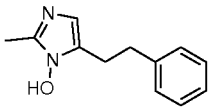


In analogy to example 5 (1-trityl-1H-imidazol-4-ylmethyl)-phosphonic acid diethyl ester (CAS 473659-21-1) was reacted with 3,5-dichlorobenzaldehyde and then converted to 4-[2-(3,5-dichloro-phenyl)-ethyl]-1H-imidazole. Off-white solid. MS (ISP): 241.1 ($[M+H]^+$)

Example 18

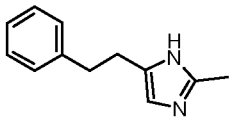
2-Methyl-5-phenethyl-1H-imidazole

a) 2-Methyl-5-phenethyl-imidazol-1-ol



To a solution of nitrosonium tetrafluoroborate (0.564 g, 4.83 mmol) in acetonitrile (8 ml) 4-phenyl-1-butene was added at -30°C. The mixture was stirred for 1 hour at this temperature, then 0.5 ml of water was added carefully. At room temperature saturated ammonium chloride solution was added and the acetonitrile was evaporated in vacuo. The pH of the remaining aqueous solution was adjusted to neutral with a small amount of sodium hydroxide and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate and evaporated. The residue was purified using flash chromatography (SiO_2, dichloromethane/methanol = 9:1) to yield an off-white solid (0.245 g, 17%); MS (ISP): 202.9 ($[M+H]^+$)

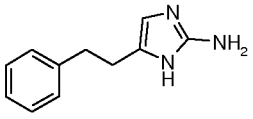
b) 2-Methyl-5-phenethyl-1H-imidazole



To a solution of 2-methyl-5-phenethyl-imidazol-1-ol (0.20 g, 1.0 mmol) in methanol (3.5 ml) titanium(III)-chloride solution (2.5 ml, 15%) was added and the mixture was stirred overnight at room temperature. First saturated sodium bicarbonate solution then diluted sodium hydroxide solution was added to achieve a basic pH. The mixture was extracted twice with dichloromethane, the combined organic layers were dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (dichloromethane/methanol = 9:1) to yield a white solid (0.14 mg, 75%); MS (EI): 186.1 ($M^{+\cdot}$).

Example 19

5-Phenethyl-1H-imidazol-2-ylamine



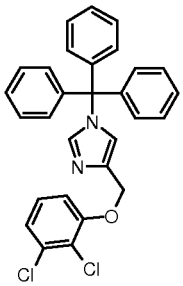
To a solution of 1-acetylguanidine (1.34 g, 13.2 mmol) in dimethylformamide (7 ml) a solution of 1-bromo-4-phenyl-butan-2-one (1.5 g, 6.6 mmol) in dimethylformamide (7 ml) was added at 0°C. The mixture was stirred overnight at room temperature and then the solvent was evaporated. Upon addition of ethyl acetate/heptane (1:1) a white solid was formed that was filtered off and washed with ethyl acetate/heptane (1:1). After drying

in vacuo the solid was dissolved in a mixture of concentrated hydrochloric acid (2 ml) and methanol (4 ml) and stirred for 2.5 hours at 85°C. The solvent was evaporated and the residue was purified by chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate/methanol=1:1) to yield a light yellow solid (0.063 mg, 5%); MS (EI): 187.2 ($M^{+\cdot}$).

Example 20

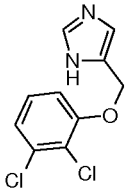
4-(2,3-Dichloro-phenoxymethyl)-1H-imidazole

a) 4-(2,3-Dichloro-phenoxymethyl)-1-trityl-1H-imidazole



To a stirred solution of 4-chloromethyl-1-trityl-1H-imidazole (400 mg; CAS 103057-10-9) at r.t. in DMF (5 ml) under an argon atmosphere were added 2,3-dichlorophenol (273 mg) and K_2CO_3 (385 mg). The reaction mixture was heated to 80°C for 5 hrs, then cooled to r.t., diluted with EtOAc and washed with 1 N NaOH. 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. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 1:1) to give 4-(2,3-dichloro-phenoxymethyl)-1-trityl-1H-imidazole (360 mg) as white solid. MS (ISP): 243.3 ($[Trt]^+$)

b) 4-(2,3-Dichloro-phenoxymethyl)-1H-imidazole

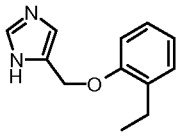


To a stirred suspension of 4-(2,3-dichloro-phenoxymethyl)-1-trityl-1H-imidazole (150 mg) at r.t. in ethanol (2 ml) under an argon atmosphere was added 2 N HCl (3 ml). The mixture was heated to reflux for 6 hrs, then concentrated to leave an off-white solid. This was taken up in saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2/MeOH 4:1. The combined organics were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 ->

