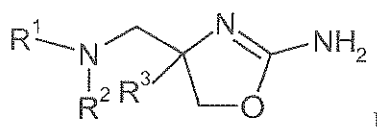


2-AMINOXAZOLINES AS TAAR1 LIGANDS

The invention relates to compounds of formula



wherein

- 5 R^1 is aryl or heteroaryl, wherein the aryl and heteroaryl groups may be unsubstituted or substituted by one to three substituents, selected from the group consisting of cycloalkyl, phenyl, phenyloxy, benzyl, benzyloxy, halogen, lower alkyl, lower alkoxy, heteroaryl, piperidin-1-yl or by lower alkyl substituted by halogen, or is aryl or heteroaryl wherein at least one hydrogen atom is replaced by deuterium or tritium;
- 10 R^2 is hydrogen, lower alkyl or is benzyl unsubstituted or substituted by alkoxy or halogen; or
- R^1 and R^2 form together with the N-atom to which they are attached 2,3-dihydroindol-1-yl or 3,4-dihydro-quinolin-1-yl;
- R^3 is hydrogen or lower alkyl
- 15 or to a pharmaceutically suitable acid addition salt thereof.

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

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

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

The compounds may be used for the treatment of anxiety disorders, depression, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related

disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of
5 energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

Some of physiological effects, (i.e. cardiovascular effects, hypotension, induction of sedation have been reported for compounds which may bind to adrenergic receptors
10 (WO02/076950, WO97/12874 or EP 0717 037). These physiological effects may be considered to be undesirable side effects in the case of medicaments aimed at treating diseases of the central nervous system as described above. Therefore it is desirable to obtain medicaments having selectivity for the TAAR1 receptor vs adrenergic receptors. Objects of the present invention show selectivity for TAAR1 receptor over adrenergic
15 receptor, in particular good selectivity vs the human and rat alpha1 and alpha2 receptors."

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
20 and reuptake after release are tightly regulated. An imbalance in the levels of biogenic amines is known to be responsible for the altered brain function under many pathological conditions [2-5]. A second class of endogenous amine compounds, the so-called trace amines (TAs) significantly overlap with the classical biogenic amines regarding structure, metabolism and subcellular localization. The TAs include p-tyramine, β -
25 phenylethylamine, tryptamine and octopamine, and they are present in the mammalian nervous system at generally lower levels than classical biogenic amines [6].

Their dysregulation has been linked to various psychiatric diseases like schizophrenia and depression [7] and for other conditions like attention deficit hyperactivity disorder, migraine headache, Parkinson's disease, substance abuse and
30 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
35 biogenic amines, by either triggering their release, inhibiting their reuptake or by "crossreacting" with their receptor systems [9,12,13]. This view changed

significantly with the recent identification of several members of a novel family of GPCRs, the trace amine associated receptors (TAARs) [7,14]. There are 9 TAAR genes in human (including 3 pseudogenes) and 16 genes in mouse (including 1 pseudogene). The TAAR genes do not contain introns (with one exception, TAAR2 contains 1 intron) and are located next to each other on the same chromosomal segment. The phylogenetic relationship of the receptor genes, in agreement with an in-depth GPCR pharmacophore similarity comparison and pharmacological data suggest that these receptors form three distinct subfamilies [7,14]. TAAR1 is in the first subclass of four genes (TAAR1-4) highly conserved between human and rodents. TAs activate TAAR1 via 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:

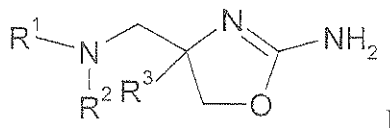
- 1 Deutch, A.Y. and Roth, R.H. (1999) Neurotransmitters. In *Fundamental Neuroscience* (2nd edn) (Zigmond, M.J., Bloom, F.E., Landis, S.C., Roberts, J.L. and Squire, L.R., eds.), pp. 193-234, Academic Press;
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1156;
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phenylethylamine and related drugs on dopamine efflux, dopamine uptake and
mazindol binding. *J. Pharmacol. Exp. Ther.* 245, 199-210;
- 5 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 for the
0 manufacture of medicaments for the treatment of diseases related to affinity to the trace
amine associated receptors, new specific compounds falling into the scope of formula I,
their manufacture, medicaments based on a compound in accordance with the invention
and their production as well as the use of compounds of formula I in the control or
prevention of illnesses such as depression, anxiety disorders, bipolar disorder, attention
5 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, substance abuse and metabolic
disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemic
disorders of energy consumption and assimilation, disorders and malfunction of body
0 temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular
disorders.

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

In a first aspect, there is provided a compound of formula



5 wherein

R¹ is aryl or heteroaryl, wherein the aryl and heteroaryl groups may be unsubstituted or substituted by one to three substituents, selected from the group consisting of cycloalkyl, phenyl, phenyloxy, benzyl, benzyloxy, halogen, C₁₋₇-alkyl, C₁₋₇-alkoxy, heteroaryl, piperidin-1-yl or by C₁₋₇-alkyl substituted by halogen, or is aryl or
10 heteroaryl wherein at least one hydrogen atom is replaced by deuterium or tritium;

R² is hydrogen, C₁₋₇-alkyl or is benzyl unsubstituted or substituted by C₁₋₇-alkoxy or halogen; or

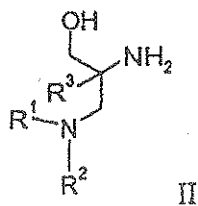
R¹ and R² form together with the N-atom to which they are attached 2,3-dihydroindol-1-yl or 3,4-dihydro-quinolin-1-yl;

15 R³ is hydrogen or C₁₋₇-alkyl

or a pharmaceutically suitable acid addition salt thereof.

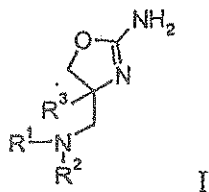
In a second aspect, there is provided a process for preparation of compounds of formula I, which process comprises

20 a) reacting a compound of formula



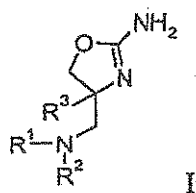
with cyanogen bromide

to a compound of formula



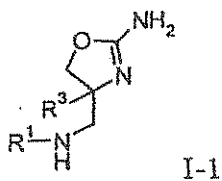
wherein the definitions are as described in claim 1, or

b) deprotecting a compound of formula



for R² being benzyl or benzyl substituted by alkoxy

to a compound of formula



wherein the definitions are as described in claim 1, or

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

In a third aspect, there is provided a medicament containing one or more compounds of formula I and pharmaceutically acceptable excipients.

