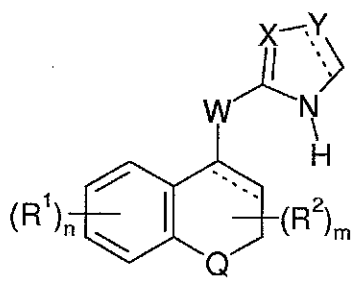


USE OF 2-IMIDAZOLES FOR THE TREATMENT OF CNS DISORDERS

The present invention relates to the use of compounds of formula I



wherein

- R^1 is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen, nitro,
 5 amino or lower alkyl substituted by halogen;
 R^2 is hydrogen, hydroxy or lower alkyl;
 X is N and Y is CH or CH₂ or CH-lower alkyl or
 X is CH and Y is N;
 Q is CH₂, O, NH, N-alkyl or N-SO₂-alkyl or N-SO₂-toluen-4-yl;
 10 W is CH₂ or a bond
 m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R^2 may
 be the same or not; when n is 2 or 3, R^1 may be the same or not;
 the dotted lines may each be independently from one another a bond or not;
- 15 and to their pharmaceutically active salts, racemic mixtures, enantiomers, optical
 isomers and tautomeric forms of compounds of formula I for the preparation of
 medicaments for the treatment of depression, anxiety disorders, bipolar disorder,
 attention deficit hyperactivity disorder, stress-related disorders, psychotic
 disorders such as schizophrenia, neurological diseases such as Parkinson's
 20 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
 25 cardiovascular disorders.

Some of the compounds disclosed in formula I are known compounds, described for example in the below mentioned references, or are disclosed in public chemical libraries. Compounds of examples 1 – 14, 26 – 55 and 57 - 74 are new.

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

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
10 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,
15 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
20 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
25 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
30 (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
35 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 G α s.

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;

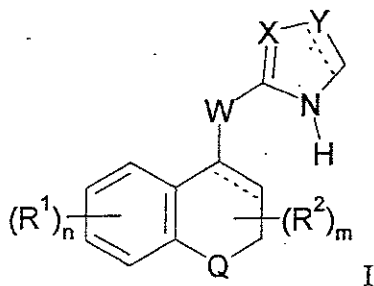
- 13 Parker, E.M. and Cubeddu, L.X. (1988) Comparative effects of amphetamine, phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding. *J. Pharmacol. Exp. Ther.* 245, 199-210;
- 14 Lindemann, L. *et al.* (2005) Trace amine associated receptors form structurally and functionally distinct subfamilies of novel G protein-coupled receptors. *Genomics* 85, 372-385.

Objects of the embodiments disclosed herein are novel compounds of formula I and the use of compounds of formula I and their pharmaceutically acceptable salts, racemic mixtures, enantiomers, optical isomers or tautomeric forms 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 disclosure 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. A further object of the embodiments disclosed herein is the use of labeled compounds of formula I as radioligand in a binding assay for trace amine associated receptors.

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

According to the first aspect, there is provided the use of compounds of formula I



wherein

R¹ is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, amino or lower alkyl substituted by halogen;

R² is hydrogen, hydroxy or lower alkyl;

X is N and Y is CH or CH₂ or CH-lower alkyl or

X is CH and Y is N;

Q is CH₂, O, NH, N-alkyl, N-SO₂-alkyl or N-SO₂-toluen-4-yl;

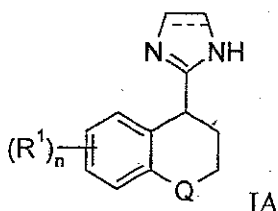
W is CH₂ or a bond

m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R² may be the same or not; when n is 2 or 3, R¹ may be the same or not;

the dotted lines may each be independently from one another a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I for the preparation of medicaments for the treatment of bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, and 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.

According to a second aspect, there is provided the use of compounds of formula IA



wherein

R¹ is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen or lower alkyl substituted by halogen;

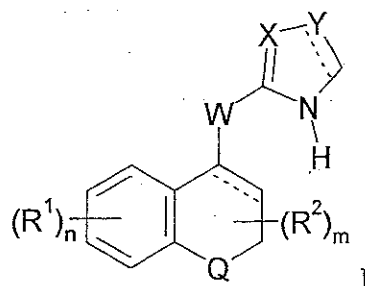
Q is CH₂ or O;

n is 1, 2 or 3; when n is 2 or 3, R¹ may be the same or not;

the dotted line may be a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I for the preparation of medicaments for the treatment of 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, 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.

According to a third aspect, there is provided the use of compounds of formula I



wherein

R^1 is tritium;

R^2 is hydrogen, hydroxy or lower alkyl;

X is N and Y is CH or CH₂ or CH-lower alkyl or

X is CH and Y is N;

Q is CH₂, O, NH, N-alkyl, N-SO₂-alkyl or N-SO₂-toluen-4-yl;

W is CH₂ or a bond

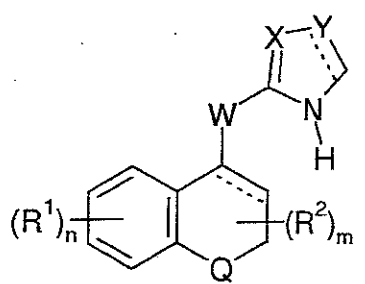
m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R^2 may be the same or not; when n is 2 or 3, R^1 may be the same or not;

the dotted lines may each be independently from one another a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I as radioligand in a binding assay for trace amine associated receptors.

According to a fourth aspect, there is provided a medicament containing one or more compounds as defined above 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, 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.

The invention relates also to novel compounds of formula I



wherein

- R^1 is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, amino or lower alkyl substituted by halogen;
 R^2 is hydrogen, hydroxy or lower alkyl;
 X is N and Y is CH or CH_2 or CH-lower alkyl or
 5 X is CH and Y is N;
 Q is CH_2 , O, NH, N-alkyl or N-SO₂-alkyl or N-SO₂-toluen-yl;
 W is CH_2 or a bond
 m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R^2 may be the same or not; when n is 2 or 3, R^1 may be the same or not;
 10 the dotted lines may each be independently from one another a bond or not;

and to their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms, with the exception of the following compounds

- rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline
 15 rac-2-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-2-(6-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-2-(6-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-2-(5-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-2-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 20 rac-2-(6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-2-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
 rac-5-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ol,
 rac-4-(1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole
 rac-5-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalene-2,3-diol
 25 or
 rac-5-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalene-1,2-diol.

The novel compounds of formula I may also be used as radioligand in a binding assay for trace amine associated receptors.

30

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.

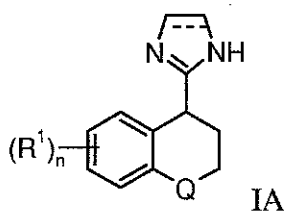
As used herein, the term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above and which is attached via an oxygen atom.

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 , $\text{CH}_2\text{CF}_2\text{CF}_3$ 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.

One embodiment of the invention is the use of compounds of formula



wherein

R^1 is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen or lower alkyl substituted by halogen;

Q is CH_2 or O;

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

the dotted line may be a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula IA for the preparation of medicaments for the treatment of 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.

Preferred compounds of formula I according to the use as described above are those, wherein X is N.

- Preferred compounds from this group are those, wherein Q is CH₂ and R¹ is halogen, for example the following compounds:
- rac-2-(5-bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
rac-2-(7-chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
rac-2-(6-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(5-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

- Preferred compounds of formula I according to the use as described above are those, wherein Q is CH₂ and R¹ is lower alkyl, for example the following compounds:
- rac-2-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole.

- Preferred compounds of formula I according to the use as described above are those, wherein Q is CH₂ and R¹ is lower alkoxy, for example the following compounds:
- rac-2-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
rac-2-(6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

- Preferred compounds of formula I according to the use as described above are those, wherein Q is O or NH and R¹ is hydrogen or halogen, for example
- rac-2-(6,8-dichloro-chroman-4-yl)-1H-imidazole or
rac-4-(1H-imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline.

- Preferred compounds of formula I according to the use as described above are those, wherein X is CH.

- Preferred compounds from this group are those, wherein Q is CH₂ and R¹ is hydrogen, for example the following compounds:
- (4-(3,4-dihydro-naphthalen-1-yl)-1H-imidazole or
rac-4-(1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole.

Preferred compounds from this group are those, wherein Q is O and R¹ is hydrogen, for example the following compound:

rac-5-chroman-4-yl-1H-imidazole hydrochloride or tautomer.

Preferred compounds from this group are further those, wherein Q is O and R¹ is lower alkyl, for example the following compounds:

- 5 rac-5-(7-methyl-chroman-4-yl)-1H-imidazole or tautomer or
rac-5-(5-methyl-chroman-4-yl)-1H-imidazole or tautomer.

Preferred compounds from this group are further those, wherein Q is O and R¹ is halogen, for example the following compounds:

- rac-5-(6-fluoro-chroman-4-yl)-1H-imidazole or tautomer
10 5-(8-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer
5-(6-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer
rac-5-(7-fluoro-chroman-4-yl)-1H-imidazole or tautomer or
rac-5-(5-fluoro-chroman-4-yl)-1H-imidazole or tautomer.

Preferred novel compounds are the followings:

- 15 - Compounds of formula I, wherein X is N, Q is CH₂ and R¹ is halogen, for example the following compounds

rac-2-(5-bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(7-chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

- 20 - Compounds of formula I, wherein X is N, Q is CH₂ and R is tritium, for example
rac-2-(7-tritio-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

- Compounds of formula I, wherein X is N and Q is -O-, for example the following compounds

- rac-2-chroman-4-yl-4,5-dihydro-1H-imidazole,
25 rac-2-chroman-4-yl-1H-imidazole or
rac-2-(6-fluoro-chroman-4-yl)-1H-imidazole.

- Compounds of formula I, wherein X is N, Q is O or NH and R¹ is hydrogen or halogen, for example

- rac-2-(6,8-dichloro-chroman-4-yl)-1H-imidazole or
30 rac-4-(1H-imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline.

- Compounds of formula I, wherein X is CH, Q is CH₂ and R¹ is hydrogen, for example the following compound:

(4-(3,4-dihydro-naphthalen-1-yl)-1H-imidazole.

- Compounds of formula I, wherein X is CH, Q is O and R¹ is hydrogen, for example the following compound:

5 rac-5-chroman-4-yl-1H-imidazole hydrochloride or tautomer.

- Compounds of formula I, wherein X is CH, Q is O and R¹ is lower alkyl, for example the following compounds:

rac-5-(7-methyl-chroman-4-yl)-1H-imidazole or tautomer or

10 rac-5-(5-methyl-chroman-4-yl)-1H-imidazole or tautomer.

- Compounds of formula I, wherein X is CH, Q is O and R¹ is halogen, for example the following compounds:

rac-5-(6-fluoro-chroman-4-yl)-1H-imidazole or tautomer

5-(8-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer

15 5-(6-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer

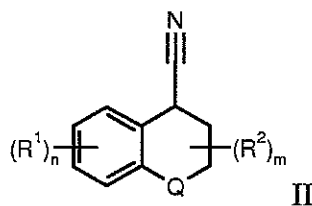
rac-5-(7-fluoro-chroman-4-yl)-1H-imidazole or tautomer or

rac-5-(5-fluoro-chroman-4-yl)-1H-imidazole or tautomer.

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,

20 which process comprises

a) reacting a compound of formula

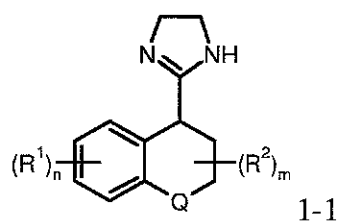


with ethylenediamine of formula



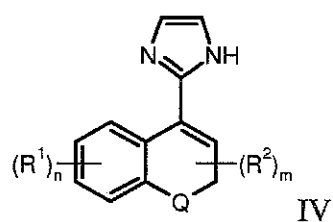
25 to a compound of formula

- 10 -



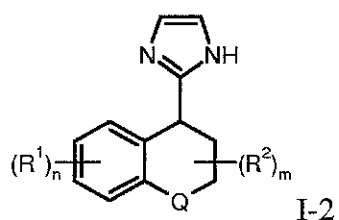
wherein R^1 , R^2 , Q, m and n are as defined above, or

b) reducing a compound of formula



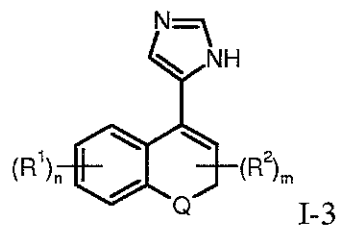
5 by catalytic hydrogenation in the presence of Pd/C or by a complex hydride

to a compound of formula



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

c) reducing a compound of formula

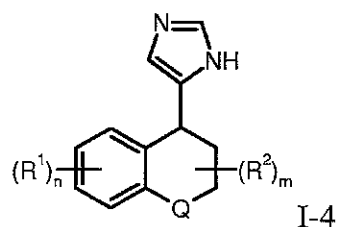


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by catalytic hydrogenation in the presence of Pd/C or by a complex hydride

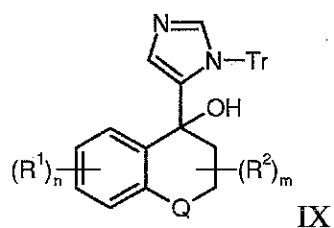
to a compound of formula

- 11 -



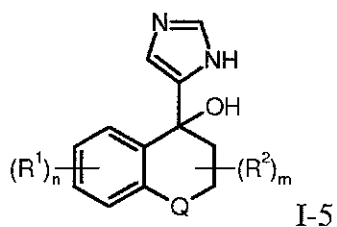
wherein R^1 , R^2 , Q, m and n are as defined above are as defined above, or

d) deprotecting a compound of formula



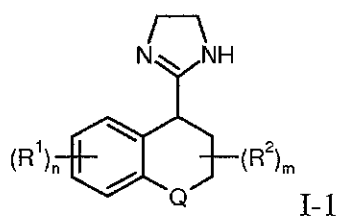
5 with formic acid

to a compound of formula



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

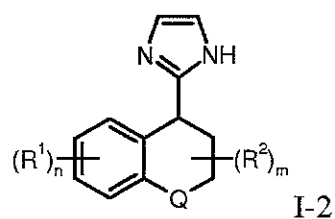
e) reacting a compound of formula



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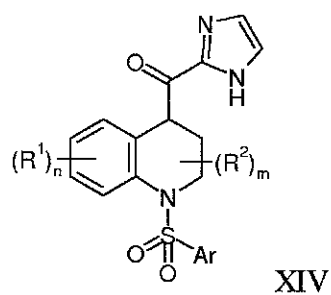
with DMSO and oxalyl chloride in dichloromethane or permanganate absorbed on silica gel in acetonitrile or with Pd/C in toluene
to a compound of formula

- 12 -

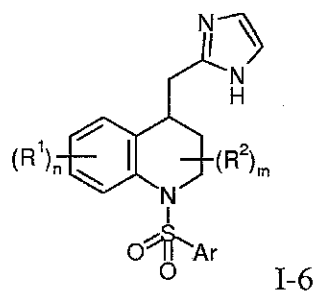


wherein R^1 , R^2 , Q, m and n are as defined above, or

f) reacting a compound of formula

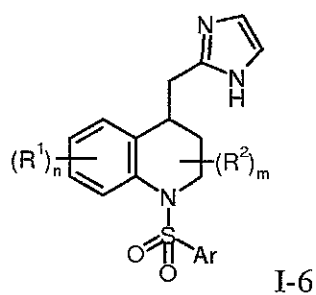


5 with NaOH and hydrazine hydrate
to a compound of formula



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

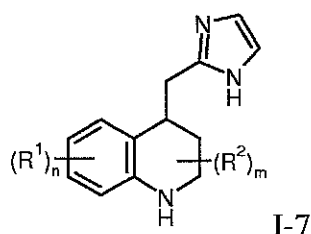
g) reacting a compound of formula



10

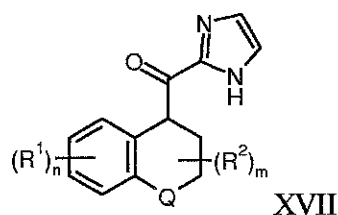
with HBr, acetic acid and anisole
to a compound of formula

- 13 -

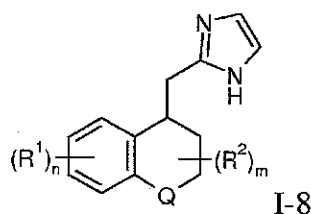


wherein R^1 , R^2 , m and n are as defined above, or

h) reacting a compound of formula



5 with NaOH and hydrazine hydrate
to a compound of formula



wherein R^1 , R^2 , m and n are as defined above and Q is O or CH_2 , and

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

The bicyclic substituted 2-imidazoline, 2-imidazole and 2-imidazole compounds described in this application were prepared in analogy to literature procedures following the pathways depicted in Schemes 1 to 6.