CH_2Cl_2/MeOH 4:1) to give 4-(2,3-dichloro-phenoxymethyl)-1H-imidazole (65 mg) as white solid. MS (ISP): 243.4 ($[M+H]^+$)

Example 21

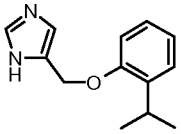
4-(2-Ethyl-phenoxymethyl)-1H-imidazole



In analogy to example 21 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-ethylphenol and then converted to 4-(2-ethyl-phenoxymethyl)-1H-imidazole. Waxy off-white solid. MS (ISP): 203.1 ($[M+H]^+$)

Example 22

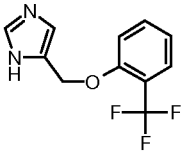
4-(2-Isopropyl-phenoxymethyl)-1H-imidazol



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-isopropylphenol and then converted to 4-(2-isopropyl-phenoxymethyl)-1H-imidazole. Waxy off-white solid. MS (ISP): 217.4 ($[M+H]^+$)

Example 23

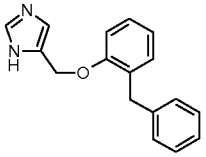
4-(2-Trifluoromethyl-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-trifluoromethylphenol and then converted to 4-(2-trifluoromethyl-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 243.4 ($[M+H]^+$)

Example 24

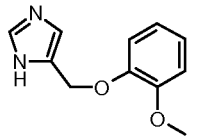
4-(2-Benzyl-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-benzylphenol and then converted to 4-(2-benzyl-phenoxymethyl)-1H-imidazole. Waxy white solid. MS (ISP): 265.1 ($[M+H]^+$)

Example 25

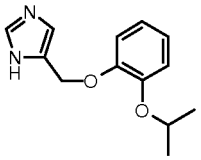
4-(2-Methoxy-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-methoxyphenol and then converted to 4-(2-methoxy-phenoxymethyl)-1H-imidazole. Off-white amorphous solid. MS (ISP): 205.1 ($[M+H]^+$)

Example 26

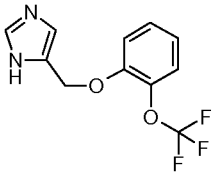
4-(2-Isopropoxy-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-isopropoxyphenol and then converted to 4-(2-isopropoxy-phenoxymethyl)-1H-imidazole. Off-white solid. MS (ISP): 233.3 ($[M+H]^+$)

Example 27

4-(2-Trifluoromethoxy-phenoxymethyl)-1H-imidazole

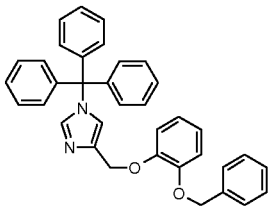


In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-trifluoromethoxyphenol and then converted to 4-(2-trifluoromethoxy-phenoxymethyl)-1H-imidazole. Off-white solid. MS (ISP): 259.1 ($[M+H]^+$)

Example 28

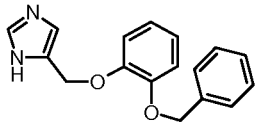
4-(2-Benzyloxy-phenoxymethyl)-1H-imidazole

a) 4-(2-Benzyloxy-phenoxymethyl)-1-trityl-1H-imidazole



In analogy to example 20.a. 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2-benzyloxyphenol to give 4-(2-benzyloxy-phenoxymethyl)-1-trityl-1H-imidazole. Yellow viscous oil. MS (ISP): 523.5 ($[M+H]^+$)

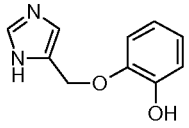
b) 4-(2-Benzyloxy-phenoxymethyl)-1H-imidazole