In a fourth aspect, there is provided the use of a compound of formula I according to the first aspect for the preparation of a medicament for the treatment of anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, Parkinson's disease,
5 neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders and malfunction of body temperature homeostasis and disorders of sleep and circadian rhythm.

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.

- 5 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 CF₃, CHF₂, CH₂F, CH₂CF₃, CH₂CH₂CF₃, CH₂CF₂CF₃ and the like.

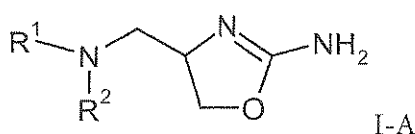
- 10 The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" as used herein is a carbocyclic ring system, containing from 6 to 10 carbon atoms forming one or more rings, and wherein at least one ring is aromatic in nature, for example phenyl, naphthyl, 5,6,7,8-tetrahydronaphthalen-1-yl or indan-5-yl.

- 15 The term "heteroaryl" as used herein is a carbocyclic ring system, containing from 5 to 10 ring atoms forming one or more rings, wherein at least one carbon atom is replaced by a heteroatom, selected from the group consisting of O, N or S, and wherein at least one ring is aromatic in nature, for example oxazolyl, pyridyl, pyrimidinyl, thiophenyl, quinolinyl, pyrrolyl, furyl, imidazolyl and the like.

- 20 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.

A preferred embodiment of the invention relates to compounds of formula



- 25 wherein

R¹ is aryl, wherein the aryl group may be unsubstituted or substituted by one to three substituents, selected from the group consisting of cycloalkyl, phenyl, phenyloxy, benzyl, benzyloxy, halogen, lower alkyl, lower alkoxy, heteroaryl or by lower alkyl

substituted by halogen, or is aryl wherein at least one hydrogen atom is replaced by deuterium or tritium;

R^2 is hydrogen, lower alkyl or is benzyl unsubstituted or substituted by alkoxy; or

R^1 and R^2 form together with the N-atom to which they are attached 2,3-dihydroindol-1-yl or 3,4-dihydro-quinolin-1-yl;

or to a pharmaceutically suitable acid addition salt thereof.

Preferred compounds of formula I are those, wherein R^1 is unsubstituted phenyl and R^2 is lower alkyl, for example the following compounds:

- 10 (R)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or
 (S)-4-[(methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

Further preferred compounds are those, wherein R^1 is phenyl substituted by halogen and R^2 is lower alkyl, for example the following compounds

- (S)-4-[(3,4-dichloro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(4-chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(3,4-dichloro-phenyl)-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(4-bromo-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 20 (S)-4-[(4-bromo-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(3,4-dichloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(3-bromo-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(3-bromo-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(3-chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 25 (S)-4-[(4-chloro-2-fluoro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(4-chloro-2-fluoro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(ethyl-(2-fluoro-phenyl)-amino)-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(2-chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 30 (R)-4-[(4-chloro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[(4-chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[(4-fluoro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[(4-chloro-phenyl)-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(2,4-difluoro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine
 35 (S)-4-[(2,4-difluoro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

- (R)-4-[[(3,4-dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
(R)-4-[[(3,4-dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
(R)-4-[[(3,4-dichloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
(S)-4-[[(3,5-dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine or
5 (S)-4-[[(3,5-dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

Further preferred compounds are those, wherein R¹ is phenyl substituted by halogen or CF₃, and R² is hydrogen, for example the following compounds

- (S)-4-[(3-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine
10 (S)-4-[(2-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine
(S)-4-[(4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine or
(S)-4-[(2,4-difluoro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

Further preferred compounds are those, wherein R¹ is phenyl substituted by
15 halogen and lower alkyl, and R² is hydrogen, for example

- (S)-4-[(2-fluoro-4-methyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

Further preferred compounds are those, wherein R¹ is phenyl substituted by CF₃ and lower alkyl or CF₃ alone and R² is lower alkyl, for example the following
20 compounds

- (S)-4-[[ethyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
(S)-4-[[methyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine or
(S)-4-[[ethyl-(2-methyl-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-
25 2-ylamine.

Further preferred compounds are those, wherein R¹ is pyridine-2-yl and R² is lower alkyl, for example the following compound

- ((S)-2-amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-chloro-pyridin-2-yl)-amine.
30

Further preferred compounds are those, wherein R¹ is phenyl, substituted simultaneously by halogen and methoxy, for example

- (S)-4-[[(4-chloro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
35 (S)-4-[[(4-chloro-3-methoxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-{{[(4-fluoro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

(R)-4-{{[(4-fluoro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

5 (R)-4-{{[ethyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

(R)-4-{{[(4-chloro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine or

10 (R)-4-{{[(4-chloro-3-methoxy-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine.

Preferred compounds of formula I are further those, wherein R¹ is phenyl, substituted simultaneously by halogen and methoxy or by halogen and R² is benzyl, for example

15 (S)-4-{{[benzyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

(S)-4-{{[benzyl-(4-fluoro-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine or

(S)-4-{{[benzyl-(4-chloro-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine.

20 Preferred compounds of formula I are further those, wherein R¹ is phenyl, substituted by lower alkyl and R² is lower alkyl, for example the following compounds

(S)-4-[(ethyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-{{[ethyl-(3-ethyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine or

(S)-4-{{[ethyl-(4-ethyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine.

25

Preferred compounds of formula I are further those, wherein R¹ is naphthyl, and R² is lower alkyl, for example the following compounds

(S)-4-[(methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(R)-4-[(methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

30 (R)-4-[(ethyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

Preferred compounds of formula I are further those, wherein R¹ is phenyl, substituted by halogen and CF₃, for example

35 (S)-4-{{[ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

(S)-4-[(3-fluoro-4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

(R)-4-{{ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine.

Preferred compounds of formula I are further those, wherein R¹ is indanyl, and R² is lower alkyl, for example the following compound

- 5 (S)-4-[(ethyl-indan-5-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

Preferred compounds of formula I are further those, wherein R¹ is phenyl, substituted by heteroaryl, for example the following compounds

(S)-4-[[methyl-(3-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

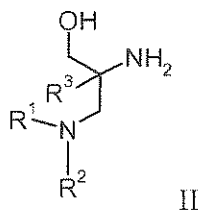
10 or

(S)-4-{{ethyl-(3-oxazol-5-yl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine.