These procedures are described in following references

- 15 [1] *J. Med. Chem.* 1986, 29, 1413
[2] *Bull. Korean Chem. Soc.* 2003, 24, 1354
[3] *J. Med. Chem.* 1987, 30, 1482
[4] *Chem. Pharm. Bull.* 1987, 35, 1058 and *Synthesis* 1990, 78.
[5] *J. Med. Chem.* 1997, 40, 3014
20 [6] *Tetrahedron* 2004, 60, 9857

[7] *Synth. Commun.* 1990, 20, 2483

[8] *Org. Lett.* 2002, 4, 3051

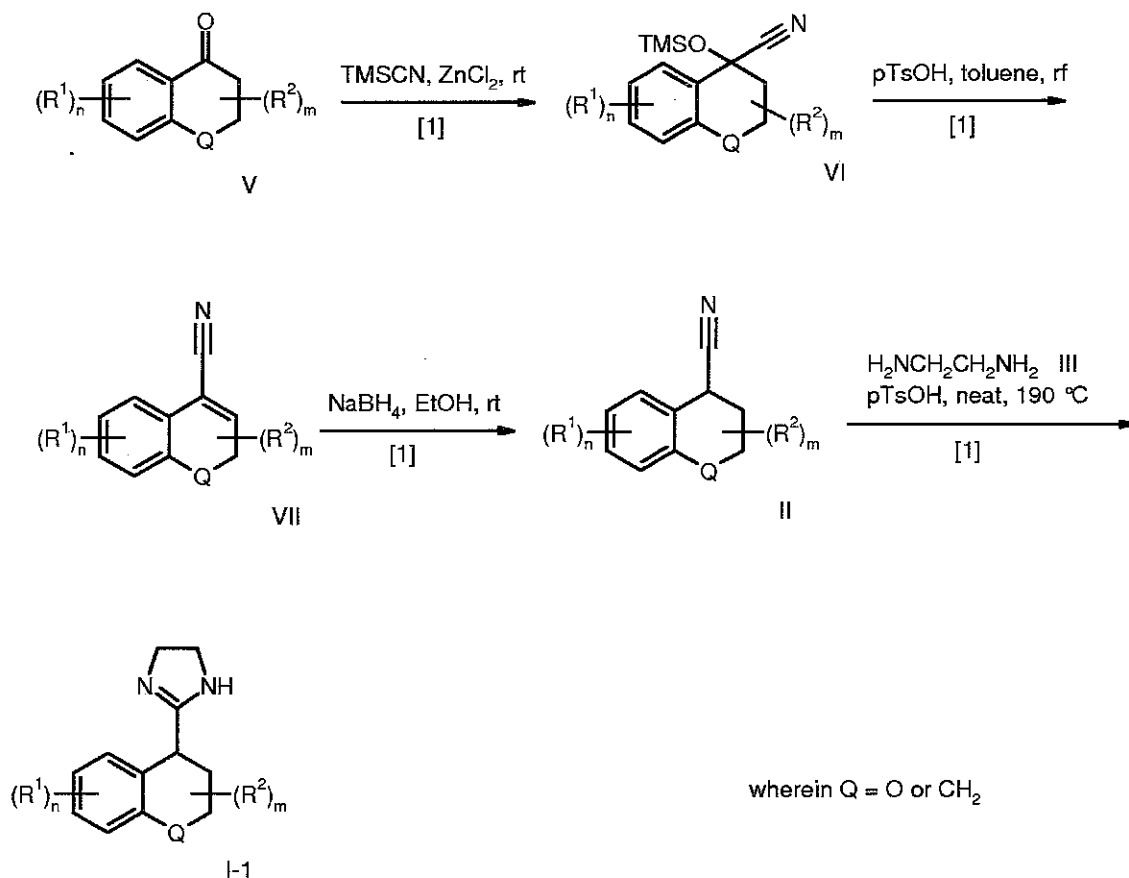
All starting materials are either commercially available, are otherwise known in the
 5 chemical literature, or may be prepared in accordance with methods well known in the
 art.

PROCEDURE A

Synthesis of bicyclic substituted imidazolines

10

Scheme 1



2-Imidazolines of formula I-1 can be prepared by reaction of a nitrile of formula II with
 15 ethylenediamine of formula III. This cyclization with a diamine can be conducted by
 heating a diamine mono p-toluenesulfonic acid salt with a nitrile neat at 100 °C to 250 °C,
 preferably at 140 °C to 240 °C, for several hours, preferably 2 to 6 hours, or by heating a
 solution of the nitrile in an excess of ethylenediamine or a derivative thereof in presence
 of a catalytic amount of sulfur, preferably 10 mol% to 50 mol%, in a sealed tube under
 20 microwave irradiation to 200 °C for 10 to 60 minutes, preferably for 15 to 30 minutes [2],

or by reaction of a complex preformed from trimethylaluminum and ethylenediamine or a derivative thereof in toluene below ambient temperature, preferably at 0 °C to 10 °C, with a nitrile in toluene at reflux temperature for 4 to 24 hours, preferably for 16 to 20 hours [3]. In the latter procedure the nitrile can be replaced by the corresponding lower
5 alkyl ester.

Nitriles of formula II derived from cyclic ketones of formula V may be prepared in a three step procedure following procedures known in the literature. The sequence starts with addition of a synthetic equivalent of hydrogen cyanide, e.g. trimethylsilyl cyanide, which
10 results in the formation of an O-protected cyanohydrin of formula VI, e.g. trimethylsilyl-O. This addition is performed in the presence of a catalyst, e.g. zinc iodide, neat at ambient temperature under vigorous stirring for 18 to 48 hours. Elimination of trimethylsilanol in the presence of a catalytic amount of an acid, preferred is p-toluenesulfonic acid, in an organic solvent like benzene, toluene, xylene and the like,
15 preferably toluene, at reflux temperature for 1 to 6 hours, preferably 2 to 3 hours, provides the α,β -unsaturated nitrile of formula VII. Reduction of the double bond in this nitrile with a complex hydride, preferred is sodium borohydride, in a lower alcohol like methanol, ethanol, isopropanol, preferred is ethanol, at reflux temperature for 0.5 to 2 hours, preferably 0.5 to 1 hour, furnishes the nitrile of formula II.

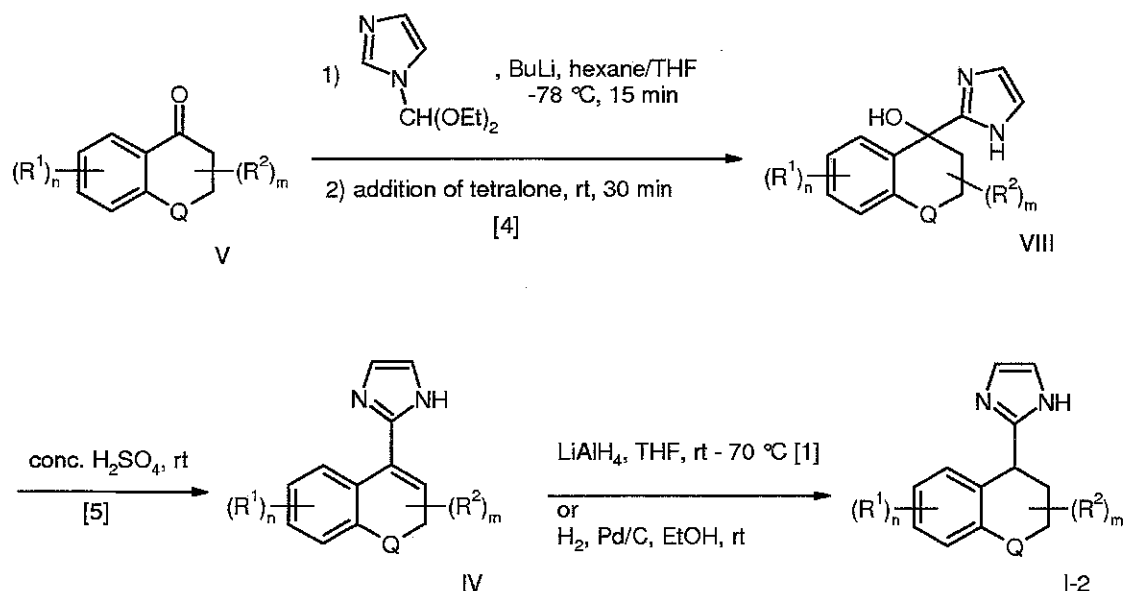
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PROCEDURE B

Synthesis of bicyclic substituted imidazolesScheme 2a: 2-imidazoles for Q is O, CH₂, N-alkyl and N-SO₂-aryl

5 wherein $Q = \text{O}, \text{CH}_2, \text{N-alkyl}, \text{N-SO}_2\text{-toluen-4-yl}$

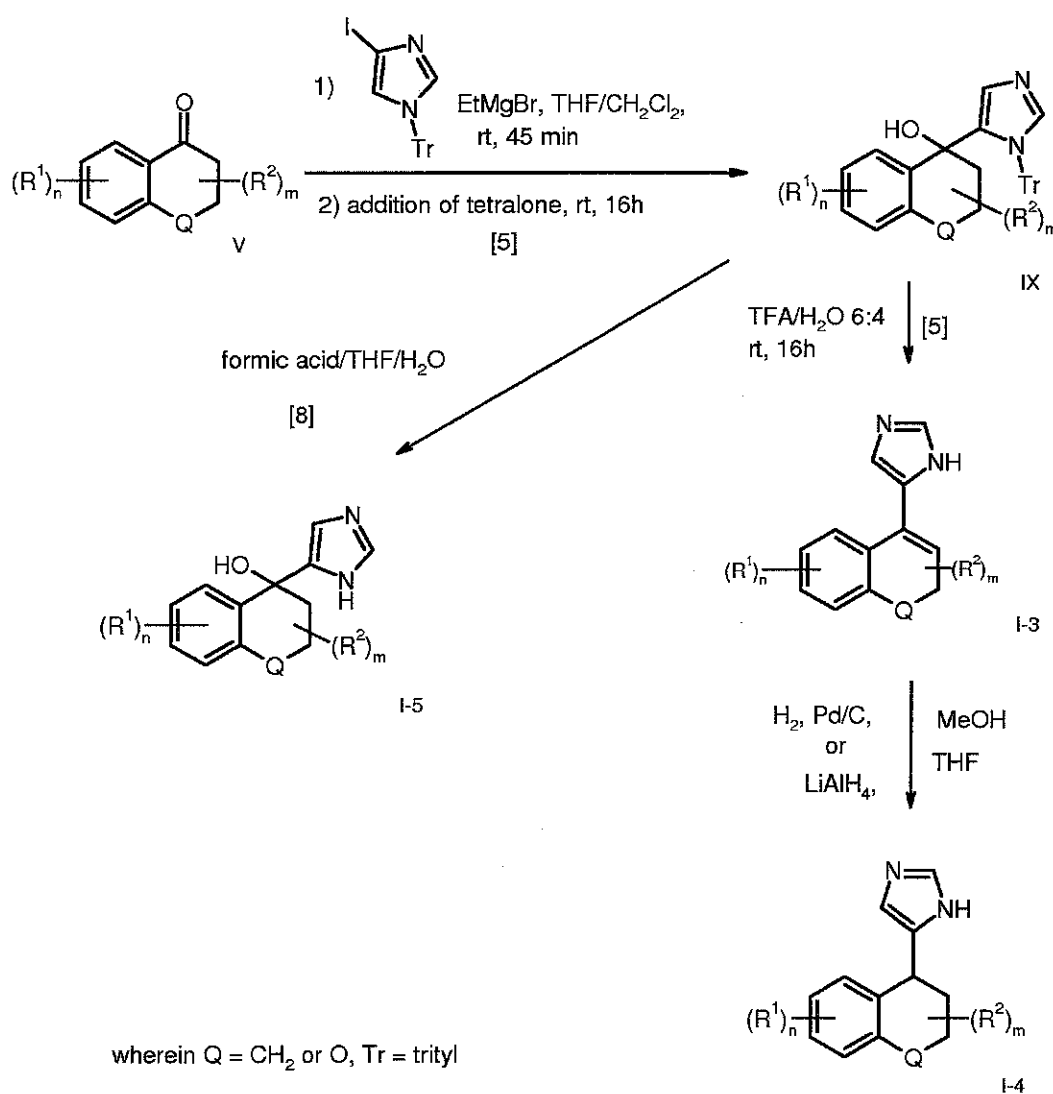
Direct introduction of the 2-imidazole residue is done by reaction of an aryl ketone **V** with a metallated N -protected imidazole, which is first prepared *in situ* by deprotonation of an N -protected imidazole with a strong base like alkyl or aryl lithium, preferably by *n*-butyl lithium, in an inert organic solvent, e.g. tetrahydrofuran or diethyl ether, below
 10 ambient temperature, preferably at -78°C . The primary product isolated is a tertiary alcohol of formula **VIII**.