A solution of 4-(2-benzyloxy-phenoxymethyl)-1-trityl-1H-imidazole (34 mg) in MeOH (2 ml) was treated with AcOH (0.1 ml) and was heated to 70°C for 5 hrs. The mixture was concentrated. The crude product was purified by column chromatography to give 4-(2-benzyloxy-phenoxymethyl)-1H-imidazole (11 mg) as colorless amorphous solid. MS (ISP): 281.4 ($[M+H]^+$)

Example 29

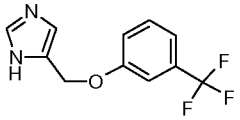
2-(1H-Imidazol-4-ylmethoxy)-phenol



Under conditions as described in example 20.b 4-(2-benzyloxy-phenoxymethyl)-1-trityl-1H-imidazole (example 28.a) was converted to 2-(1H-Imidazol-4-ylmethoxy)-phenol. Off-white solid. MS (ISP): 191.4 ($[M+H]^+$)

Example 30

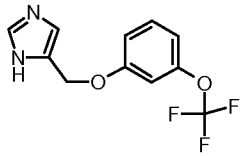
4-(3-Trifluoromethyl-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3-trifluoromethylphenol and then converted to 4-(3-trifluoromethyl-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 243.3 ($[M+H]^+$)

Example 31

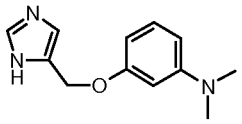
4-(3-Trifluoromethoxy-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3-trifluoromethoxyphenol and then converted to 4-(3-trifluoromethoxy-phenoxymethyl)-1H-imidazole. Colorless oil. MS (ISP): 259.0 ($[M+H]^+$)

Example 32

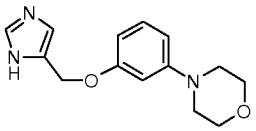
[3-(1H-Imidazol-4-ylmethoxy)-phenyl]-dimethyl-amine



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3-dimethylaminophenol and then converted to [3-(1H-imidazol-4-ylmethoxy)-phenyl]-dimethyl-amine. Off-white solid. MS (ISP): 218.4 ($[M+H]^+$)

Example 33

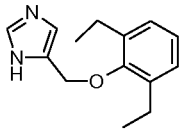
4-[-(1H-Imidazol-4-ylmethoxy)-phenyl]-morpholine



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3-morpholinophenol and converted to 4-[3-(1H-imdazol-4-ylmethoxy)-phenyl]-morpholine. White solid. MS (ISP): 260.3 ($[M+H]^+$)

Example 34

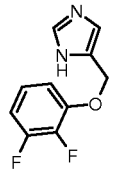
4-(2,6-Diethyl-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2,6-diethylphenol and converted to 4-(2,6-diethyl-phenoxymethyl)-1H-imidazole. Colorless oil. MS (ISP): 231.4 ($[M+H]^+$)

Example 35

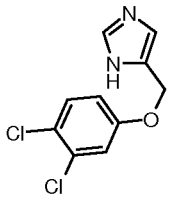
4-(2,3-Difluoro-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 2,3-difluorophenol and converted to 4-(2,3-difluoro-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 211.1 ($[M+H]^+$)

Example 36

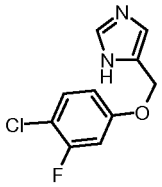
4-(3,4-Dichloro-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3,4-dichlorophenol and converted to 4-(3,4-dichloro-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 243.1 ($[M+H]^+$)

Example 37

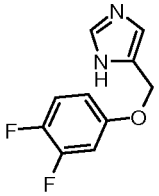
4-(4-Chloro-3-fluoro-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 4-chloro-3-fluorophenol and converted to 4-(4-chloro-3-fluoro-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 227.1 ($[M+H]^+$)

Example 38

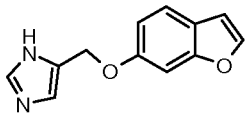
4-(3,4-Difluoro-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3,4-difluorophenol and converted to 4-(3,4-difluoro-phenoxymethyl)-1H-imidazole. White solid. MS (ISP): 211.1 ($[M+H]^+$)

Example 39

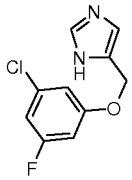
5-(Benzofuran-6-yloxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 6-hydroxybenzofurane and converted to 5-(benzofuran-6-yloxymethyl)-1H-imidazole.