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,

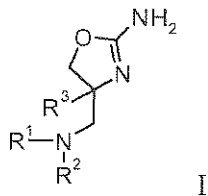
15 which processes comprise

- a) reacting a compound of formula



with cyanogen bromide

to a compound of formula

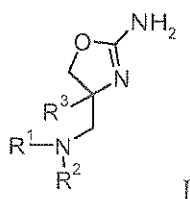


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wherein the definitions are as described above, or

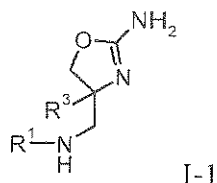
- b) deprotecting a compound of formula

- 10 -



for R^2 being benzyl or benzyl substituted by alkoxy

to a compound of formula



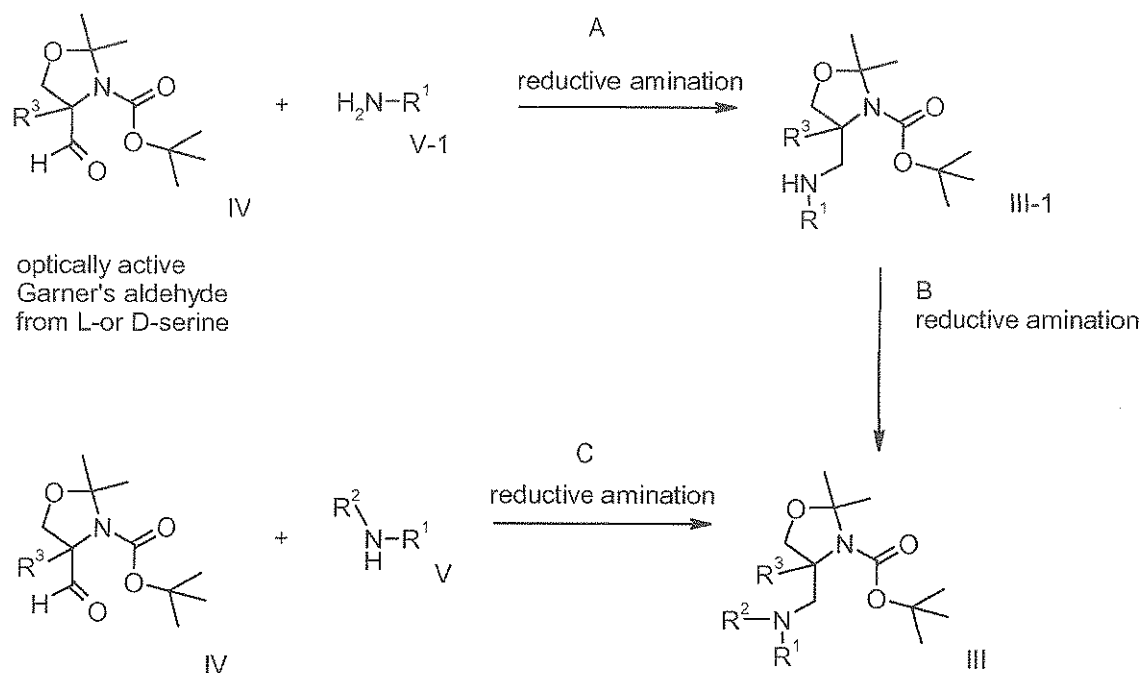
5 wherein the definitions are as described above, or

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

The compounds of formula I may be prepared in accordance with the process variants as described above and with the following schemes 1 - 4. The starting materials
10 are commercially available (e.g. from one or more of the following chemical suppliers such as Aldrich, Fluka, Acros, Maybridge, Avocado, TCI, or additional suppliers as indicated in databases such as Chemical Abstracts [American Chemical Society, Columbus, Ohio] or Available Chemicals Directory [Elsevier MDL, San Ramon, California]), or are otherwise known in the chemical literature, or may be prepared as
15 described in the Examples section.

20

25

GENERAL PROCEDURE 1Scheme 1

5

Step A: Reductive amination of optically active Garner's aldehyde ($\text{R}^3=\text{H}$; from L- or D-serine; Garner, P.; Park, J.M. *Org. Synth.* 1998, IX, 300) or α -methyl-substituted Garner's aldehyde ($\text{R}^3=\text{methyl}$; from L- or D- α -methylserine; Avenoza, A. *et al. Tetrahedron Asymm.* 2001, 12, 949) with a compound of formula V-1 can be accomplished by a

10 reducing agent such as NaBH_4 , LiBH_4 , $\text{NaBH}(\text{OAc})_3$ or $\text{Na}(\text{CN})\text{BH}_3$ in a solvent such as MeOH, EtOH, dichloromethane, 1,2-dichloroethane, THF, dioxane or mixtures thereof in the presence of an activating protic acid such as HCl or a carboxylic acid or an activating Lewis acid such as ZnCl_2 or $\text{Ti}(\text{OiPr})_4$ at a temperature of -10 to 60 °C for

15 1-40 h.

Preferred conditions for $\text{R}^1 = \text{aryl}$ and $\text{R}^3=\text{H}$ are NaBH_3CN and ZnCl_2 in MeOH at r.t. to 40 °C overnight.

Preferred conditions for $\text{R}^1 = \text{aryl}$ and $\text{R}^3=\text{alkyl}$ are heating the aniline and the ketone in MeOH at 80 °C overnight, followed by treatment with NaBH_4 in MeOH at 60 °C

20 overnight.

Preferred conditions for $\text{R}^1 = \text{heteroaryl}$ and $\text{R}^3=\text{H}$ are $\text{NaBH}(\text{OAc})_3$ and HOAc in 1,2-dichloroethane at 60 °C overnight.

Step B: Alkylation of the compound of formula III-1 can be accomplished by treatment with a suitable (protected) aldehyde or ketone in the presence of a reducing agent such as NaBH_4 , LiBH_4 , $\text{NaBH}(\text{OAc})_3$ or $\text{Na}(\text{CN})\text{BH}_3$ in a solvent such as MeOH, EtOH, dichloromethane, 1,2-dichloroethane, THF, dioxane or mixtures thereof in the presence of an activating protic acid such as HCl or a carboxylic acid or an activating Lewis acid such as ZnCl_2 or $\text{Ti}(\text{OiPr})_4$ at a temperature of -10 to 60 °C for 1-40 h.

Preferred conditions for introduction of a methyl group: the corresponding compound of formula III-1 is treated with 37 % aqueous formaldehyde solution or paraformaldehyde in the presence of NaBH_3CN and ZnCl_2 in MeOH at 40 °C for 2hrs.