The α,β -unsaturated 2-imidazoles of formula **IV** are obtained from the corresponding tertiary alcohols by acid catalysed elimination of water. Preferred catalyst is *p*-toluenesulfonic acid and the reaction is run in an azeotrope-forming solvent like benzene or toluene, preferred is toluene, at reflux temperature for 1 to 4 hours, preferred are 2 to 3
 15 hours. The reaction can also be performed by adding the corresponding tertiary alcohols to conc. sulfuric acid at 0°C to ambient temperature, preferred is 0°C to 10°C , and then stirring the mixture at ambient temperature for 5 to 30 minutes, preferred is 10 to 15
 20 minutes.

The 2-imidazoles of formula **I-2** are prepared from the corresponding α,β -unsaturated 2-imidazoles of formula **IV** by reduction of the double bond either by catalytic hydrogenation in the presence of Pd/C in a polar solvent, preferred is a lower alcohol, or by a complex hydride like lithium aluminum hydride in an aprotic solvent like

tetrahydrofuran or diethylether at ambient temperature or elevated temperature for 2 to 12 hours, preferably 4 to 8 hours. In the case where Q is N-SO₂-aryl, reduction using lithium aluminium hydride at elevated temperature affords a mixture of the corresponding products of formula I-2 where Q is N-SO₂-aryl and Q is NH. Formation of the latter compound is favoured by extended reaction times or increased reaction temperatures.

Scheme 2b: 4-imidazoles for Q is O and CH₂



- 10 Direct introduction of the 4-imidazole residue is done by reaction of an aryl ketone of formula V with a metallated N-protected imidazole which is first generated *in situ* from an N-protected 4-iodo-imidazole by treatment with an organomagnesium reagent, preferably ethylmagnesium bromide, in an inert organic solvent, preferably in a mixture of dichloromethane and tetrahydrofuran, at ambient temperature. The primary product
- 15 isolated is a tertiary alcohol of formula IX.

The α,β -unsaturated and N-deprotected 4-imidazoles of formula I-3 are obtained from the corresponding tertiary alcohols by acid catalyzed elimination of water as described for the 2-imidazoles. The trityl group on the imidazole is also eliminated under these reaction conditions. In addition to the procedures mentioned for the preparation of α,β -unsaturated 2-imidazoles, the reaction with 30% to 80% trifluoroacetic acid in water, preferred is 60%, at ambient temperature for 12 to 24 hours, preferred is 14 to 18 hours, also provides the α,β -unsaturated and detritylated 4-imidazoles of formula I-3.

The N-deprotected 4-imidazoles of formula I-5 still bearing the tertiary alcohol are obtained by acid catalysed deprotection of the corresponding N-trityl-imidazole with a mixture of formic acid/THF/water 1:1:0.1.

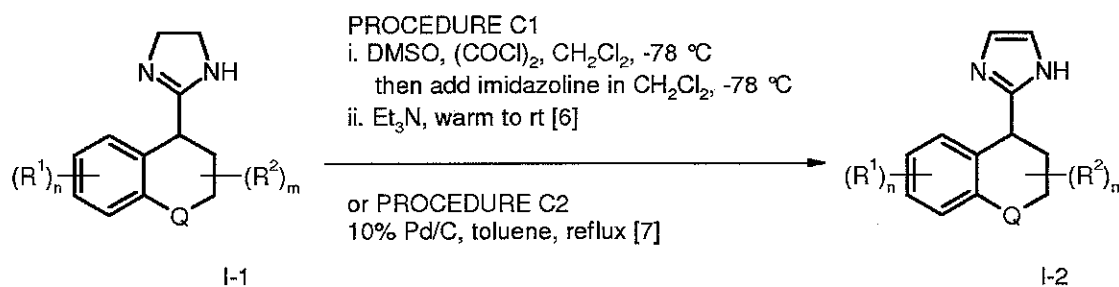
In analogy to the 2-imidazoles the 4-imidazoles of formula I-4 are prepared from the corresponding α,β -unsaturated 4-imidazoles of formula I-3 by reduction of the double bond either by catalytic hydrogenation in the presence of Pd/C in a polar solvent like methanol, ethanol, propanol, isopropanol or ethyl acetate, preferred is a lower alcohol like methanol or ethanol, or by reduction using a complex hydride like lithium aluminum hydride in an aprotic solvent like tetrahydrofuran or diethylether at ambient temperature for 2 to 12 hours, preferably for 4 to 8 hours.

PROCEDURE C (C1 and C2)

Dehydrogenation of imidazolines to imidazoles

20

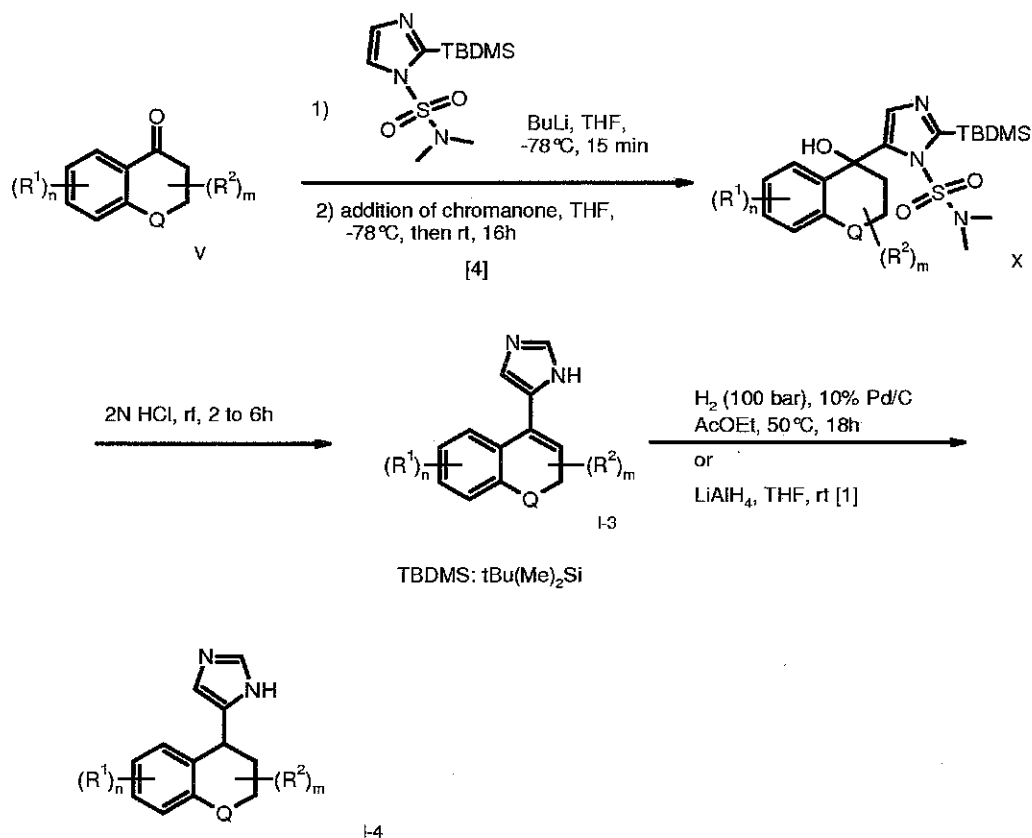
Scheme 3



The 2-imidazoles of formula I-2 can also be prepared by dehydrogenation of the corresponding 2-imidazolines. Two procedures described in the literature have been used for this transformation, Swern type oxidation and catalytic dehydrogenation.

PROCEDURE D

Scheme 4



Direct introduction of the 4-imidazole residue can also be done in analogy to the
 5 procedure published by S. Ohta *et al.* (*Synthesis* 1990, 78) by reaction of an aryl ketone of
 formula V with a metallated N(1)-and C(2)-diprotected imidazole, preferred is 2-(tert-
 butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide, which is deprotonated
in situ with a strong base like alkyl or aryl lithium, preferably by n-butyl lithium, in an
 inert organic solvent, e.g. tetrahydrofuran or diethyl ether, below ambient temperature,
 10 preferably at -78 °C. The primary product isolated is a tertiary alcohol of formula X.

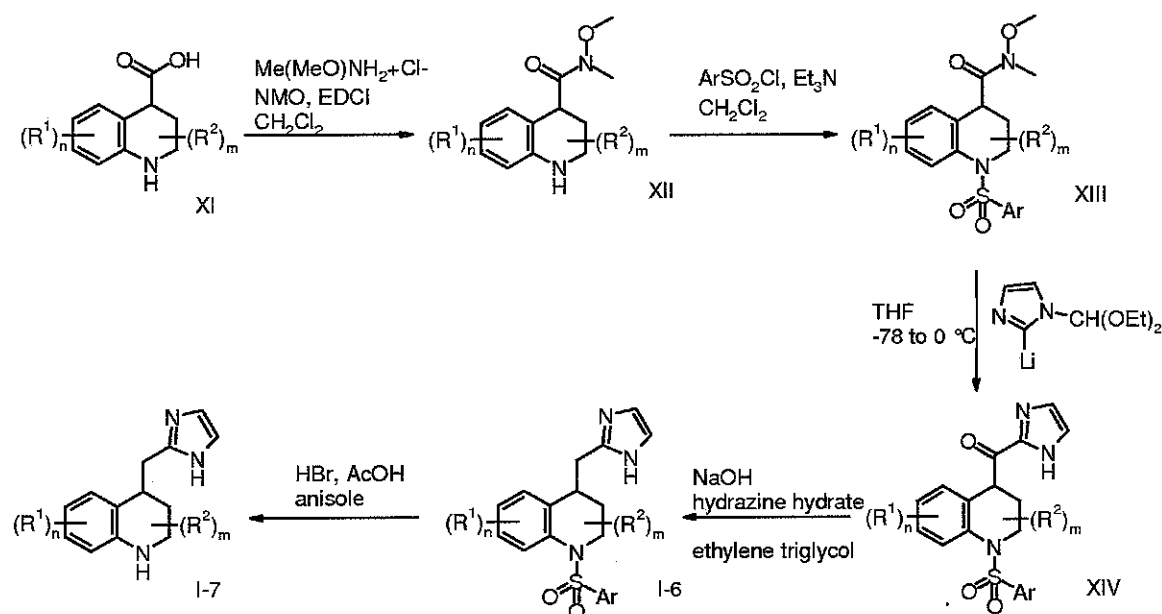
Heating of a solution of the tertiary alcohol X in diluted mineral acid, preferred is 1 N to
 4 N HCl, at reflux for 2 to 6 hours provides the α,β-unsaturated bicyclic product of
 formula I-3 bearing a deprotected 4-imidazolyl residue.

The 4-imidazoles of formula I-4 are prepared from the corresponding α,β-unsaturated 2-
 15 imidazoles of formula I-3 by reduction of the double bond either by catalytic
 hydrogenation with pressurized hydrogen at 50 to 150 bar, preferred is 100 bar, in the
 presence of Pd/C in a polar solvent like methanol, ethanol, propanol, isopropanol or ethyl
 acetate, preferred is ethyl acetate, at a temperature between ambient temperature and 150

°C, preferred is 50 °C, for 12 to 24 hours, preferred is 16 to 20 hours, or by reduction using a complex hydride like lithium aluminum hydride in an aprotic solvent like tetrahydrofuran or diethyl ether at ambient temperature for 2 to 12 hours, preferably for 4 to 8 hours.

5 PROCEDURE E

Scheme 5



- 10 2-imidazole compounds of formula I-7 where W is CH₂ and Q is NH, N-alkyl, N-SO₂-alkyl or N-SO₂-toluen-4-yl may be prepared as shown in scheme 5. The starting materials are 1,2,3,4-tetrahydro-quinoline-4-carboxylic acid compounds of formula XI, which may be prepared by methods already reported in the literature, for instance by Raney nickel reduction of the corresponding quinoline-4-carboxylic acid compounds, as
- 15 reported in *Khimiya Geterotsiklicheskikh Soedinenii* 1988, 77-9. The carboxylic acid compounds of formula XI are converted to the corresponding Weinreb amide derivatives of formula XII by treatment with N,O-dimethylhydroxylamine hydrochloride and a coupling reagent such as 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in the presence of a tertiary amine base such as triethylamine or N-methylmorpholine. The reaction is carried out in a halogenated organic solvent such as dichloromethane.

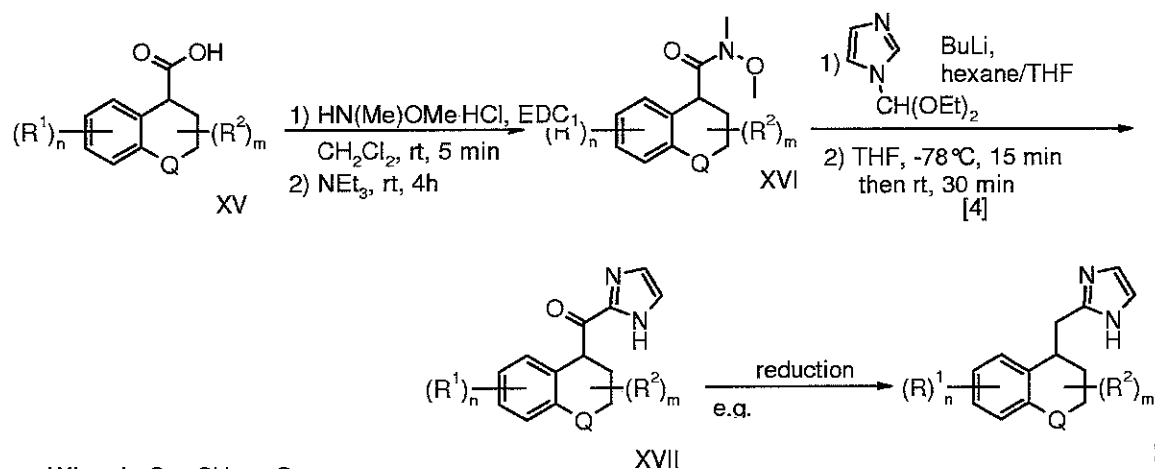
Following preparation of the Weinreb amide compounds of formula XII, the nitrogen atom of the 1,2,3,4-tetrahydro-quinoline ring system is protected, for instance as the

corresponding arylsulphonamide, by treatment with an arylsulphonyl chloride in the presence of a tertiary amine base such as triethylamine in a halogenated organic solvent such as dichloromethane or 1,2-dichloroethane. The reaction may be performed at room temperature or at the reflux temperature of the solvent used.