Example 40

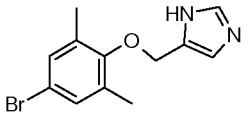
4-(3-Chloro-5-fluoro-phenoxymethyl)-1H-imidazole



In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 3-chloro-5-fluorophenol and converted to 4-(3-chloro-5-fluoro-phenoxymethyl)-1H-imidazole. Off-white amorphous solid. MS (ISP): 227.1 ($[M+H]^+$)

Example 41

5-(4-Bromo-2,6-dimethyl-phenoxymethyl)-1H-imidazole

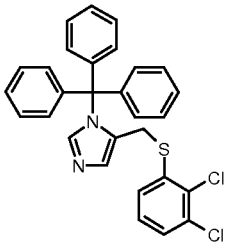


In analogy to example 20 4-chloromethyl-1-trityl-1H-imidazole (CAS 103057-10-9) was reacted with 4-bromo-2,6-dimethylphenol and converted to 5-(4-bromo-2,6-dimethyl-phenoxymethyl)-1H-imidazole.

Example 42

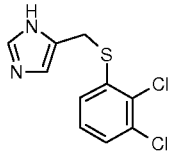
5-(2,3-Dichloro-phenylsulfanylmethyl)-1-imidazole

a) 5-(2,3-Dichloro-phenylsulfanylmethyl)-1-trityl-1-imidazole



A solution of 4-chloromethyl-1-trityl-1H-imidazole (600 mgl; CAS 103057-10-9) in DMF (12 ml) was treated under an Argon atmosphere with potassium carbonate (578 mg) and 2,3-dichlorobenzenethiol (449 mg). The reaction mixture was heated to 80°C for 5 hrs, then cooled to r.t., taken up in water and extracted with EtOAc. The organic layer was washed with water, dried over MgSO4 and concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 1:1) to give 5-(2,3-dichloro-phenylsulfanylmethyl)-1-trityl-1-imidazole (564 mg) as off-white solid. MS (ISP): 243.3 ($[Trt]^+$)

b) 5-(2,3-Dichloro-phenylsulfanylmethyl)-1-imidazole

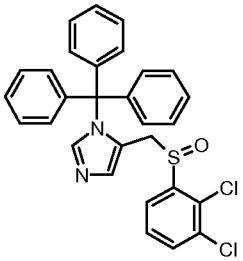


In analogy to example 20.b 5-(2,3-dichloro-phenylsulfanylmethyl)-1-trityl-1-imidazole was converted to 5-(2,3-dichloro-phenylsulfanylmethyl)-1-imidazole. Off-white solid. MS (ISP): 259.0 ($[M+H]^+$)

Example 43

5-(2,3-Dichloro-benzenesulfinylmethyl)-1-imidazole

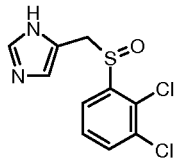
a) 5-(2,3-Dichloro-benzenesulfinylmethyl)-1-trityl-1-imidazole



A solution of 5-(2,3-dichloro-phenylsulfanylmethyl)-1-trityl-1-imidazole (250 mg; example 42.a) in CH_2Cl_2 (20 ml) was cooled under an Argon atmosphere to 0° and treated with meta-chloroperbenzoic acid (86 mg). The reaction mixture was stirred for 3 hrs at 0°C, then concentrated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 98:2) to give 5-(2,3-

dichloro-benzenesulfinylmethyl)-1-trityl-1-imidazole (121 mg) as white solid. MS (ISP): 517.3 ($[M+H]^+$)

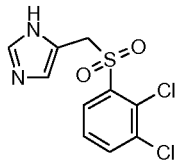
b) 5-(2,3-Dichloro-benzenesulfinylmethyl)-1-imidazole



In analogy to example 20.b 5-(2,3-dichloro-benzenesulfinylmethyl)-1-trityl-1-imidazole was converted to 5-(2,3-dichloro-benzenesulfinylmethyl)-1-imidazole. White solid. MS (ISP): 275.1 ($[M+H]^+$)

Example 44

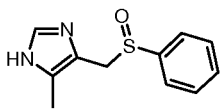
5-(2,3-Dichloro-benzenesulfonylmethyl)-1H-imidazole



In analogy to example 43, but using 2 equivalents of meta-chloroperbenzoic acid in the first reaction step 5-(2,3-dichloro-phenylsulfanylmethyl)-1-trityl-1-imidazole (250 mg; example 42.a) was converted to 5-(2,3-dichloro-benzenesulfonylmethyl)-1H-imidazole. White solid. MS (ISP): 291.0 ($[M+H]^+$)

Example 45

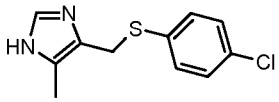
4-Benzenesulfinylmethyl-5-methyl-1H-imidazole



The title compound was prepared in analogy to example 43 using 4-chloromethyl-5-methyl-1-trityl-1H-imidazole (CAS 106147-85-7) for the alkylation of benzenethiol.