Preferred conditions for introduction of an ethyl group for $\text{R}^1=\text{aryl}$: the corresponding compound of formula III-1 is treated with acetaldehyde in the presence of NaBH_3CN and ZnCl_2 in MeOH at 40 °C for 2hrs.

Preferred conditions for introduction of an ethyl group for $\text{R}^1=\text{heteroaryl}$: the corresponding compound of formula III-1 is treated with acetaldehyde in the presence of $\text{NaBH}(\text{OAc})_3$ and HOAc in 1,2-dichloroethane at r.t. overnight.

Preferred conditions for introduction of an isopropyl group: the corresponding compound of formula III-1 is treated with 2-methoxypropene in the presence of $\text{NaBH}(\text{OAc})_3$ and trifluoroacetic acid in 1,2-dichloroethane overnight.

Preferred conditions for introduction of a benzyl, p-methoxy-benzyl, p-bromo-benzyl or p-chloro-benzyl group: the corresponding compound of formula III-1 is treated with benzaldehyde dimethyl acetal, p-methoxy-benzaldehyde dimethyl acetal, p-bromo-benzaldehyde dimethyl acetal or p-chloro-benzaldehyde dimethyl acetal in the presence of $\text{NaBH}(\text{OAc})_3$ and trifluoroacetic acid in 1,2-dichloroethane overnight.

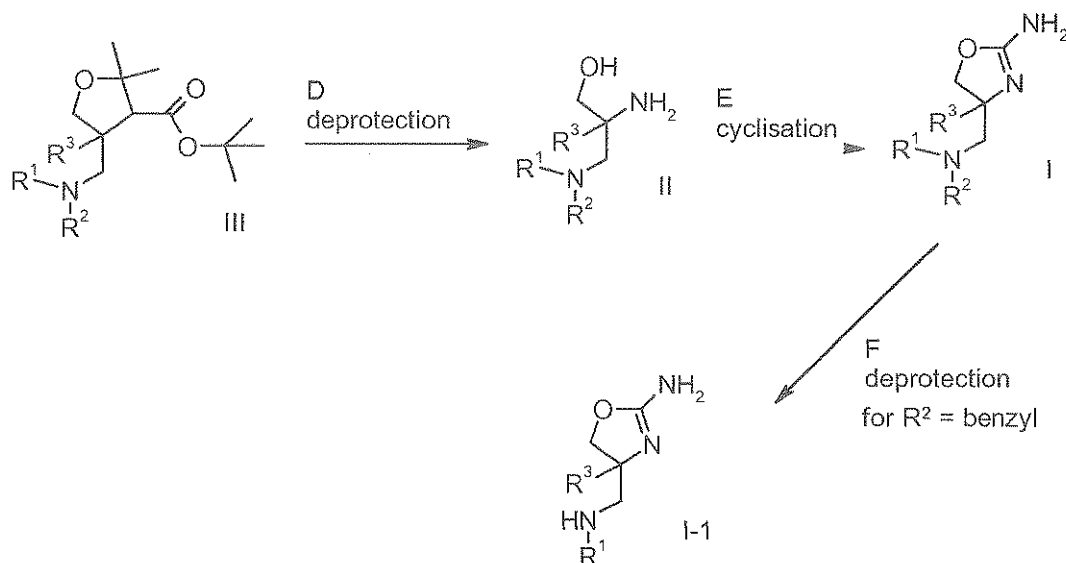
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Step C: Preparation of an alkyl-substituted compound of formula III may alternatively be accomplished by reductive amination of a compound of formula V and Garner's aldehyde (from L- or D-serine; Garner, P.; Park, J.M. *Org. Synth.* 1998, IX, 300) in the presence of a reducing agent such as NaBH_4 , LiBH_4 , $\text{NaBH}(\text{OAc})_3$ or $\text{Na}(\text{CN})\text{BH}_3$ in a solvent such as MeOH, EtOH, dichloromethane, 1,2-dichloroethane, THF, dioxane or mixtures thereof in the presence of an activating protic acid such as HCl or a carboxylic acid or an activating Lewis acid such as ZnCl_2 or $\text{Ti}(\text{OiPr})_4$ at a temperature of -10 to 60 °C for 1-40 h.

Preferred conditions are NaBH_3CN and ZnCl_2 in MeOH at r.t. - 40 °C overnight.

35

Scheme 2



Step D: Simultaneous cleavage of the amino alcohol protecting groups can be effected with a mineral acid such as HCl, H₂SO₄ or H₃PO₄ or a organic acid such as CF₃COOH, CHCl₂COOH, HOAc or p-toluenesulfonic acid in a solvent such as CH₂Cl₂, CHCl₃, THF, MeOH, EtOH or H₂O at 0 to 60 °C.

Preferred conditions are 2N HCl in EtOH at reflux for 1 -3 hrs or 4N HCl in dioxane at r.t. overnight.

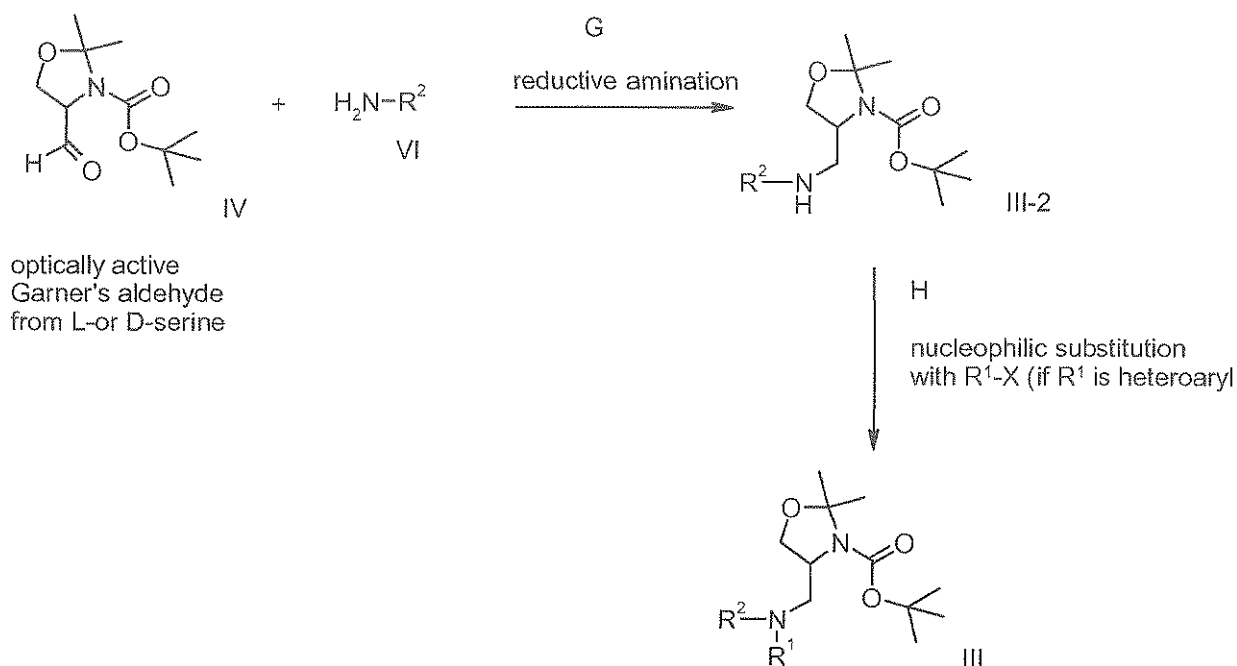
Step E: Cyclisation of the aminoalcohol to the corresponding 2-aminooxazoline of formula I can be accomplished by treatment with cyanogen bromide in THF as solvent and K₂CO₃ as base at r.t. overnight.