- 5 The Weinreb amide moiety present in the compounds of formula XIII may then be reacted with a metallated N-protected imidazole, for instance with 2-(1-diethoxymethyl-1H-imidazol-2-yl)-lithium, which is first prepared *in situ* by deprotonation of the corresponding N-protected imidazole with a strong base like alkyl or aryl lithium, preferably by n-butyl lithium, in an inert ethereal solvent, e.g. tetrahydrofuran or diethyl ether,
- 10 ether, below ambient temperature, preferably at -78 °C. The reaction between the Weinreb amide compound of formula XIII and the metallated N-protected imidazole is performed in an inert ethereal solvent, e.g. tetrahydrofuran or diethyl ether, below ambient temperature, preferably at a temperature between -78 °C and 0 °C. The primary product isolated is a ketone of formula XIV.
- 15 The ketone of formula XIV may then be subjected to Wolff-Kischner reduction to afford a compound of formula I-6, for instance using the procedure reported in *Arch. Pharm.* 1989, 322, 363-367 which involves treatment with sodium hydroxide and hydrazine hydrate in a high boiling point organic solvent such as triethylene glycol, at elevated temperature, preferably at temperatures between 110 °C and 200 °C.
- 20 Finally, the protecting group in the compound of formula I-6 may be removed, for instance by reaction with a protic acid such as HBr in acetic acid in the presence of anisole, to afford the desired compounds of formula I-7.

PROCEDURE F

Scheme 6



The starting material, a Weinreb type amide of formula XVI, is prepared from the corresponding carboxylic acid of formula XV following procedures known in the art (*cf.* Scheme 5). Direct introduction of the 2-imidazole residue is done by reaction of the Weinreb type amide with a metallated N-protected imidazole which is generated *in situ* from an N-protected-imidazole with a strong base like alkyl or aryl lithium, preferably n-butyl lithium, in an inert organic solvent, e.g. tetrahydrofuran or diethyl ether, below ambient temperature, preferably at -78 °C. The primary product isolated is a ketone of formula XVII.

Reduction of this ketone following procedures known in the art, e.g. a Wolff-Kishner type reduction (*cf.* Scheme 5), provides the final product of formula I-8.

The corresponding 4-imidazoles are accessible following the route depicted in Scheme 4 by using the 1,2-diprotected imidazoles shown in Scheme 4.

Compounds of formula I, wherein R is tritium may be prepared from the corresponding halogenated (chloro, bromo or iodo) compound, preferred is the bromo-substituted compound, by catalytic hydrogenation with tritium gas.

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
5 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.

10

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.

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

Materials and Methods

Construction of TAAR expression plasmids and stably transfected cell lines

20

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 Mg²⁺ and purified PCR products were cloned into pCR2.1-TOPO
25 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
30 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
35 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.

5 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
10 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
15 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
20 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 [3H]-rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-
25 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 [3H]-rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline bound in the presence of the appropriate unlabelled ligand (10 μ M).
30 Competing ligands were tested in a wide range of concentrations (10 pM – 30 μ M). 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%,
35 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 μ l/well, Packard Instrument Company) and bound

radioactivity was counted by a TopCount Microplate Scintillation Counter (Packard Instrument Company).

The preferred compounds show a K_i value (μM) on mouse TAAR1 in the range of
5 0.009 – 0.060 as shown in the table below.

Example	K_i (μM) mouse	Example	K_i
1	0.009	41	0.061
2	0.011	55	0.011
3	0.054	56	0.006
10	0.013	60	0.008
11	0.017	62	0.004
12	0.054	63	0.020
18	0.058	64	0.016
19	0.013	65	0.004
20	0.051	66	0.037
21	0.009	67	0.032
22	0.025	69	0.025
36	0.053		

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
10 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.

5 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

10 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.

15 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

20 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).

25 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

30 addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
	1. Compound of formula I	5	25	100	500
5	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

10 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.

15

Capsule Formulation

Item	Ingredients	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg
	1. Compound of formula I	5	25	100	500
	2. Hydrous Lactose	159	123	148	---
20	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

- 25 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.

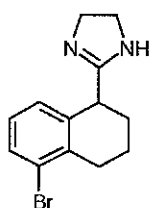
Experimental

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

5 PROCEDURE A

Example 1

rac-2-(5-Bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

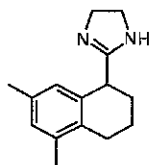


- 10 A mixture of 400 mg (1.7 mmol) rac-5-bromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile and 511 mg (2.2 mmol) ethylene diamine p-toluenesulfonic acid mono salt was heated neat to 150°C and the liquid stirred for 6 hours at this temperature. Then the cooled reaction mixture was diluted with water and saturated aqueous solution of potassium carbonate. The solution was extracted with ethyl acetate, the combined
15 extracts washed with brine, dried over Na₂SO₄, filtered and evaporated. Purification of the crude product by flash-chromatography over silica gel with methanol/concentrated ammonia 98:2 as eluent provided pure rac-2-(5-bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-im as colourless solid; MS (ISP): 281.0 and 279.0 ((M+H)⁺).

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Example 2

rac-2-(5,7-Dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole



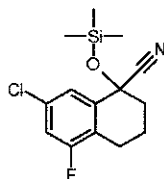
- rac-2-(5,7-Dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was
25 prepared from rac-5,7-dimethyl-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 1: colourless solid; MS (EI): 228.3 (M⁺).

Example 3

rac-2-(7-Chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

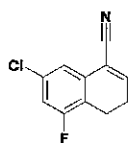
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a) rac-7-Chloro-5-fluoro-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



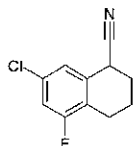
To 2.00 g (11.3 mmol) 7-chloro-5-fluoro-3,4-dihydro-2H-naphthalen-1-one were added
10 0.11 g (0.35 mmol) zinc iodide and under vigorous stirring 3.72 g (4.69 ml, 37.4 mmol)
trimethylsilyl cyanide drop-wise over 15 min. The mixture was stirred at ambient
temperature over night, and then diluted with ethyl acetate. The organic phase was
washed twice with saturated aqueous sodium bicarbonate solution, brine, dried over
Na₂SO₄, filtered and evaporated. The crude product was filtered through a silica gel pad
15 with heptane/ethyl acetate 4:1 as eluent: rac-7-Chloro-5-fluoro-1-trimethylsilanyloxy-
1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was obtained as a light yellow liquid: MS
(EI): 297.2 (M⁺), 282.2 ((M-CH₃)⁺), 271.2 ((M-CN)⁺), 255.1 (((M-(CH₃+HCN))⁺,
100%), 207.1 ((M-(CH₃)₃SiOH)⁺).

20 b) 7-Chloro-5-fluoro-3,4-dihydro-naphthalene-1-carbonitrile



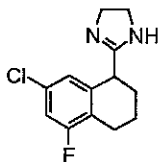
To 4.5 ml concentrated (96%) sulfuric acid cooled to 0°C were added under vigorous
stirring 1.00 g (3.4 mmol) rac-7-chloro-5-fluoro-1-trimethylsilanyloxy-1,2,3,4-
tetrahydro-naphthalene-1-carbonitrile drop-wise over 5 min. Then the cooling bath was
25 removed and the mixture stirred for 10 min. Then ice was added and the mixture made
alkaline by addition of concentrated aqueous sodium hydroxide solution. The aqueous
solution was extracted with dichloromethane, the combined organic extracts washed with
brine, dried over Na₂SO₄, filtered and evaporated. The crude product was filtered through
a silica gel with heptane/ethyl acetate 1:1 as eluent: 0.63 g (90%) 7-chloro-5-fluoro-3,4-
30 dihydro-naphthalene-1-carbonitrile.

c) rac-7-Chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



To a solution of 300mg (1.44 mmol) 7-chloro-5-fluoro-3,4-dihydro-naphthalene-1-carbonitrile in 4 ml ethanol were added 328 mg (8.67 mmol) sodium borohydride and the mixture was heated to reflux for 30 min. The reaction mixture was cooled down and concentrated. The residue was distributed between water and dichloromethane. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and evaporated. The crude product was purified by flash-chromatography with a heptane/ethyl acetate gradient as eluent. rac-7-Chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was obtained as colourless oil: MS (EI): 209.2 (M⁺), 182.1 ((M-HCN)⁺), 156.1 ((M-CH₂=CHCN)⁺), 147.2 (((M-(Cl+HCN))⁺), 100%).

d) rac-2-(7-Chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

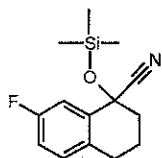


rac-2-(7-Chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from rac-7-chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 1 but heated to 240°C for 2 hours: colourless crystalline solid; MS (ISP): 253.1 ((M+H)⁺).

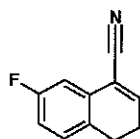
Example 4

rac-2-(7-Fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

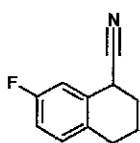
a) rac-7-Fluoro-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



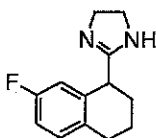
rac-7-Fluoro-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 7-fluoro-3,4-dihydro-2H-naphthalen-1-one in analogy to Example 3 a): light yellow liquid; MS (EI): 263.2 (M⁺), 248.2 ((M-CH₃)⁺), 237.2 ((M-CN)⁺), 221.2 ((M-(CH₃+HCN))⁺), 173.2 (((M-(CH₃)₃SiOH)⁺), 100%).

b) 7-Fluoro-3,4-dihydro-naphthalene-1-carbonitrile

7-Fluoro-3,4-dihydro-naphthalene-1-carbonitrile was prepared from rac-7-fluoro-1-trimethyl-silanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 3 b).

c) rac-7-Fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile

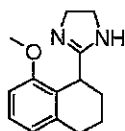
rac-7-Fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 7-fluoro-3,4-dihydro-naphthalene-1-carbonitrile in analogy to Example 3 c): light yellow liquid; MS (EI): 175.2 (M^+), 148.2 ($((M-HCN)^+)$, 100%), 122.1 ($((M-CH_2=CHCN)^+)$).

d) rac-2-(7-Fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

rac-2-(7-Fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from rac-7-fluoro-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 3 d): light yellow solid; MS (EI): 218.2 (M^+).

Example 5

rac-2-(8-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

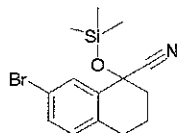


rac-2-(8-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from rac-8-Methoxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 3 d): light yellow gum; MS (ISP): 231.2 ($(M+H)^+$).

Example 6

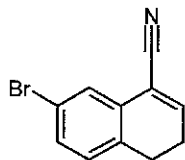
rac-2-(7-Bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

5 a) rac-7-Bromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



rac-7-Bromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 7-bromo-3,4-dihydro-2H-naphthalen-1-one in analogy to Example 3 a): colourless solid, m.p. 45-47°C; MS (EI): 325.1 and 323.1 (M^+), 310.1 and 308.1 (($M-CH_3$) $^+$), 283.1 and 281.0 (($M-(CH_3+HCN)$) $^+$), 235.1 and 233.1 ((($M-(CH_3)_3SiOH$) $^+$), 100%), 202.2 (($M-(CH_3+HCN+Br)$) $^+$).

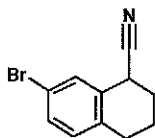
b) 7-Bromo-3,4-dihydro-naphthalene-1-carbonitrile



15 7-Bromo-3,4-dihydro-naphthalene-1-carbonitrile was prepared from rac-7-bromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 3 b): colourless solid, m.p. 113-115°C; 1H -NMR ($CDCl_3$): 2.48-2.55 m, 2H (=CH-CH₂), 2.81 t, J = 8.1 Hz, 2H (CH₂-aryl), 6.94 t, J = 4.2 Hz, 1H (=CH), 7.03 d, J = 7.8 Hz, 1H, and 7.38 dd, J = 7.8 and 1.8 Hz, 1H, and 7.59 d, J = 1.8 Hz, 1H (aryl-H).

20

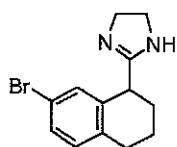
c) rac-7-Bromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



rac-7-Bromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 7-bromo-3,4-dihydro-naphthalene-1-carbonitrile in analogy to Example 3 c): colourless oil; MS (EI): 236.0 and 234.9 (M^+), 210.0 and 207.9 (($M-HCN$) $^+$), 129.0 ((($M-(HCN+Br)$) $^+$), 100%).

25

d) rac-2-(7-Bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

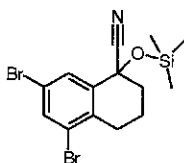


- rac-2-(7-Bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from rac-7-bromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 1 but heated to 210°C for 2 hours: colourless solid, m.p. 156-158°C; MS (ISP):
- 5 281.1 and 279.0 ((M+H)⁺).

Example 7

rac-2-(5,7-Dibromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

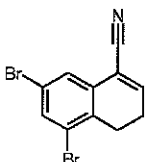
a) rac-5,7-Dibromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



10

rac-5,7-Dibromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 5,7-dibromo-3,4-dihydro-2H-naphthalen-1-one in analogy to Example 3 a): grey solid.

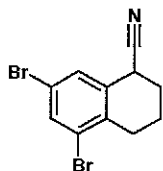
15 b) 5,7-Dibromo-3,4-dihydro-naphthalene-1-carbonitrile



5,7-Dibromo-3,4-dihydro-naphthalene-1-carbonitrile was prepared from rac-5,7-dibromo-1-trimethylsilanyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 3 b): off-white solid.

20

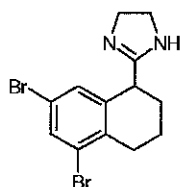
c) rac-5,7-Dibromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile



rac-5,7-Dibromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile was prepared from 5,7-dibromo-3,4-dihydro-naphthalene-1-carbonitrile in analogy to Example 3 c): colourless

25 liquid.

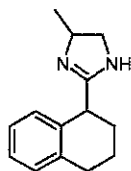
d) rac-2-(5,7-Dibromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole



- rac-2-(5,7-Dibromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from rac-5,7-dibromo-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile in analogy to Example 1 but heated to 210°C for 2 hours: light brown solid; MS (EI): 360.0 and 358.0 (100%) and 356.0 (M⁺).

Example 8

- rac-4-Methyl-2-(1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or tautomer



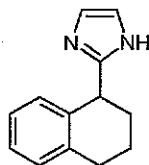
- rac-4-Methyl-2-(1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from 1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester and the complex of trimethylaluminum with 1,2-diaminopropane in toluene at reflux for 1 hour in analogy to [3]: orange gum; MS (ISP): 215.1 ((M+H)⁺).