Example 46

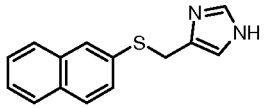
4-(4-Chloro-phenylsulfanylmethyl)-5-methyl-1H-imidazole



The title compound was prepared in analogy to example 42 using 4-chloromethyl-5-methyl-1-trityl-1H-imidazole (CAS 106147-85-7) for the alkylation of 4-chlorobenzenethiol.

Example 47

4-(Naphthalen-2-ylsulfanylmethyl)-1H-imidazole

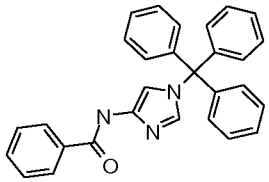


The title compound was prepared in analogy to example 42 starting from naphthalene-2-thiol.

Example 48

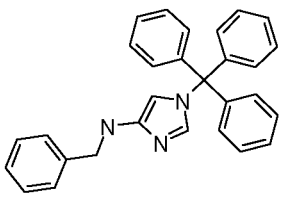
Benzyl-(1H-imidazol-4-yl)-amine hydrochloride

a) N-(1-Trityl-1H-imidazol-4-yl)-benzamide



To a solution of 4-amino-1-tritylimidazole (0.30 g, 0.92 mmol) in dichloromethane (4 ml) were added sequentially triethylamine (0.19 ml, 1.37 mmol) and benzoyl chloride (0.13 ml, 1.12 mmol). The reaction mixture was stirred at room temperature for 30 min, then diluted with dichloromethane and washed sequentially with water, saturated aq. $NaHCO_3$ solution, water and saturated brine. The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant: methanol/dichloromethane 0:100 to 10:90) to yield the title compound as an orange solid (0.36 g, 92%); MS (ISP): 430.3 ($[M+H]^+$).

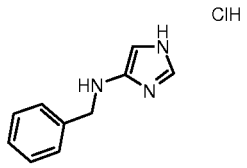
b) Benzyl-(1-trityl-1H-imidazol-4-yl)-amine



To a solution of N-(1-trityl-1H-imidazol-4-yl)-benzamide (0.36 g, 0.83 mmol) in tetrahydrofuran (10 ml) was added portionwise lithium aluminium hydride (0.16 g, 4.14 mmol). The reaction mixture was stirred at 80 °C for 16 hours, then cooled to room temperature and water added dropwise. The mixture was stirred at room temperature for 20 minutes and then extracted with ethyl acetate. The organic layer was separated, washed

with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluant: methanol/dichloromethane 0:100 to 10:90) to yield the title compound as a white solid (0.15 g, 44%); MS (ISP): 416.5 ($[M+H]^+$).

c) Benzyl-(1H-imidazol-4-yl)-amine hydrochloride



Benzyl-(1-trityl-1H-imidazol-4-yl)-amine (0.15 g, 0.35 mmol) was dissolved in a 4 M solution of HCl in dioxane (5 ml). The mixture was stirred at room temperature for 90 min and then concentrated *in vacuo*. The residue was triturated in ether to yield the title compound as an off-white solid (73 mg, 100%); MS (ISP): 174.4 ($[M+H]^+$).

Compounds of examples 1 – 48 are new. Compounds of examples A – N are known.