Step F: In cases where R² is the protecting group benzyl, deprotection can be accomplished by treatment with ammonium formate as reductant and palladium on activated charcoal as catalyst in methanol as solvent at elevated temperature (75°C) overnight. In cases where R² is the protecting group p-methoxy-benzyl, deprotection can be accomplished by treatment with acids such as trifluoroacetic acid in the presence of a nucleophilic scavenging agent such as anisole in dichloromethane as solvent at r.t. overnight.

GENERAL PROCEDURE 2

If R¹ is a heteroaryl substituent such as pyrimidinyl or pyridyl the intermediate III can also be produced as follows:

Scheme 3



- 5 **Step G:** Reductive amination of optically active Garner's aldehyde (from L- or D-serine; Garner, P.; Park, J.M. *Org. Synth.* 1998, IX, 300) with a compound of formula VI can be accomplished by a reducing agent such as H_2 with a catalyst such as palladium, platinum, ruthenium or the like on a carrier such as charcoal or NaBH_4 , LiBH_4 , $\text{NaBH}(\text{OAc})_3$, $\text{Na}(\text{CN})\text{BH}_3$ in a solvent such as MeOH, EtOH, dichloromethane, 1,2-dichloroethane,
- 10 THF, dioxane or mixtures thereof in the presence of molecular sieves or an activating protic acid such as HCl or a carboxylic acid or an activating Lewis acid such as ZnCl_2 or $\text{Ti}(\text{OiPr})_4$ at a temperature of -10 to 60°C for 1-40 h. Preferred conditions are Pd/C and H_2 in MeOH at r.t. overnight at atmospheric pressure.
- 15 **Step H:** Preparation of an heteroaryl-substituted compound of formula III can be accomplished by nucleophilic substitution of III-2 with an halogen substituted heterocycle such as 2-fluoropyridine, 4-fluoropyridine, 2-chloro-pyrimidine, 4-chloropyrimidine or further substituted analogs at elevated temperature in the range of 60 - 240°C in an inert solvent such as ethanol, propanol or isopropanol. This substitution
- 20 reaction can be achieved by conventional or microwave heating for several minutes to hours. Preferred conditions are microwave heating in a closed vessel at 180°C for 30 min in isopropanol.

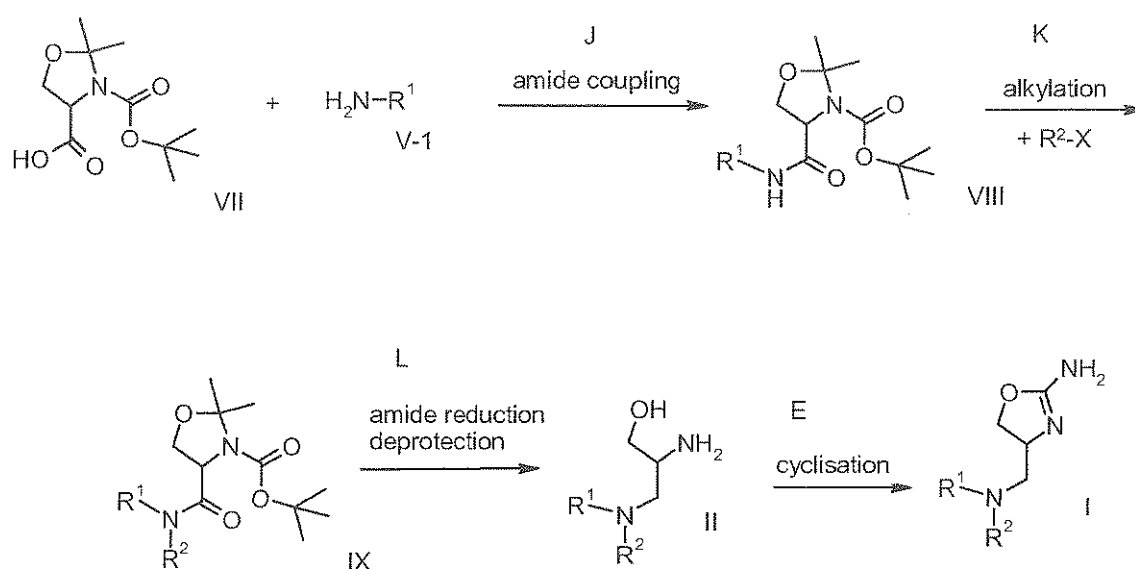
Intermediate III is then further carried on to product I as described in General Procedure 1 Scheme 2.

GENERAL PROCEDURE 3

5

Compounds of formula I can also be produced as follows:

Scheme 4



10

Step J: Amide coupling of chiral acid VII (the (S)-isomer available according to Chattopadhyay *et al Synthesis* 2006, 8, 1289; the (R)-isomer according to Micalé *et al in J. Med. Chem.* 2006, 49, 3064) with a compound of formula V-1 can be accomplished by an amide coupling reagent such as bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), 2-(1h-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or 2-(1h-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or o-(7-azabenzotriazol-1-yl)-n,n,n',n'-tetramethyluronium hexafluorophosphate (HATU) and a base such as triethylamine or ethyldiisopropylamine in a solvent such as THF, DMF, or dichloromethane at a temperature of -10 to 60 °C for 1 - 40 h.