PROCEDURE C1

Example 9

20

rac-2-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-1H-imidazole



- To a solution of 390 mg (0.354 ml, 5 mmol) dimethylsulfoxide in 20 ml dichloromethane cooled to -78°C was added a solution of 634 mg (0.422 ml, 5 mmol) oxalyl chloride in 20 ml dichloromethane. The mixture was stirred for 30 minutes at -78°C and then a solution of 200 mg (2 mmol) rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline in 20 ml dichloromethane was added and stirring continued at -78°C for 1 hour. Then 1.01 g (1.4

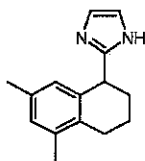
ml) triethylamine were added and the reaction mixture warmed to ambient temperature and stirring continued for 20 minutes. Concentrated ammonia was added and the reaction mixture extracted with dichloromethane, the combined extracts washed with brine, dried over Na₂SO₄, filtered and evaporated. Purification on silica gel by flash-chromatography with a heptane/ethyl acetate gradient provided 71 mg rac-2-(1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole as colourless solid; MS (EI): 198.1 (M⁺).

PROCEDURE C2

Example 10

10

rac-2-(5,7-Dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole



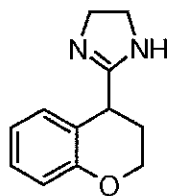
A mixture of 57 mg (0.25 mmol) rac-2-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole and 57 mg 10% Pd on charcoal in 10 ml toluene were heated to reflux for 40 hours. Then additional 30 mg 10% Pd on charcoal were added and heating to reflux continued for another 24 hours. This was repeated after 8 hours and 16 hours. After totally 88 hours at reflux temperature the reaction mixture was cooled down, filtered through a silica gel pad: 28 mg of a brown oil which was purified by flash-chromatography on silica gel with ethyl acetate as eluent. rac-2-(5,7-Dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole was obtained as colourless crystalline solid, m.p. 161-163°C; MS (EI): 226.3 (M⁺).

20

Example 11

PROCEDURE A

rac-2-Chroman-4-yl-4,5-dihydro-1H-imidazole



25

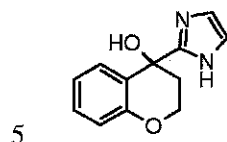
rac-2-Chroman-4-yl-4,5-dihydro-1H-imidazole was prepared from rac-chroman-4-carbonitrile in analogy to Example 1 but heated to 210°C for 2 hours: colourless solid; MS (ISP): 202.8 ((M+H)⁺).

PROCEDURE B

Example 12

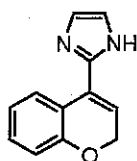
rac-2-Chroman-4-yl-1H-imidazole

a) rac-4-(1H-Imidazol-2-yl)-chroman-4-ol



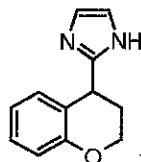
rac-4-(1H-Imidazol-2-yl)-chroman-4-ol was prepared from 4-chromanone and 2-(1-diethoxymethyl-1H-imidazol-2-yl)-lithium (prepared *in situ* from 1-(diethoxymethyl)imidazole by treatment with butyl lithium in tetrahydrofuran at -78°C) following Ohta's procedure (*Synthesis* 1990, 78): colourless solid; MS (EI): 216.2 (M^+), 95.1
10 (((O=C-2-imidazole) $^+$), 100%).

b) 2-(2H-Chromen-4-yl)-1H-imidazole



2-(2H-Chromen-4-yl)-1H-imidazole was prepared from rac-4-(1H-Imidazol-2-yl)-chroman-4-ol in analogy to Example 3 b) but temperature was kept at 0°C: light green
15 solid; MS (ISP): 199.1 (($M+H$) $^+$).

c) rac-2-Chroman-4-yl-1H-imidazole



To a solution of 100 mg (0.50 mmol) 2-(2H-chromen-4-yl)-1H-imidazole in 5 ml tetrahydrofuran were added 2.02 ml of a 1M solution of lithium aluminium hydride in
20 tetrahydrofuran and the mixture heated to reflux for 2 hours. Then the reaction mixture was cooled down to ambient temperature and the reaction quenched by slow addition of isopropanol. Water was added and the mixture was extracted with tert-butyl methyl

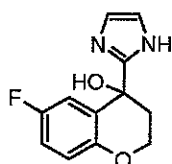
ether, the combined organic phase washed with brine, dried over Na_2SO_4 , filtered and evaporated. Purification of the crude product by flash-chromatography over a Si-NH_2 column with ethyl acetate as eluent provided rac-2-chroman-4-yl-1H-imidazole as colourless solid; MS (EI): 200.1 (M^+), 185.1 ($((\text{M}-\text{CH}_3)^+)$), 100%).

- 5 In analogy to Example 12, Example 13 was prepared.

Example 13

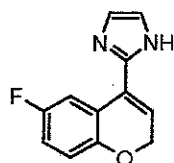
rac-2-(6-Fluoro-chroman-4-yl)-1H-imidazole

a) rac-6-Fluoro-4-(1H-imidazol-2-yl)-chroman-4-ol



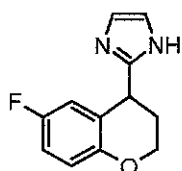
- 10 rac-6-Fluoro-4-(1H-imidazol-2-yl)-chroman-4-ol was prepared from 6-fluoro-chroman-4-one in analogy to Example 12 a); colourless solid; MS (ISP): 234.9 ($(\text{M}+\text{H})^+$).

b) 2-(6-Fluoro-2H-chromen-4-yl)-1H-imidazole



- 15 2-(6-Fluoro-2H-chromen-4-yl)-1H-imidazole was prepared from rac-6-fluoro-4-(1H-imidazol-2-yl)-chroman-4-ol in analogy to Example 12 b); colourless solid; MS (EI): 216.2 (M^+).

c) rac-2-(6-Fluoro-chroman-4-yl)-1H-imidazole



rac-2-(6-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 2-(6-fluoro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): colourless solid: MS (EI): 218.2 (M^+), 203.2 ($((M-CH_3)^+)$), 100%).

Tritium labeled Compounds

5

Synthesis of [3H]-labeled compounds by Pd-catalyzed tritio-dehalogenation reaction of brominated precursors with tritium gas: General procedure.

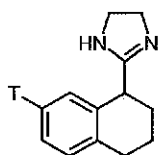
A 2 ml reaction flask containing a solution of 25 – 50 μ mol of the brominated precursor, 15 - 20 mg of Pd/C (10%) and 6 - 10 μ l of triethylamine in 1 ml of methanol was
10 connected to the tritium manifold system (RC TRITEC AG, Teufen, Switzerland). The reaction vessel and its contents were degassed by freeze-thaw evacuation cycle and then exposed to 10 - 18 Ci of carrier-free tritium gas. Stirring was continued for 2 - 5 h at room temperature.

The solution was evaporated in vacuo and any exchangeable tritium was removed by
15 repeated lyophilization from 3 x 1 ml of methanol. The residue was dissolved in 1 - 2 ml of ethanol and filtered through a PTFE syringe filter (0.2 μ m) to remove the catalyst. After rinsing the filter with 4 - 8 ml of ethanol the solvent was evaporated, the residue dissolved in methanol and purified subsequently by HPLC on a standard C-18 or C-8 column.

20

Example 14

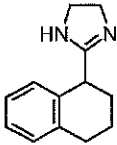
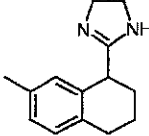
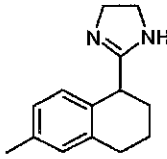
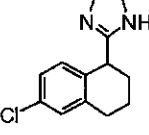
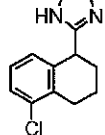
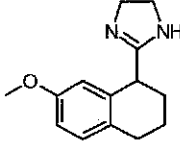
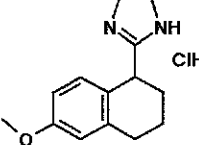
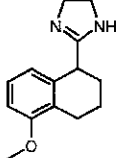
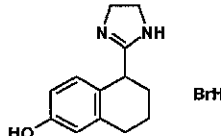
rac-2-(7-Tritio-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

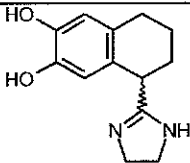
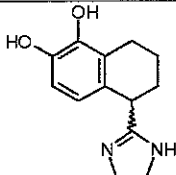
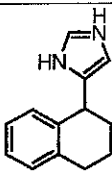


rac-2-(7-Tritio-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was
25 prepared from rac-2-(7-Bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole by catalytic hydrogenation with tritium gas: > 98% radiochemical purity, specific activity 32 Ci/mmol.

30

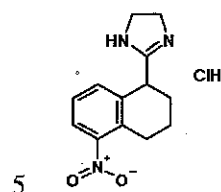
Known compounds:

Example No.	Structure	Name
15		rac-2-(1,2,3,4-tetrahydro-1-naphthyl)-2-imidazoline
16		rac-2-(7-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
17		rac-2-(6-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
18		rac-2-(6-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
19		rac-2-(5-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
20		rac-2-(7-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
21		rac-2-(6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
22		rac-2-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
23		rac-5-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ol

24		rac-5-(4,5-Dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalene-2,3-diol
25		rac-5-(4,5-Dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalene-1,2-diol
56		rac-4-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-1H-imidazole

Example 26

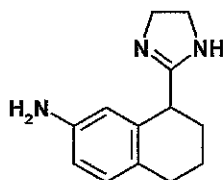
rac-2-(5-Nitro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
hydrochloride



rac-2-(5-Nitro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole was prepared from 5-nitro-3,4-dihydro-2H-naphthalen-1-one in analogy to Example 3: colourless solid; MS (ISP): 246.1 ((M+H)⁺).

Example 27

10 rac-8-(4,5-Dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ylamine

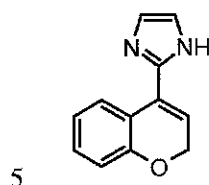


rac-8-(4,5-Dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-ylamine was prepared from 7-nitro-3,4-dihydro-2H-naphthalen-1-one in analogy to Example 3 providing rac-2-(7-nitro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

which was reduced to the title compound by methods known in the art: colourless solid;
MS (ISP): 216.4 ((M+H)⁺).

Example 28

2-(2H-Chromen-4-yl)-1H-imidazole

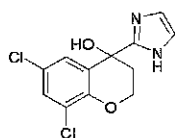


2-(2H-Chromen-4-yl)-1H-imidazole was prepared from rac-4-(1H-Imidazol-2-yl)-chroman-4-ol in analogy to Example 3 b) but temperature was kept at 0°C: light green solid; MS (ISP): 199.1 ((M+H)⁺).

Example 29

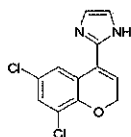
10 2-(6,8-Dichloro-2H-chromen-4-yl)-1H-imidazole

a) rac-6,8-Dichloro-4-(1H-imidazol-2-yl)-chroman-4-ol



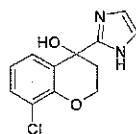
rac-6,8-Dichloro-4-(1H-imidazol-2-yl)-chroman-4-ol was prepared from 6,8-dichloro-chroman-4-one in analogy to Example 12 a): colourless solid; MS (ISP): 284.8 ((M+H)⁺).

15 b) 2-(6,8-Dichloro-2H-chromen-4-yl)-1H-imidazole



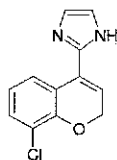
2-(6,8-Dichloro-2H-chromen-4-yl)-1H-imidazole was prepared from rac-6,8-dichloro-4-(1H-imidazol-2-yl)-chroman-4-ol in analogy to Example 3 b) but temperature was kept at 0°C: colourless solid; MS (EI): 266.1 ((M⁺), 100%).

2-(8-Chloro-2H-chromen-4-yl)-1H-imidazole

a) rac-8-Chloro-4-(1H-imidazol-2-yl)-chroman-4-ol

rac-8-Chloro-4-(1H-imidazol-2-yl)-chroman-4-ol was prepared from 8-chloro-chroman-4-one in analogy to Example 12 a): colourless solid; MS (ISP): 250.9

5 (((M+H)⁺), 100%).

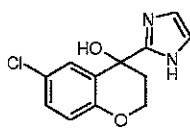
b) 2-(8-Chloro-2H-chromen-4-yl)-1H-imidazole

2-(8-Chloro-2H-chromen-4-yl)-1H-imidazole was prepared from rac-8-chloro-4-(1H-imidazol-2-yl)-chroman-4-ol in analogy to Example 3 b) but temperature was kept at

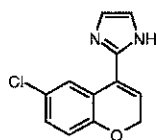
10 0°C: off-white solid: MS (EI): 232.1 ((M⁺), 100%).

Example 31

2-(6-Chloro-2H-chromen-4-yl)-1H-imidazole

a) rac-6-Chloro-4-(1H-imidazol-2-yl)-chroman-4-ol

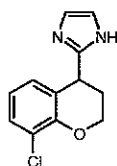
15 rac-6-Chloro-4-(1H-imidazol-2-yl)-chroman-4-ol was prepared from 6-chloro-chroman-4-one in analogy to Example 12 a): off-white solid; MS (ISP): 250.9
(((M+H)⁺), 100%).

b) 2-(6-Chloro-2H-chromen-4-yl)-1H-imidazole

2-(6-Chloro-2H-chromen-4-yl)-1H-imidazole was prepared from rac-6-chloro-4-(1H-imidazol-2-yl)-chroman-4-ol in analogy to Example 3 b) but temperature was kept at 0°C: light brown solid: MS (EI): 232.1 ((M^+) , 100%).

Example 32

5 rac-2-(8-Chloro-chroman-4-yl)-1H-imidazole

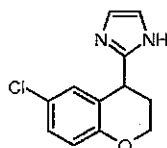


rac-2-(8-Chloro-chroman-4-yl)-1H-imidazole was prepared from 2-(8-chloro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): colourless solid: MS (EI): 234.2 (M^+), 219.1 ($((M-CH_3)^+)$, 100%).

10

Example 33

rac-2-(6-Chloro-chroman-4-yl)-1H-imidazole



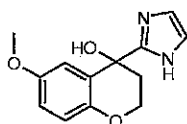
rac-2-(6-Chloro-chroman-4-yl)-1H-imidazole was prepared from 2-(6-chloro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): colourless solid: MS (ISP):

15 235.1 ($((M+H)^+)$, 100%).

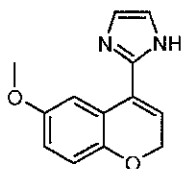
Example 34

rac-2-(6-Methoxy-chroman-4-yl)-1H-imidazole

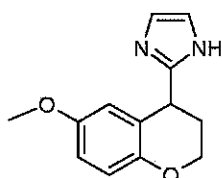
a) rac-4-(1H-Imidazol-2-yl)-6-methoxy-chroman-4-ol



20 rac-4-(1H-Imidazol-2-yl)-6-methoxy-chroman-4-ol was prepared from 6-methoxy-chroman-4-one in analogy to Example 12 a): off-white solid; MS (ISP): 247.0 ($((M+H)^+)$).