Examples A - N

Additionally the following known compounds were prepared as TAAR1 agonists using procedures analogous to those describe above:

A: 5-Phenethyl-1*H*-imidazole (CAS 94714-36-0)

B: 5-(2-Phenyl-propyl)-1H-imidazole (CAS 86347-25-3)

C: 1-(1H-Imidazol-4-yl)-2-phenyl-ethanol (CAS 79928-10-2)

D: 5-(2,2-Diphenyl-ethyl)-1H-imidazole (CAS 102390-63-6)

E: 4-(2-m-Tolyl-ethyl)-1H-imidazole (CAS 79928-27-1)

F: 4-[2-(2,6-Dimethyl-phenyl)-ethyl]-1H-imidazole (CAS 79924-13-3)

G: 4-(Biphenyl-2-yloxymethyl)-1H-imidazole (CAS 527696-96-4)

H: 5-(2-Methyl-2-phenyl-propyl)-1H-imidazole (Beilstein Registry Number 4407995)

I: 4-(2-Chloro-phenoxymethyl)-1H-imidazole (CAS 27325-27-5)

J: 4-(2-Fluoro-phenoxymethyl)-1H-imidazole (CAS 401-45-6)

K: 4-o-Tolyloxymethyl-1H-imidazole (CAS 762177-70-8)

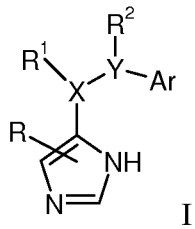
L: 4-(3-Chloro-phenoxymethyl)-1H-imidazole (CAS 802322-21-0)

M: 4-(2,6-Dimethyl-phenoxymethyl)-1H-imidazole (CAS 771450-63-6)

N: 5-Methyl-4-phenylsulfanylmethyl-1H-imidazole (CAS 700355-78-8)

Claims

1. Compounds of formula



I

wherein

R is hydrogen, lower alkyl or amino;

X-R^1 is $–CH_2$-, -CH(lower alkoxy)- or –CH(OH)- and
Y-R^2 is $–CH_2$, -CH(lower alkyl)-, -CH(lower alkoxy)- -O-, -S-, -S(O)-, -$S(O)_2$-, -CH(phenyl)- or -C(lower $alkyl)_2$-;

or

X-R^1 is –NH- and
Y-R^2 is $–CH_2$, -CH(lower alkyl)-, -CH(lower alkoxy)-, -CH(phenyl)- or -C(lower $alkyl)_2$- ;

Ar is phenyl, napthtyl or benzofuranyl, which rings are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy, lower alkoxy substituted by halogen, hydroxy, amino, di-alkylamino, morpholinyl, phenyl, benzyl or by O-benzyl;

or pharmaceutically suitable acid addition salts with the exception of
5-phenethyl-1*H*-imidazole
5-(2-phenyl-propyl)-1H-imidazole
1-(1H-imidazol-4-yl)-2-phenyl-ethanol
5-(2,2-diphenyl-ethyl)-1H-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole
4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole
4-(biphenyl-2-yloxymethyl)-1H-imidazole
5-(2-methyl-2-phenyl-propyl)-1H-imidazole

4-(2-chloro-phenoxymethyl)-1H-imidazole
4-(2-fluoro-phenoxymethyl)-1H-imidazole
4-o-tolyloxymethyl-1H-imidazole
4-(3-chloro-phenoxymethyl)-1H-imidazole
4-(2,6-dimethyl-phenoxymethyl)-1H-imidazole and
5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

2. Compounds of formula I according to claim 1, wherein X-R^1 and Y-R^2 are both CH_2.

3. Compounds of formula I according to claim 2, wherein the compounds are
4-[2-(2-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(2-methoxy-phenyl)-ethyl]-1H-imidazole
4-[2-(3-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(3-fluoro-phenyl)-ethyl]-1H-imidazole
4-[2-(3-trifluoromethyl-phenyl)-ethyl]-1H-imidazole
4-[2-(3-methoxy-phenyl)-ethyl]-1H-imidazole
4-[2-(4-chloro-phenyl)-ethyl]-1H-imidazole
4-[2-(3,5-dichloro-phenyl)-ethyl]-1H-imidazole
5-phenethyl-1*H*-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole or
4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole.

4. Compounds of formula I according to claim 1, wherein X-R^1 is CH_2 and Y-R^2 is –CH(lower alkyl).

5. Compounds of formula I according to claim 4, wherein the compounds are
4-(2-phenyl-butyl)-1H-imidazole or
5-(2-phenyl-propyl)-1H-imidazole.