Preferred conditions are the use of bis(2-oxo-3-oxazolidinyl)phosphinic chloride and diisopropylethylamine in dichloromethane at r.t. overnight.

Step K: The alkylation of amide VIII can be accomplished using a base such as NaH, Cs_2CO_3 , KOH, LiOH, NaOMe or NaOEt in a solvent such as acetone, DMF, DMSO, acetonitrile, toluene, EtOH or MeOH and optionally if appropriate a phase transfer

25

catalyst such as tetrabutylammonium bromide or an additive such as a crown ether, tetrabutylammonium iodide or potassium iodide at r.t. – 120 °C for 1 -24 hrs. Preferred conditions are sodium hydride in dimethylsulfoxide at room temperature overnight.

5

Step L: Reduction of the amide can be achieved by borane, borane-tetrahydrofurane complex, borane-dimethylsulfide complex or sodiumborohydride/bortrifluoride etherate in inert solvents such as tetrahydrofurane, dioxane or other ethers followed by acidic workup that leads in addition to simultaneous cleavage of the amino alcohol protecting groups. Acidic workup can be effected with a mineral acid such as HCl, H₂SO₄ or H₃PO₄ 10 or a organic acid such as CF₃COOH, CHCl₂COOH, HOAc or p-toluenesulfonic acid in a solvent such as CH₂Cl₂, CHCl₃, THF, MeOH, EtOH or H₂O at 0 to 60 °C. Preferred conditions are treatment with borane/THF for 2 hours at 60 °C followed by heating with 4N HCl for 2 hours at 60 °C.

15

Step E: Cyclisation of the aminoalcohol to the corresponding 2-aminooxazoline of formula I can be accomplished by treatment with cyanogen bromide in THF as solvent and K₂CO₃ as base at r.t. overnight.

20 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 25 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.

30 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, 35 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
5 resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

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

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

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

For the construction of expression plasmids the coding sequences of human, rat and
20 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 cloning vector (Invitrogen) following the instructions of the manufacturer. PCR products were subcloned into the pIRESneo2 vector (BD Clontech, Palo Alto, California), and
25 expression vectors were sequence verified before introduction in cell lines.

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

manufacturer. Monoclonal cell lines which displayed a stable EC₅₀ for a culture period of 15 passages were used for all subsequent studies.

Membrane preparation and radioligand binding

5 Cells at confluence were rinsed with ice-cold phosphate buffered saline without Ca²⁺ and Mg²⁺ containing 10 mM EDTA and pelleted by centrifugation at 1000 rpm for 5 min at 4 °C. The pellet was then washed twice with ice-cold phosphate buffered saline and cell pellet was frozen immediately by immersion in liquid nitrogen and stored until use at -80 °C. Cell pellet was then suspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing
10 10 mM EDTA, and homogenized with a Polytron (PT 3000, Kinematica) at 10,000 rpm for 10 s. The homogenate was centrifuged at 48,000×g for 30 min at 4 °C and the pellet resuspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing 0.1 mM EDTA (buffer A), and homogenized with a Polytron at 10,000 rpm for 10 s. The homogenate was then centrifuged at 48,000×g for 30 min at 4 °C and the pellet resuspended in 20 ml buffer A,
15 and homogenized with a Polytron at 10,000 rpm for 10 s. Protein concentration was determined by the method of Pierce (Rockford, IL). The homogenate was then centrifuged at 48,000×g for 10 min at 4 °C, resuspended in HEPES-NaOH (20 mM), pH 7.0 including MgCl₂ (10 mM) and CaCl₂ g protein per ml and (2 mM) (buffer B) at 200 homogenized with a Polytron at 10,000 rpm for 10 s.

20

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-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
25 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 μM). Competing ligands were tested in a wide range of concentrations (10 pM – 30 μM). The final dimethylsulphoxide concentration in the assay was 2%, and it did not affect
30 radioligand binding. Each experiment was performed in duplicate. All incubations were terminated by rapid filtration through UniFilter-96 plates (Packard Instrument Company) and glass filter GF/C, pre-soaked for at least 2 h in polyethylenimine 0.3%, and using a Filtermate 96 Cell Harvester (Packard Instrument Company). The tubes and filters were then washed 3 times with 1 ml aliquots of cold buffer B. Filters were not dried
35 and soaked in Ultima gold (45 μl/well, Packard Instrument Company) and bound radioactivity was counted by a TopCount Microplate Scintillation Counter (Packard Instrument Company).

The preferred compounds show a K_i value (μM) in mouse and/or rat on TAAR1 in the range of lower than $0.01 \mu\text{M}$ as shown in the table below.

Example	K_i (μM) mouse/rat	Example	K_i (μM) mouse/rat	Example	K_i (μM) mouse/rat
1	0.0009/0.0019	87	-/0.0073	133	0.0042/0.0049
3	0.001/0.001	92	-/0037	134	0.0057/0.0036
7	0.0014/0.0003	94	-/0051	135	0.0087/0.0489
11	0.0035/0.0009	95	-/0.0015	138	0.0044/0.0093
15	0.0224/0.0008	99	0.006/0.0032	139	0.0041/0.0016
27	0.0073/0.0016	100	0.0027/0.003	140	0.0026/0.0041
28	0.0023/0.0006	105	0.0038/0.0635	141	0.0034/0.0009
30	0.0163/0.0017	106	0.0041/0.0188	145	0.0082/0.0048
31	0.0013/0.0019	107	0.0039/0.0149	146	0.0031/0.0062
32	0.0028/0.0006	109	0.0025/0.0017	152	0.0032/0.0072
33	0.0022/0.0002	111	0.006/0.0587	157	0.0017/0.0021
34	0.0012/0.0047	113	0.0028/0.0062	158	0.0022/0.0004
37	0.0097/0.0018	117	0.0028/0.0182	159	0.0053/0.0014
40	0.0011/0.002	119	0.0011/0.0042	160	0.0013/0.0009
42	0.0264/0.0011	125	0.0023/0.0056	162	0.0077/0.0155
53	0.0187/0.0009	126	0.0016/0.0012	163	0.0029/0.0052
55	0.0288/0.0006	127	0.0046/0.0157	165	0.0014/0.0009
65	0.0019/0.0027	128	0.0047/0.0116	167	0.0051/0.0097
77	0.0004/-	129	0.0088/0.0027	175	0.0092/0.0083

83	-/0.001	132	0.0047/0.0248		
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The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).