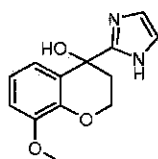
b) 2-(6-Methoxy-2H-chromen-4-yl)-1H-imidazole

2-(6-Methoxy-2H-chromen-4-yl)-1H-imidazole was prepared from rac-6-fluoro-4-(1H-imidazol-2-yl)-chroman-4-ol in analogy to Example 12 b): off-white solid; MS (EI): 228.2
 5 ((M⁺), 100%), 213.1 ((M-CH₃)⁺).

c) rac-2-(6-Methoxy-chroman-4-yl)-1H-imidazole

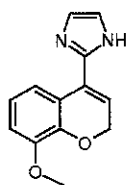
rac-2-(6-Methoxy-chroman-4-yl)-1H-imidazole was prepared from 2-(6-methoxy-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): off-white solid; MS (EI): 230.2
 10 ((M⁺), 100%), 215.2 ((M-CH₃)⁺).

Example 35

rac-2-(8-Methoxy-chroman-4-yl)-1H-imidazolea) rac-4-(1H-Imidazol-2-yl)-8-methoxy-chroman-4-ol

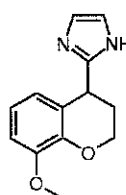
15 rac-4-(1H-Imidazol-2-yl)-8-methoxy-chroman-4-ol was prepared from 8-methoxy-chroman-4-one in analogy to Example 12 a): colourless solid; MS (EI): 246.2 (M⁺), 228.2 ((M-H₂O)⁺), 95.2 (((C(=O)-2-imidazolyl)⁺), 100%).

b) 2-(8-Methoxy-2H-chromen-4-yl)-1H-imidazole



2-(8-Methoxy-2H-chromen-4-yl)-1H-imidazole was prepared from rac-4-(1H-imidazol-2-yl)-8-methoxy-chroman-4-ol in analogy to Example 12 b): off-white solid: MS (EI): 228.1 ((M^+) , 100%).

5 c) rac-2-(8-Methoxy-chroman-4-yl)-1H-imidazole

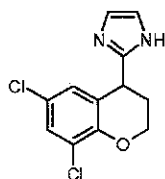


rac-2-(8-Methoxy-chroman-4-yl)-1H-imidazole was prepared from 2-(8-methoxy-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): colourless solid: MS (ISP): 231.1 ($(M+H)^+$).

10

Example 36

rac-2-(6,8-Dichloro-chroman-4-yl)-1H-imidazole

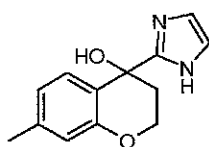


15 rac-2-(6,8-Dichloro-chroman-4-yl)-1H-imidazole was prepared from 2-(6,8-dichloro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 3 b) but temperature was kept at ambient temperature for 2 hours: colourless solid: MS (EI): 268.1 ((M^+)), 253.1 ($((M-CH_3)^+)$, 100%).

Example 37

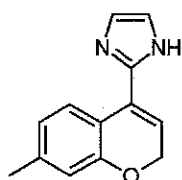
rac-2-(7-Methyl-chroman-4-yl)-1H-imidazole

a) rac-4-(1H-Imidazol-2-yl)-7-methyl-chroman-4-ol



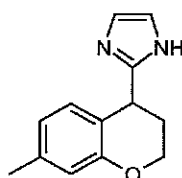
rac-4-(1H-Imidazol-2-yl)-7-methyl-chroman-4-ol was prepared from 7-methyl-chroman-4-one in analogy to Example 12 a): colourless solid; MS (EI): 230.2 (M^+), 212.2 ($(M-H_2O)^+$), 183.2 ($(M-(H_2O+H+CO))^+$), 95.2 ($((C=O)-2\text{-imidazolyl})^+$),
 5 100%).

b) 2-(7-Methyl-2H-chromen-4-yl)-1H-imidazole



2-(7-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from rac-4-(1H-imidazol-2-yl)-7-methyl-chroman-4-ol in analogy to Example 12 b): light yellow solid; MS (EI):
 10 212.2 (M^+), 100%).

c) rac-2-(7-Methyl-chroman-4-yl)-1H-imidazole

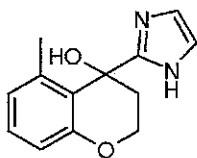


rac-2-(7-Methyl-chroman-4-yl)-1H-imidazole was prepared from 2-(7-methyl-2H-chromen-4-yl)-1H-imidazole in analogy to Example 3 b) but temperature was kept at
 15 ambient temperature for 18 hours: colourless solid; MS (EI): 214.2 (M^+), 199.2 ($((M-CH_3)^+)$), 100%).

Example 38

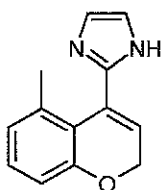
2-(5-Methyl-2H-chromen-4-yl)-1H-imidazole

a) rac-4-(1H-Imidazol-2-yl)-5-methyl-chroman-4-ol



rac-4-(1H-Imidazol-2-yl)-5-methyl-chroman-4-ol was prepared from 5-methyl-chroman-4-one in analogy to Example 12 a): colourless solid; MS (EI): 230.2 ((M^+) , 100%), 95.2 ($(C(=O)-2\text{-imidazolyl})^+$).

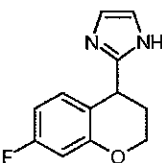
5 b) 2-(5-Methyl-2H-chromen-4-yl)-1H-imidazole



2-(5-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared by heating a solution of rac-4-(1H-imidazol-2-yl)-5-methyl-chroman-4-ol in 4N aqueous HCl for 16 hours. The reaction mixture was cooled to ambient temperature, pH adjusted to 10 by addition of ammonia and extracted with tert.-butyl methyl ether. The collected organic phases were washed with brine, dried over Na_2SO_4 , filtered and evaporated: colourless solid; MS (ISP): 213.1 ($(M+H)^+$).

Example 39

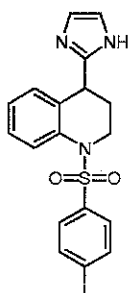
rac-2-(7-Fluoro-chroman-4-yl)-1H-imidazole



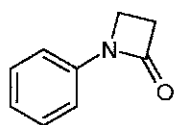
rac-2-(7-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 7-fluoro-chroman-4-one in analogy to Example 13: colourless solid; MS (EI): 218.1 (M^+), 203.1 ($(M-CH_3)^+$, 100%).

Example 40

20 rac-4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline

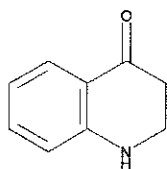


a) 1-Phenyl-azetidin-2-one



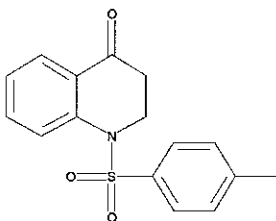
- 1-Phenyl-azetidin-2-one was prepared from azetidin-2-one and iodobenzene by treatment with trans-1,2-diaminocyclohexane, copper(I) iodide and potassium carbonate according to the procedure described in *J. Am. Chem. Soc.* 2001, 123, 7727-7729; off-white crystalline solid; MS (ISP): 148.4 ($[M+H]^+$, 100%).

b) 2,3-Dihydro-4(1H)-quinolinone



- 2,3-Dihydro-4(1H)-quinolinone was prepared from 1-phenyl-azetidin-2-one by treatment with trifluoromethanesulfonic acid in 1,2-dichloroethane according to the procedure described in *Tetrahedron* 2002, 58, 8475-8481; yellow oil; MS (ISP): 148.3 ($[M+H]^+$, 100%).

c) 1-(Toluene-4-sulfonyl)-2,3-dihydro-1H-quinolin-4-one

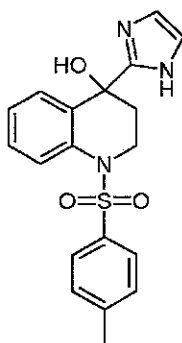


15

To a solution of 2.57 g (17.5 mmol) 2,3-dihydro-4(1H)-quinolinone in 20 ml dichloromethane at 0 °C was added dropwise 9.09 ml (65.6 mmol) triethylamine. Then

5.25 g (27.5 mmol) p-toluenesulphonyl chloride was added and the reaction mixture was heated at reflux for 16 hours. After cooling to room temperature the mixture was diluted with dichloromethane and washed sequentially with 1 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated brine. The phases were separated and the organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, ethyl acetate/heptane) to afford 1.55 g (29%) of the title compound as a white crystalline solid. MS (ISP): 302.4 ($[\text{M}+\text{H}]^+$, 100%).

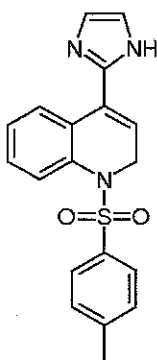
d) rac-4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinolin-4-ol



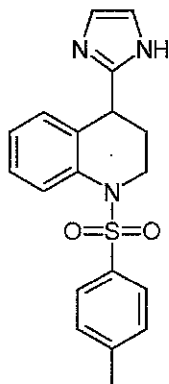
10

rac-4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinolin-4-ol was prepared from 1-(toluene-4-sulfonyl)-2,3-dihydro-1H-quinolin-4-one and 2-(1-diethoxymethyl-1H-imidazol-2-yl)-lithium in analogy to Example 12 a): off-white foam; MS (ISP): 370.1 ($[\text{M}+\text{H}]^+$, 100%).

15 e) 4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2-dihydro-quinoline



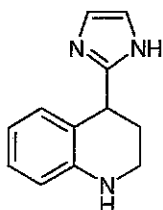
20 MS (ISP): 352.3 ($[\text{M}+\text{H}]^+$, 100%).

f) rac-4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline

- rac-4-(1H-Imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline was prepared from 4-(1H-imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2-dihydro-quinoline and lithium aluminium hydride in tetrahydrofuran at reflux in analogy to Example 12 c): off-white foam; MS (ISP): 354.3 ($[M+H]^+$, 100%).

Example 41

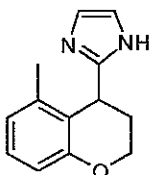
rac- 4-(1H-Imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline



- rac- 4-(1H-Imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline was obtained as a by-product during the preparation of rac-4-(1H-imidazol-2-yl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline as described in Example 40f): off-white amorphous solid; MS (ISP): 200.4 ($[M+H]^+$, 100%).

Example 42

- rac-2-(5-Methyl-chroman-4-yl)-1H-imidazole



rac-2-(5-Methyl-chroman-4-yl)-1H-imidazole was prepared from 2-(5-methyl-2H-chromen-4-yl)-1H-imidazole by hydrogenation at 100 bar with 10% Pd/C as catalyst in ethyl acetate at 50°C for 18 hours. After usual workup the residue was purified by flash-chromatography on silica gel with a gradient of ethyl acetate/methanol 5% - 30% as
5 eluent: colourless solid; MS (ISP): 215.2 ((M+H)⁺).

Example 43

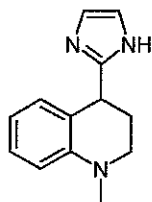
rac-2-(5-Fluoro-chroman-4-yl)-1H-imidazole



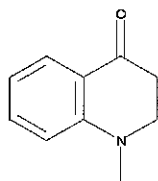
rac-2-(5-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 5-fluoro-chroman-4-one in analogy to Example 13: colourless solid; MS (ISP): 219.1 ((M+H)⁺).
10

Example 44

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



a) 1-Methyl-2,3-dihydro-1H-quinolin-4-one

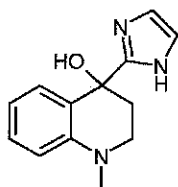


15

This compound was prepared according to the procedure described in *J. Med. Chem.* 2003, 46, 1962-1979. To a solution of 220 mg (1.49 mmol) 2,3-dihydro-4(1H)-quinolinone in 3 ml acetone in a pressure tube was added 620 mg (4.48 mmol) potassium carbonate. Then 0.38 ml (5.98 mmol) iodomethane was added dropwise, the tube was
20 sealed, and the reaction mixture was heated at 80 °C for 16 hours. After cooling to room temperature the mixture was diluted with ethyl acetate and washed with saturated brine.

The phases were separated and the organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, ethyl acetate/heptane) to afford 147 mg (61%) of the title compound as a light yellow oil. MS (ISP): 162.1 ($[\text{M}+\text{H}]^+$, 100%).

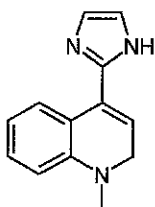
5 b) rac-4-(1H-Imidazol-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-4-ol



rac-4-(1H-Imidazol-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-4-ol was prepared from 1-methyl-2,3-dihydro-1H-quinolin-4-one and 2-(1-diethoxymethyl-1H-imidazol-2-yl)-lithium in analogy to Example 12 a): off-white crystalline solid; MS (ISP): 230.4

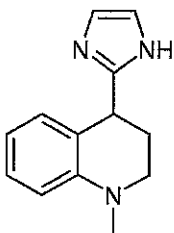
10 ($[\text{M}+\text{H}]^+$, 54%), 212.1 ($[\text{M}+\text{H}-\text{H}_2\text{O}]^+$, 100%).

c) 4-(1H-Imidazol-2-yl)-1-methyl-1,2-dihydro-quinoline



4-(1H-Imidazol-2-yl)-1-methyl-1,2-dihydro-quinoline was prepared from rac-4-(1H-imidazol-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-4-ol and sulfuric acid in ethanol at
15 50 °C in analogy to Example 12 b): orange crystalline solid: MS (ISP): 212.3 ($[\text{M}+\text{H}]^+$, 100%).

d) rac-4-(1H-Imidazol-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinoline



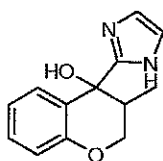
rac-4-(1H-Imidazol-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinoline was prepared from 4-(1H-imidazol-2-yl)-1-methyl-1,2-dihydro-quinoline and lithium aluminium hydride in
20

tetrahydrofuran at reflux in analogy to Example 12 c): off-white crystalline solid; MS (ISP): 214.1 ($[M+H]^+$, 100%).

Example 45

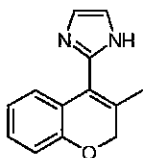
2-(3-Methyl-2H-chromen-4-yl)-1H-imidazole

5 a) rac-4-(1H-Imidazol-2-yl)-3-methyl-chroman-4-ol



rac-4-(1H-Imidazol-2-yl)-3-methyl-chroman-4-ol was prepared from 3-methyl-chroman-4-one in analogy to Example 12 a): colourless solid; MS (ISP): 231.1 ($(M+H)^+$).

10 b) 2-(3-Methyl-2H-chromen-4-yl)-1H-imidazole

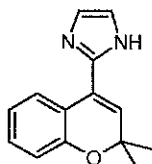


2-(3-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from rac-4-(1H-imidazol-2-yl)-3-methyl-chroman-4-ol in analogy to Example 38 b): light brown solid; MS (ISP): 213.0 ($(M+H)^+$).