6. Compounds of formula I according to claim 1, wherein X-R^1 is CH_2 and Y-R^2 is O.

7. Compounds of formula I according to claim 6, wherein the compounds are
4-(2,3-dichloro-phenoxymethyl)-1H-imidazole
4-(2,3-difluoro-phenoxymethyl)-1H-imidazole
4-(3,4-dichloro-phenoxymethyl)-1H-imidazole
4-(4-chloro-3-fluoro-phenoxymethyl)-1H-imidazole
5-(benzofuran-6-yloxymethyl)-1H-imidazole

4-o-tolyloxymethyl-1H-imidazole

4-(3-chloro-phenoxymethyl)-1H-imidazole or

4-(2-fluoro-phenoxymethyl)-1H-imidazole.

8. Compounds of formula I according to claim 1, wherein X-R^1 is CH_2 and Y-R^2 is S.

9. Compounds of formula I according to claim 8, wherein the compounds are

5-(2,3-dichloro-phenylsulfanylmethyl)-1-imidazole

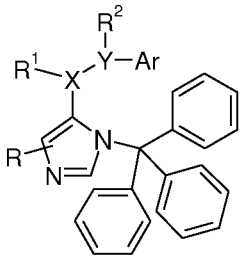
4-(4-chloro-phenylsulfanylmethyl)-5-methyl-1H-imidazole

4-(naphthalen-2-ylsulfanylmethyl)-1H-imidazole or

5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

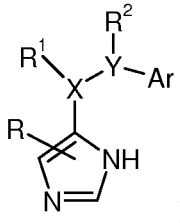
10. A process for preparation of compounds of formula I, which process comprises

a) deprotecting a compound of formula



II

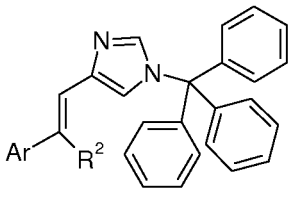
to a compound of formula



I

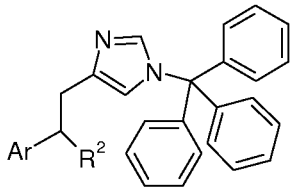
wherein the definitions are as described above, or

b) hydrogenating a compound of formula



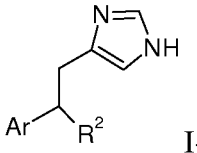
V

to a compound of formula



II-1

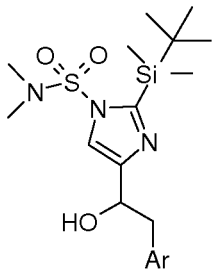
and deprotecting according to step a) to a compound of formula



I-1

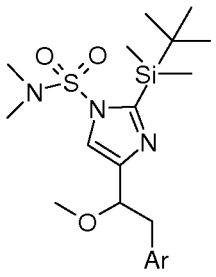
wherein Ar is as defined above and R^2 is hydrogen, lower alkyl or lower alkoxy, or

c) alkylating a compound of formula



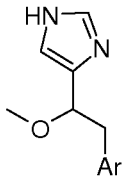
IX

to a compound of formula



II-2

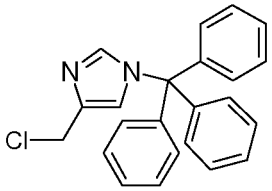
and deprotecting according to step a) to a compound of formula



I-2

wherein Ar is as defined above; or

d) reacting a compound of formula

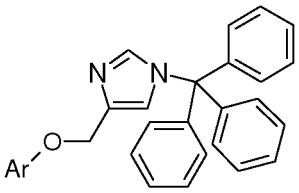


XI

and a compound of formula

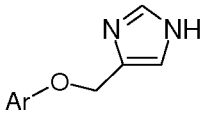
ArOH X

to a compound of formula



II-3

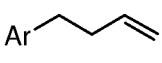
and deprotecting according to step a) to a compound of formula



I-3

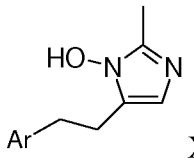
wherein the definitions are as described above, or

e) reacting a compound of formula



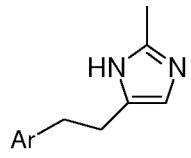
XII

with acetonitrile to a compound of formula



XIII

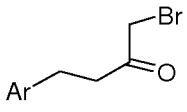
and removing the hydroxy group to a compound of formula