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

Tablet Formulation (Wet Granulation)

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

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
- 20 4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

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

Manufacturing Procedure

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

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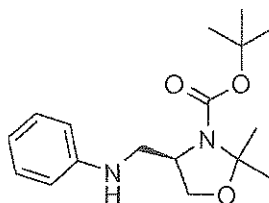
Experimental

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

Example 1

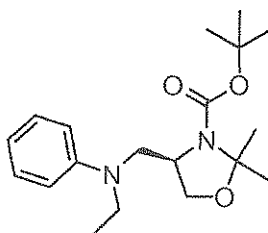
(R)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

- 10 a) (R)-2,2-Dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester



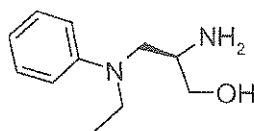
- To a stirred solution of tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (2.07 g) at r.t. in methanol (25 ml) under an argon atmosphere were added aniline (763 mg), ZnCl₂ (4.47 g) and NaBH₃CN (1.55 g). The mixture was stirred at 40°C for 16 h,
 15 then cooled to r.t. and concentrated to leave a yellow paste. This was taken up in EtOAc and H₂O. The aqueous phase was back extracted with EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂; gradient: cyclohexane -> cyclohexane/EtOAc 4:1) to give (R)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (2.21 g, 88 %) as off-white solid. MS (ISP): 307.4 ([M+H]⁺)

- b) (R)-4-[(Ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



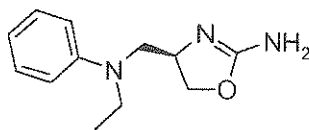
To a stirred solution of (R)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (730 mg) at r.t. in methanol (20 ml) under an argon atmosphere were added acetaldehyde (0.67 ml), ZnCl_2 (1.30 g) and NaBH_3CN (0.45 g). The mixture was warmed to 40 °C and stirring at that temperature was continued for 17 h. The mixture was cooled to r.t., directly adsorbed on silica gel and purified by column chromatography (SiO_2 ; gradient: cyclohexane -> cyclohexane/EtOAc 4:1) to give (R)-4-[(ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (614 mg, 77 %) as colorless viscous oil. MS (ISP): 335.5 ($[\text{M}+\text{H}]^+$)

10 c) (R)-2-Amino-3-(ethyl-phenyl-amino)-propan-1-ol



To a stirred solution of (R)-4-[(ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (608 mg) at r.t. in dioxane (5.5 ml) under an argon atmosphere was added HCl solution (4 M in dioxane; 4.54 ml). The mixture was stirred at r.t. overnight and concentrated. The residue was taken up in EtOAc and washed with 1N NaOH. The aqueous layer was back extracted with EtOAc. The combined organics were washed with brine, dried over MgSO_4 and concentrated. The crude product was purified by column chromatography (Isolute® SPE flash NH_2 column, aminopropyl-functionalized silica; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) to give (R)-2-amino-3-(ethyl-phenyl-amino)-propan-1-ol (297 mg, 84 %) as off-white amorphous solid. MS (ISP): 195.3 ($[\text{M}+\text{H}]^+$)

d) ((R)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



To a stirred solution of (R)-2-amino-3-(ethyl-phenyl-amino)-propan-1-ol (235 mg) at r.t. in THF (10 ml) under an argon atmosphere were added potassium carbonate (334 mg) and a solution of cyanogen bromide (256 mg) in THF (5 ml). Stirring at r.t. was continued for 18 h. The mixture (off-white suspension) was diluted with EtOAc and washed with H_2O . The aqueous phase was back extracted with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by column chromatography (Isolute® SPE flash NH_2 column, aminopropyl-functionalized silica; gradient: CH_2Cl_2 -> $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) to provide

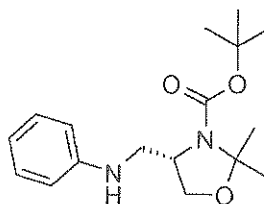
(R)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (142 mg, 54 %) as off-white solid. MS (ISP): 220.1 ($[M+H]^+$)

Example 2

(S)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

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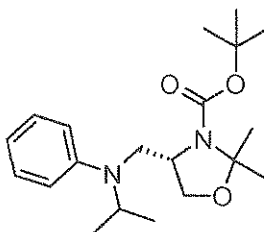
a) (S)-2,2-Dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester



In analogy to example 1.a tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate was reacted with aniline to give (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester. Light yellow solid. MS (ISP): 307.3 ($[M+H]^+$)

10

b) (S)-4-[(Isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



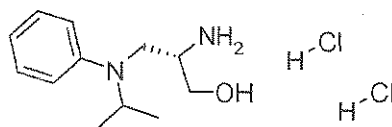
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To a stirred solution of (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (650 mg) at r.t. in 1,2-dichloroethane (15 ml) under an argon atmosphere were added 2-methoxypropene (0.30 ml), trifluoroacetic acid (0.16 ml) and sodium triacetoxyborohydride (674 mg). The mixture was heated to 40°C overnight. The mixture was cooled to r.t., directly adsorbed on silica gel and purified by chromatography (SiO₂; gradient: cyclohexane -> cyclohexane/EtOAc 7:3) to give (S)-4-[(isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (659 mg, 89 %) as light yellow viscous oil. MS (ISP): 349.5 ($[M+H]^+$)

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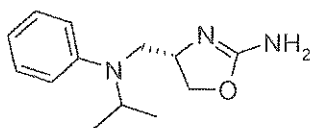
c) ((S)-2-Amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride

25



To a stirred solution of (S)-4-[(isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (650 mg) in dioxane (5 ml) under an argon atmosphere was added HCl solution (4M in dioxane; 9.33 ml). The mixture was stirred overnight. The mixture was concentrated and the residue was dried to give (S)-2-amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride (616 mg, quant.) as off-white amorphous solid. MS (ISP): 209.3 ($[M+H]^+$)

d) (S)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

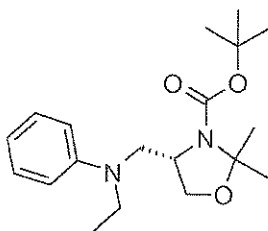


10 In analogy to example 1.d (S)-2-amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride was reacted with cyanogen bromide to give (S)-4-[(isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine as light yellow amorphous solid. MS (ISP): 234.3 ($[M+H]^+$)

Example 3

15 (S)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

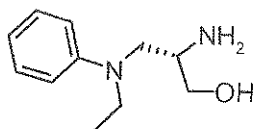
a) (S)-4-[(Ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