15

Example 46

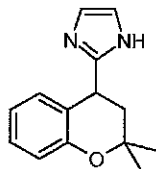
2-(2,2-Dimethyl-2H-chromen-4-yl)-1H-imidazole



2-(2,2-Dimethyl-2H-chromen-4-yl)-1H-imidazole was prepared from 2,2-dimethyl-chroman-4-one in analogy to Example 38: yellow solid; MS (ISP): 227.0 ($(M+H)^+$).

Example 47

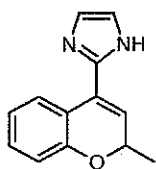
rac-2-(2,2-Dimethyl-chroman-4-yl)-1H-imidazole



- 5 rac-2-(2,2-Dimethyl-chroman-4-yl)-1H-imidazole was prepared from 2-(2,2-dimethyl-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: colourless solid; MS (ISP): 229.2 ((M+H)⁺).

Example 48

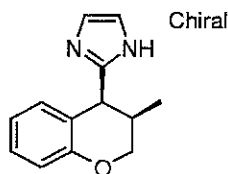
rac-2-(2-Methyl-2H-chromen-4-yl)-1H-imidazole



- 10 rac-2-(2-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from rac-2-methyl-chroman-4-one in analogy to Example 38: light brown solid; MS (ISP): 213.0 ((M+H)⁺).

Example 49

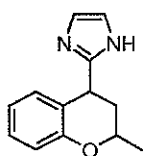
(3R,4S or 3S,4R)-2-(3-Methyl-chroman-4-yl)-1H-imidazole



- 15 (3R,4S or 3S,4R)-2-(3-Methyl-chroman-4-yl)-1H-imidazole was obtained by chromatographic separation of a diastereomeric mixture of rac-2-(3-methyl-chroman-4-yl)-1H-imidazole (Example 53) on a Chiralpak AD column with heptane/ethanol 93:7 as eluent: colourless solid; MS (ISP): 215.1 ((M+H)⁺).

Example 50

- 20 rac-2-(2-Methyl-chroman-4-yl)-1H-imidazole

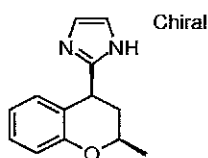


rac-2-(2-Methyl-chroman-4-yl)-1H-imidazole was prepared from rac-2-(2-methyl-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: light green solid; MS (ISP): 215.1 ((M+H)⁺).

5

Example 51

(2R,4S or 2S,4R)-2-(2-Methyl-chroman-4-yl)-1H-imidazole

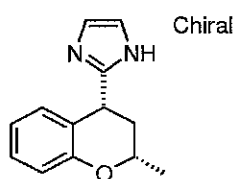


(2R,4S or 2S,4R)-2-(2-Methyl-chroman-4-yl)-1H-imidazole was obtained from rac-2-(2-methyl-chroman-4-yl)-1H-imidazole in analogy to Example 49: colourless solid; MS

10 (ISP): 215.1 ((M+H)⁺).

Example 52

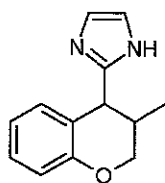
(2S,4R or 2R,4S)-2-(2-Methyl-chroman-4-yl)-1H-imidazole



15 (2S,4R or 2R,4S)-2-(2-Methyl-chroman-4-yl)-1H-imidazole was obtained from rac-2-(2-methyl-chroman-4-yl)-1H-imidazole in analogy to Example 49: colourless solid; MS (ISP): 215.1 ((M+H)⁺).

Example 53

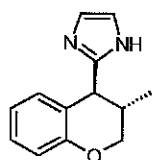
rac-2-(3-Methyl-chroman-4-yl)-1H-imidazole



- rac-2-(3-Methyl-chroman-4-yl)-1H-imidazole was prepared from rac-4-(1H-imidazol-2-yl)-3-methyl-chroman-4-ol by reduction with lithium in liquid ammonia for 30 min. The blue reaction mixture was quenched by addition of solid ammonium chloride, the ammonia evaporated and the residue distributed between water and t-butyl methyl ether. The organic phase was washed with brine, dried over sodium sulfate, filtered and evaporated. rac-2-(3-Methyl-chroman-4-yl)-1H-imidazole was obtained as colourless solid; MS (ISP): 215.1 ((M+H)⁺).

Example 54

- (3S,4S and 3R,4R)-2-(3-Methyl-chroman-4-yl)-1H-imidazole

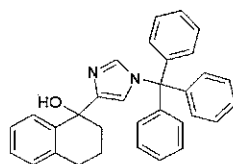


- The racemic mixture of (3S,4S and 3R,4R)-2-(3-methyl-chroman-4-yl)-1H-imidazole was obtained (together with both separated cis-isomers) from rac-2-(3-methyl-chroman-4-yl)-1H-imidazole in analogy to Example 49: colourless solid; MS (ISP): 215.1 ((M+H)⁺).

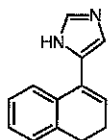
Example 55

(4-(3,4-Dihydro-naphthalen-1-yl)-1H-imidazole

a) 1-(1-Trityl-1H-imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol



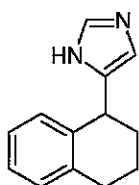
- 1-(1-Trityl-1H-imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol was prepared from 4-iodo-1-trityl-1H-imidazole and alpha-tetralone following the procedure described by X. Zhang et al., J. Med. Chem. 40, 3014 (1997): colourless solid; MS (ISP): 457.5 ((M+H)⁺).

b) 4-(3,4-Dihydro-naphthalen-1-yl)-1H-imidazole

4-(3,4-Dihydro-naphthalen-1-yl)-1H-imidazole was prepared by reaction of 1-(1-trityl-1H-imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol with a solution of trifluoroacetic acid in water 6:4 following the procedure described by X. Zhang et al., J. Med. Chem. 40, 3014 (1997); colourless solid; MS (ISP): 197.3 ((M+H)⁺).

Example 56

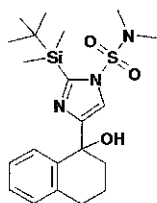
rac-4-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-1H-imidazole



rac-4-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-1H-imidazole was prepared from 4-(3,4-dihydro-naphthalen-1-yl)-1H-imidazole in analogy to Example 42 but hydrogen pressure was kept at 3.5 bar and the reaction run at ambient temperature for 5 hours: colourless solid; MS (EI): 198.2 ((M⁺), 100%).

Example 57

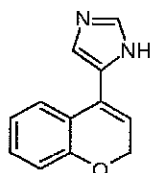
15 4-(3,4-Dihydro-naphthalen-1-yl)-1H-imidazole

a) 2-(tert-Butyl-dimethyl-silanyl)-4-(1-hydroxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-imidazole-1-sulfonic acid dimethylamide


2-(tert-Butyl-dimethyl-silanyl)-4-(1-hydroxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-imidazole-1-sulfonic acid dimethylamide was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and chroman-4-one in analogy to the

procedure published by S. Ohta et al., Synthesis 1990, 78: light brown viscous oil; MS (ISP): 438.5 ((M+H)⁺).

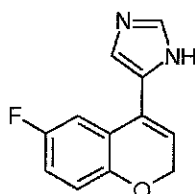
b) 5-(2H-Chromen-4-yl)-1H-imidazole or tautomer



- 5 5-(2H-Chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-4-(1-hydroxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-imidazole-1-sulfonic acid dimethylamide in analogy to Example 38 b) but in aqueous 2N HCl solution at reflux for 2 hours: colourless solid; MS (EI): 198.2 ((M⁺), 100%).

Example 58

- 10 5-(6-Fluoro-2H-chromen-4-yl)-1H-imidazole or tautomer

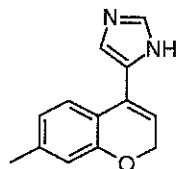


5-(6-Fluoro-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 6-fluoro-chroman-4-one in analogy to Example 57: off-white solid; MS (EI): 216.1 ((M⁺), 100%).

15

Example 59

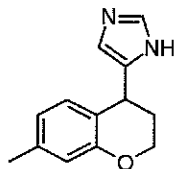
- 5-(7-Methyl-2H-chromen-4-yl)-1H-imidazole or tautomer



- 5-(7-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 7-methyl-chroman-4-one in analogy to Example 57: light brown solid; MS (EI): 212.2 ((M⁺), 100%).
- 20

Example 60

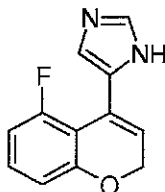
rac-5-(7-Methyl-chroman-4-yl)-1H-imidazole or tautomer



- 5 rac-5-(7-Methyl-chroman-4-yl)-1H-imidazole was prepared from 5-(7-methyl-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: colourless solid; MS (EI): 214.2 ((M⁺), 100%).

Example 61

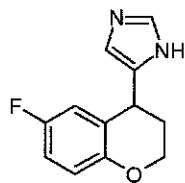
5-(5-Fluoro-2H-chromen-4-yl)-1H-imidazole or tautomer



- 10 5-(5-Fluoro-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 5-fluoro-chroman-4-one in analogy to Example 57: colourless solid; MS (EI): 216.2 ((M⁺), 100%).

Example 62

rac-5-(6-Fluoro-chroman-4-yl)-1H-imidazole or tautomer

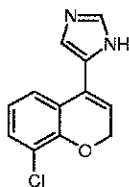


15

- rac-5-(6-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 5-(6-fluoro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c): colourless solid; MS (EI): 218.2 ((M⁺), 100%).

Example 63

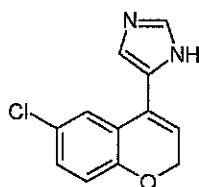
5-(8-Chloro-2H-chromen-4-yl)-1H-imidazole or tautomer



5-(8-Chloro-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 8-chloro-chroman-4-one in analogy to Example 57: off-white solid; MS (EI): 232.1 ((M^+) , 100%).

Example 64

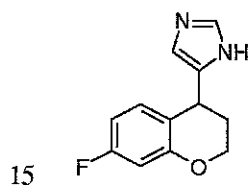
5-(6-Chloro-2H-chromen-4-yl)-1H-imidazole or tautomer



10 5-(6-Chloro-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 6-chloro-chroman-4-one in analogy to Example 57: off-white solid; MS (EI): 232.1 ((M^+) , 100%).

Example 65

rac-5-(7-Fluoro-chroman-4-yl)-1H-imidazole or tautomer

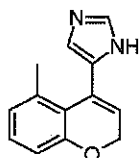


15 rac-5-(7-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 5-(7-fluoro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: colourless solid; MS (ISP): 219.1 ($(M+H)^+$).

Example 66

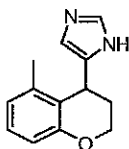
rac-5-(5-Methyl-chroman-4-yl)-1H-imidazole or tautomer

a) 5-(5-Methyl-2H-chromen-4-yl)-1H-imidazole or tautomer



- 5 5-(5-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 5-methyl-chroman-4-one in analogy to Example 57: colourless solid; MS (EI): 212.2 ((M⁺), 100%).

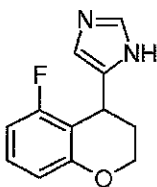
b) rac-5-(5-Methyl-chroman-4-yl)-1H-imidazole or tautomer



- 10 rac-5-(5-Methyl-chroman-4-yl)-1H-imidazole was prepared from 5-(5-methyl-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: colourless solid; MS (ISP): 215.2 ((M+H)⁺).

Example 67

rac-5-(5-Fluoro-chroman-4-yl)-1H-imidazole or tautomer

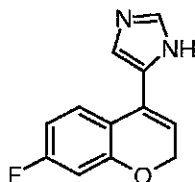


15

rac-5-(5-Fluoro-chroman-4-yl)-1H-imidazole was prepared from 5-(5-fluoro-2H-chromen-4-yl)-1H-imidazole in analogy to Example 42: colourless solid; MS (ISP): 219.1 ((M+H)⁺).

Example 68

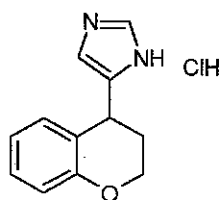
5-(7-Fluoro-2H-chromen-4-yl)-1H-imidazole or tautomer



5-(7-Fluoro-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 7-fluoro-chroman-4-one in analogy to Example 57: light brown solid; MS (ISP): 217.1 ((M+H)⁺).

Example 69

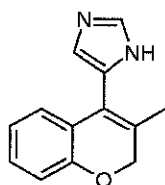
rac-5-Chroman-4-yl-1H-imidazole hydrochloride or tautomer



10 rac-5-Chroman-4-yl-1H-imidazole was prepared from 5-(2H-chromen-4-yl)-1H-imidazole in analogy to Example 12 c). Compound was isolated as hydrochloride: off-white solid; MS (ISP): 201.1 ((M+H)⁺).

Example 70

5-(3-Methyl-2H-chromen-4-yl)-1H-imidazole or tautomer

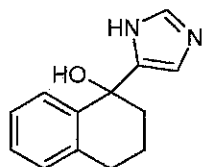


15

5-(3-Methyl-2H-chromen-4-yl)-1H-imidazole was prepared from 2-(tert-butyl-dimethyl-silanyl)-imidazole-1-sulfonic acid dimethylamide and 3-methyl-chroman-4-one in analogy to Example 57: light brown solid; MS (ISP): 213.0 ((M+H)⁺).

Example 71

rac-1-(1H-Imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol or tautomer

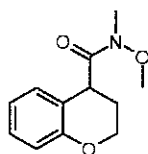


rac-1-(1H-Imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol was prepared from rac-1-(1-trityl-1H-imidazol-4-yl)-1,2,3,4-tetrahydro-naphthalen-1-ol (Example 55 a)) by deprotection with formic acid/tetrahydrofuran/water 1:1:0.1 in analogy of a procedure described by A. Ojima et al., Org. Lett. 4, 3051 (2002): colourless solid; MS (ISP): 215.3 ((M+H)⁺).

Example 72

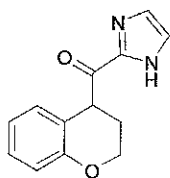
10 rac-2-Chroman-4-ylmethyl-1H-imidazole

a) rac-Chroman-4-carboxylic acid methoxy-methyl-amide



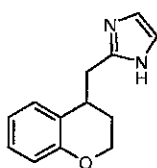
To a solution of 500 mg (2.8 mmol) chroman-4-carboxylic acid in 10 ml dichloromethane were added 330 mg (3.2 mmol) N,O-dimethylhydroxylamine hydrochloride and 993 mg (3.2 mmol) N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride and the mixture stirred at ambient temperature for 5 min. Then 710 mg (0.98 ml, 10 mmol) triethylamine were added drop-wise and the resulting mixture stirred at ambient temperature for 4 hours. For workup 2M HCl solution was added, the organic solvent evaporated and the residue extracted with tert-butyl methyl ether. the combined organic phase was washed with brine, dried over Na₂SO₄, filtered and evaporated: 503 mg rac-chroman-4-carboxylic acid methoxy-methyl-amide as light brown oil; MS (EI): 221.2 (M⁺), 133.1 (((M - C(=O)N(CH₃)OCH₃)⁺), 100%).

b) rac-Chroman-4-yl-(1H-imidazol-2-yl)-methanone



rac-Chroman-4-yl-(1H-imidazol-2-yl)-methanone was prepared from rac-chroman-4-carboxylic acid methoxy-methyl-amide in analogy to Example 12 a): colourless gum; MS (ISP): 228.9 ((M+H)⁺).