I-4

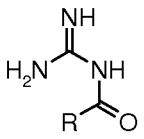
wherein Ar is as defined above, or

f) reacting a compound of formula



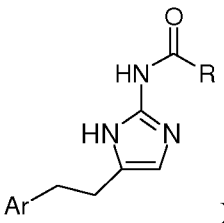
XIII

with a compound of formula



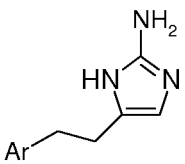
XIV

to a compound of formula



XV

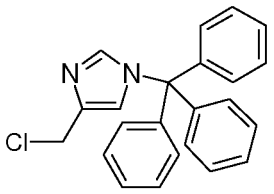
and deprotecting to a compound of formula



I-5

wherein R is lower alkyl and Ar is as described above, or

g) reacting a compound of formula

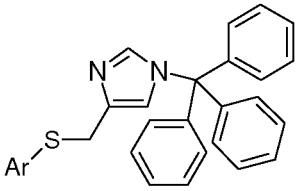


XI

and a compound of formula

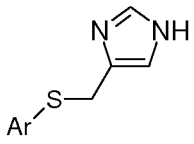
ArSH X'

to a compound of formula



II-4

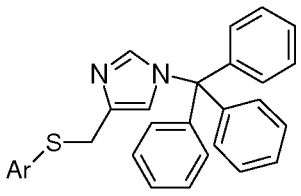
and deprotecting according to step a) to a compound of formula



I-6

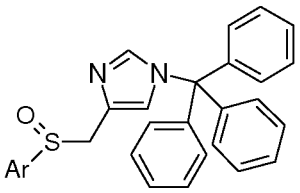
wherein Ar is as defined above, or

h) oxidizing a compound of formula

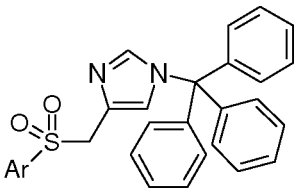


II-4

to compounds of formulas

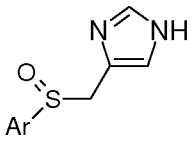


II-5 or

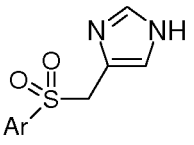


II-6

and deprotecting according to step a) to compounds of formulas



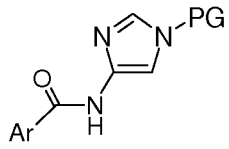
I-7 or



I-8

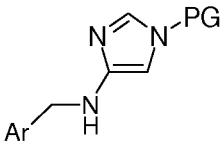
wherein Ar is as defined above; or

i) reducing a compound of formula



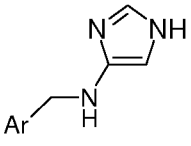
IXX

to a compound of formula



II-7

and deprotecting according to step a) to compounds of formula



I-9

wherein Ar is as described above and PG is a common N-protecting group; 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 and of
5-phenethyl-1*H*-imidazole
5-(2-phenyl-propyl)-1H-imidazole
1-(1H-imidazol-4-yl)-2-phenyl-ethanol

5-(2,2-diphenyl-ethyl)-1H-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole
4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole
4-(biphenyl-2-yloxymethyl)-1H-imidazole
5-(2-methyl-2-phenyl-propyl)-1H-imidazole
4-(2-chloro-phenoxymethyl)-1H-imidazole
4-(2-fluoro-phenoxymethyl)-1H-imidazole
4-o-tolyloxymethyl-1H-imidazole
4-(3-chloro-phenoxymethyl)-1H-imidazole
4-(2,6-dimethyl-phenoxymethyl)-1H-imidazole and
5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

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 and of
5-phenethyl-1*H*-imidazole
5-(2-phenyl-propyl)-1H-imidazole
1-(1H-imidazol-4-yl)-2-phenyl-ethanol
5-(2,2-diphenyl-ethyl)-1H-imidazole
4-(2-m-tolyl-ethyl)-1H-imidazole
4-[2-(2,6-dimethyl-phenyl)-ethyl]-1H-imidazole
4-(biphenyl-2-yloxymethyl)-1H-imidazole
5-(2-methyl-2-phenyl-propyl)-1H-imidazole
4-(2-chloro-phenoxymethyl)-1H-imidazole
4-(2-fluoro-phenoxymethyl)-1H-imidazole

4-o-tolyloxymethyl-1H-imidazole
4-(3-chloro-phenoxymethyl)-1H-imidazole
4-(2,6-dimethyl-phenoxymethyl)-1H-imidazole and
5-methyl-4-phenylsulfanylmethyl-1H-imidazole.

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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