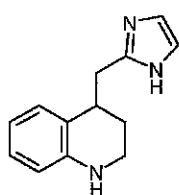
5 c) rac-2-Chroman-4-ylmethyl-1H-imidazole



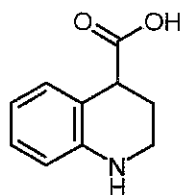
rac-2-Chroman-4-ylmethyl-1H-imidazole was prepared from rac-chroman-4-yl-(1H-imidazol-2-yl)-methanone in a Wolff-Kishner type reduction following the published procedure of E. Reimann et al., Arch. Pharm. (Weinheim) 322, 363 (1989): yellow gum;
10 MS (ISP): 215.1 M+H⁺).

Example 73

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



a) rac-1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid

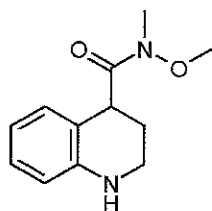


15

rac-1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid was prepared from quinoline-4-carboxylic acid by treatment with Raney nickel in aqueous sodium hydroxide according to the procedure described in *Khimiya Geterotsiklicheskikh Soedinenii* 1988, 77-9; brown

crystals; $^1\text{H-NMR}$ (CDCl_3): 2.04 (1H, m), 2.29 (1H, m), 3.24-3.46 (br m, 3 H, CH_2N and NH), 3.77 (1H, t, CHCO_2), 6.55 (1H, d, ArH), 6.67 (1H, dd, ArH), 7.04 (1H, dd, ArH), 7.15 (1H, d, ArH).

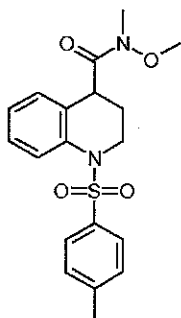
b) rac-1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid methoxy-methyl-amide



5

To a solution of 0.50 g (2.82 mmol) rac-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid in 12 ml dichloromethane were added 0.36 g (3.67 mmol) N,O-dimethylhydroxylamine hydrochloride and 0.40 ml (3.67 mmol) N-methylmorpholine. The mixture was cooled to 0 °C, then 0.70 g (3.67 mmol) 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) was added and the reaction mixture was stirred at room temperature for 16 hours. The mixture was then concentrated *in vacuo* and the residue was purified by chromatography (silica gel, ethyl acetate/heptane gradient) to afford 0.29 g (47%) of the title compound as a yellow crystalline solid. MS (ISP): 221.4 ($[\text{M}+\text{H}]^+$, 100%).

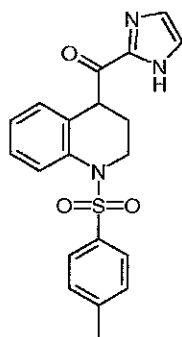
15 c) rac-1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methoxy-methyl-amide



To a solution of 0.29 g (1.32 mmol) rac-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methoxy-methyl-amide in 5 ml 1,2-dichloroethane was added dropwise 0.46 ml (3.29 mmol) triethylamine. Then 0.33 g (1.71 mmol) p-toluenesulphonyl chloride was added and the reaction mixture was heated at 70 °C for 4 hours. After cooling to room temperature the mixture was concentrated *in vacuo* and the residue was purified by chromatography (silica gel, methanol/dichloromethane gradient) to afford 0.44 g (90%) of the title compound as a brown crystalline solid. MS (ISP): 375.1 ($[\text{M}+\text{H}]^+$, 100%).

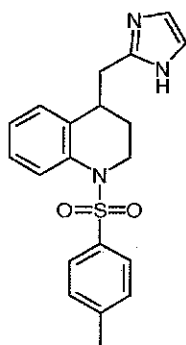
20

d) rac-(1H-Imidazol-2-yl)-[1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-methanone



To a solution of 0.21 ml (1.29 mmol) 1-(diethoxymethyl)imidazole in 2 ml
5 tetrahydrofuran at -78°C was added dropwise 0.88 ml (1.41 mmol) of a 1.6 M solution
of n-butyllithium in hexane. The resulting solution of 2-(1-diethoxymethyl-1H-imidazol-
2-yl)-lithium was stirred at -78°C , and then added dropwise to a solution of 0.44 g (1.18
mmol) rac-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid
methoxy-methyl-amide in 4 ml tetrahydrofuran at 0°C . The reaction mixture was then
10 stirred at 0°C for 1 h, before being quenched by dropwise addition of 2 M aqueous
hydrochloric acid. The mixture was made basic by addition of aqueous sodium
bicarbonate solution and diluted with ethyl acetate. The phases were separated and the
organic phase was washed with saturated brine, dried over Na_2SO_4 , filtered and
concentrated *in vacuo*. The residue was purified by chromatography (silica gel, ethyl
15 acetate/heptane gradient) to afford 0.23 g (52%) of the title compound as a light yellow
crystalline solid. MS (ISP): 382.3 ($[\text{M}+\text{H}]^+$, 100%).

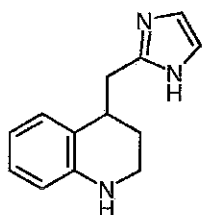
e) rac-4-(1H-Imidazol-2-ylmethyl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline



This compound was prepared following methodology reported in *Arch. Pharm.* 1989,
20 322, 363-367. To a solution of 0.23 g (0.60 mmol) rac-(1H-imidazol-2-yl)-[1-(toluene-4-
sulfonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-methanone in 3 ml triethylene glycol were
added sequentially 96 mg (2.41 mmol) sodium hydroxide powder and 0.10 ml (1.99
mmol) hydrazine hydrate. The reaction mixture was stirred at 110°C for 1 h, and then at

200 °C for 2 h. After cooling to room temperature the mixture was diluted with ethyl acetate and washed sequentially with 2 N aqueous hydrochloric acid, aqueous sodium bicarbonate solution, water, and saturated brine. The phases were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was
5 purified by chromatography (silica gel, methanol/dichloromethane gradient) to afford 41 mg (19%) of the title compound as a yellow crystalline solid. MS (ISP): 368.1 ([M+H]⁺, 100%).

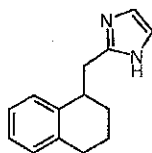
f) rac-4-(1H-Imidazol-2-ylmethyl)-1,2,3,4-tetrahydro-quinoline



10 This compound was prepared following methodology reported in *J. Med. Chem.* 1997, 40, 105-111. To 40 mg (0.11 mmol) rac-4-(1H-imidazol-2-ylmethyl)-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-quinoline were added sequentially 0.57 ml (3.27 mmol) of a 33% solution of HBr in acetic acid and 0.06 ml (0.54 mmol) anisole. The reaction mixture was stirred at room temperature for 3 h and then poured onto 2 N aqueous sodium
15 hydroxide solution. The mixture was diluted with ethyl acetate, the phases were separated, and the organic phase was washed with saturated brine. The phases were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, methanol/dichloromethane gradient) to afford 16 mg (69%) of the title compound as a
20 white foam. MS (ISP): 214.3 ([M+H]⁺, 100%).

Example 74

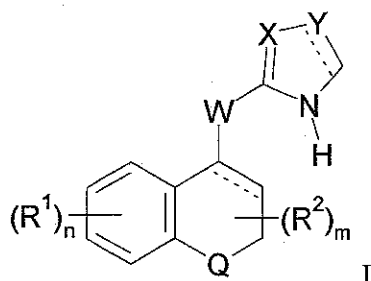
rac-2-(1,2,3,4-Tetrahydro-naphthalen-1-ylmethyl)-1H-imidazole



rac-2-(1,2,3,4-Tetrahydro-naphthalen-1-ylmethyl)-1H-imidazole was prepared from rac-
25 1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methoxy-methyl-amide in analogy to Example 72 b) and c): colourless solid; MS (ISP): 213.0 M+H⁺).

Claims

1. The use of compounds of formula I



wherein

R^1 is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen, nitro, amino or lower alkyl substituted by halogen;

R^2 is hydrogen, hydroxy or lower alkyl;

X is N and Y is CH or CH₂ or CH-lower alkyl or

X is CH and Y is N;

Q is CH₂, O, NH, N-alkyl, N-SO₂-alkyl or N-SO₂-toluen-4-yl;

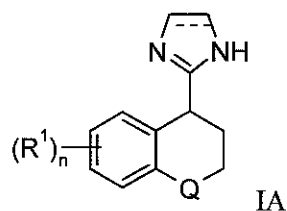
W is CH₂ or a bond

m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R^2 may be the same or not; when n is 2 or 3, R^1 may be the same or not;

the dotted lines may each be independently from one another a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I for the preparation of medicaments for the treatment of bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, and 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.

2. The use of compounds of formula IA



wherein

R^1 is hydrogen, tritium, hydroxy, lower alkyl, lower alkoxy, halogen or lower alkyl substituted by halogen;

Q is CH_2 or O;

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

the dotted line may be a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I for the preparation of medicaments for the treatment of 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, 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.

3. The use of compounds of formula I according to claim 1, wherein X is N.

4. The use according to claim 3, wherein Q is CH_2 and R^1 is halogen.

5. The use according to claim 4, wherein the compounds are

rac-2-(5-bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

rac-2-(7-chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole

rac-2-(6-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or

rac-2-(5-chloro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

6. The use according to claim 3, wherein Q is CH_2 and R^1 is lower alkyl.

7. The use according to claim 6, wherein the compounds are

rac-2-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole.

8. The use according to claim 3, wherein Q is CH₂ and R¹ is lower alkoxy.

5

9. The use according to claim 8, wherein the compounds are

rac-2-(7-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole
rac-2-(6-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or
rac-2-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

10

10. The use according to claim 3, wherein Q is O or NH and R¹ is hydrogen or halogen.

11. The use according to claim 10, wherein the compounds are

rac-2-(6,8-dichloro-chroman-4-yl)-1H-imidazole or

15 rac-4-(1H-imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline.

12. The use of compounds of formula I according to claim 1 wherein wherein X is CH.

13. The use according to claim 12, wherein Q is CH₂ and R¹ is hydrogen.

20

14. The use according to claim 13, wherein the compounds are

(4-(3,4-dihydro-naphthalen-1-yl)-1H-imidazole or
rac-4-(1,2,3,4-tetrahydro-naphthalen-1-yl)-1H-imidazole.

15. The use according to claim 12, wherein Q is O and R¹ is hydrogen.

25

16. The use according to claim 15, wherein the compound is
rac-5-chroman-4-yl-1H-imidazole hydrochloride or tautomer.

17. The use according to claim 12, wherein Q is O and R¹ is lower alkyl.

30

18. The use according to claim 17, wherein the compounds are
rac-5-(7-methyl-chroman-4-yl)-1H-imidazole or tautomer or
rac-5-(5-methyl-chroman-4-yl)-1H-imidazole or tautomer.

19. The use according to claim 12, wherein Q is O and R¹ is halogen.
20. The use according to claim 19, wherein the compounds are
rac-5-(6-fluoro-chroman-4-yl)-1H-imidazole or tautomer
5-(8-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer
5-(6-chloro-2H-chromen-4-yl)-1H-imidazole or tautomer
rac-5-(7-fluoro-chroman-4-yl)-1H-imidazole or tautomer or
rac-5-(5-fluoro-chroman-4-yl)-1H-imidazole or tautomer.

21. The use according to claim 1, wherein X is N,

Q is CH₂ and R¹ is halogen

which compounds are

rac-2-(5-bromo-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole or

rac-2-(7-chloro-5-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

22. The use according to claim 1, wherein Q is CH₂ and R¹ is tritium.

23. The use according to claim 22, which compound is

rac-2-(7-tritio-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,5-dihydro-1H-imidazole.

24. The use according to claim 1, wherein Q is -O-

which compounds are

rac-2-chroman-4-yl-4,5-dihydro-1H-imidazole,

rac-2-chroman-4-yl-1H-imidazole or

rac-2-(6-fluoro-chroman-4-yl)-1H-imidazole.

25. The use according to claim 1, wherein Q is O or NH and R¹ is hydrogen or halogen

which compounds are

rac-2-(6,8-dichloro-chroman-4-yl)-1H-imidazole or

rac-4-(1H-Imidazol-2-yl)-1,2,3,4-tetrahydro-quinoline.

26. The use according to claim 1, wherein Q is O and R¹ is lower alkyl

which compounds are

rac-5-(7-methyl-chroman-4-yl)-1H-imidazole or tautomer or

rac-5-(5-methyl-chroman-4-yl)-1H-imidazole or tautomer.

27. The use according to claim 1, wherein Q is O and R¹ is halogen.

28. The use according to claim 27, which compounds are

rac-5-(6-Fluoro-chroman-4-yl)-1H-imidazole or tautomer

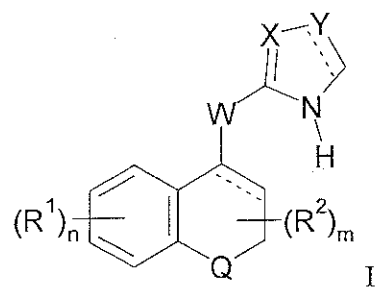
5-(8-Chloro-2H-chromen-4-yl)-1H-imidazole or tautomer

5-(6-Chloro-2H-chromen-4-yl)-1H-imidazole or tautomer

rac-5-(7-Fluoro-chroman-4-yl)-1H-imidazole or tautomer or

rac-5-(5-Fluoro-chroman-4-yl)-1H-imidazole or tautomer.

29. The use of compounds of formula I



wherein

R^1 is tritium;

R ²	is hydrogen, hydroxy or lower alkyl;
X	is N and Y is CH or CH ₂ or CH-lower alkyl or
X	is CH and Y is N;
Q	is CH ₂ , O, NH, N-alkyl, N-SO ₂ -alkyl or N-SO ₂ -toluen-4-yl;
W	is CH ₂ or a bond

m, n are independently from one another 1, 2 or 3; when m is 2 or 3, R² may

be the same or not; when n is 2 or 3, R¹ may be the same or not;

the dotted lines may each be independently from one another a bond or not;

and their pharmaceutically active salts, racemic mixtures, enantiomers, optical isomers and tautomeric forms of compounds of formula I as radioligand in a binding assay for trace amine associated receptors.

30. A medicament containing one or more compounds as claimed in claim 1 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, 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.

31. A medicament according to claim 30 containing one or more compounds as claimed in claim 1 for the treatment of depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).