20 To a stirred solution of tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (681 mg) at r.t. in 1,2-dichloroethane (10 ml) under an argon atmosphere were added molecular sieves 4Å (1.5 g) and N-ethylaniline (0.25 ml). After stirring for 15 min at r.t., sodium triacetoxyborohydride (1.68 g) was added in one portion, followed by acetic acid (5 drops) and stirring at r.t. was continued overnight. The mixture was quenched by the
25 careful addition of 10 % KHCO_3 (15 ml). The biphasic mixture was stirred at r.t. for 20 min and filtered. The aqueous phase of the filtrate was back extracted with CH_2Cl_2 . The combined organics were washed with H_2O and brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 ; gradient: cyclohexane -> cyclohexane/EtOAc 4:1) to give (S)-4-[(ethyl-phenyl-amino)-

methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (469 mg, 57 %) as orange viscous oil. MS (ISP): 335.5 ($[M+H]^+$)

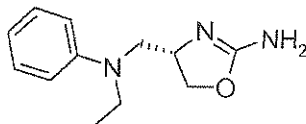
b) (S)-2-Amino-3-(ethyl-phenyl-amino)-propan-1-ol



5

In analogy to example 1.c (S)-4-[(ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to (S)-2-amino-3-(ethyl-phenyl-amino)-propan-1-ol. Light brown viscous oil. MS (ISP): 195.1 ($[M+H]^+$)

10 c) (S)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

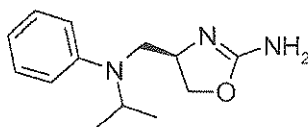


In analogy to example 1.d (S)-2-amino-3-(ethyl-phenyl-amino)-propan-1-ol was reacted with cyanogen bromide to give (S)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine. Off-white solid. MS (ISP): 220.4 ($[M+H]^+$)

15

Example 4

(R)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



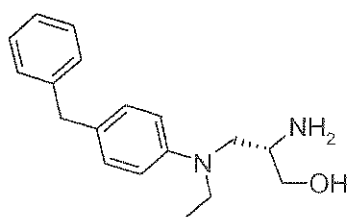
The title compound was prepared in analogy to example 2 starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and aniline. MS (ISP): 234.3 ($[M+H]^+$)

20

Example 5

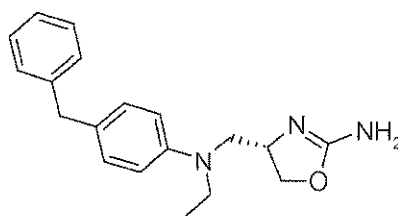
(S)-4-[[(4-Benzyl-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

25 a) (S)-2-Amino-3-[(4-benzyl-phenyl)-ethyl-amino]-propan-1-ol



- To a stirred solution of (S)-4-[[4-benzyl-phenyl]-ethyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (405 mg; prepared in analogy to example 1.a and 1.b starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-benzylaniline) at r.t. in dioxane (5 ml) under an argon atmosphere was added HCl solution (4M in dioxane; 4.77 ml). The mixture was stirred overnight 16 h, then concentrated. The residue was taken up in CH₂Cl₂/MeOH 95:5 and 1 N NaOH. The aqueous phase was back extracted with CH₂Cl₂/MeOH 95:5. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated.
- 10 The crude product was purified by column chromatography (Isolute® SPE flash NH₂ column, aminopropyl-functionalized silica; gradient: CH₂Cl₂ -> CH₂Cl₂/MeOH 9:1) to give (S)-2-amino-3-[(4-benzyl-phenyl)-isopropyl-amino]-propan-1-ol (192 mg, 71 %) as colorless amorphous solid. MS (ISP): 285.3 ([M+H]⁺)

- 15 b) (S)-4-[[4-Benzyl-phenyl]-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



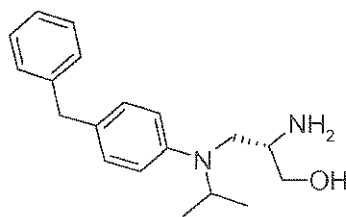
- In analogy to example 1.d (S)-2-amino-3-[(4-benzyl-phenyl)-isopropyl-amino]-propan-1-ol was reacted with cyanogen bromide to give (S)-4-[[4-benzyl-phenyl]-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine. Colorless gum. MS (ISP): 310.4 ([M+H]⁺)

20

Example 6

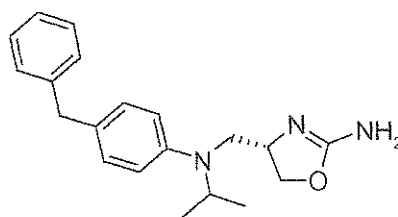
(S)-4-[[4-Benzyl-phenyl]-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

- a) (S)-2-Amino-3-[(4-benzyl-phenyl)-isopropyl-amino]-propan-1-ol



In analogy to example 5.a (S)-4-[[[(4-benzyl-phenyl)-isopropyl-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (prepared in analogy to example 2.a and 2.b starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-benzylaniline) was converted to (S)-2-amino-3-[(4-benzyl-phenyl)-isopropyl-amino]-propan-1-ol. Colorless amorphous solid. MS (ISP): 299.5 ([M+H]⁺)

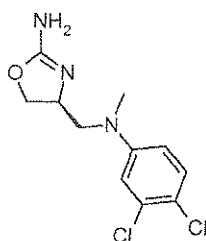
b) (S)-4-[[[(4-Benzyl-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1.d (S)-2-amino-3-[(4-benzyl-phenyl)-isopropyl-amino]-propan-1-ol was reacted with cyanogen bromide to give (S)-4-[[[(4-benzyl-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine. Light yellow gum. MS (ISP): 324.4 ([M+H]⁺)

Example 7

(S)-4-[[[(3,4-Dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

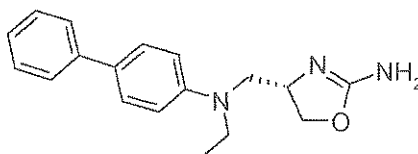


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. White solid. MS (ISP): 278.2 ([³⁷Cl³⁷Cl]M+H]⁺), 276.1 ([³⁷Cl³⁵Cl]M+H]⁺), 274.2 ([³⁵Cl³⁵Cl]M+H]⁺)

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Example 8

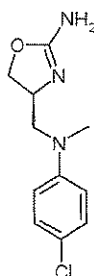
(S)-4-[(Biphenyl-4-yl-ethyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-
 5 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-aminobiphenyl. White solid.
 MS (ISP): 296.1 ($[M+H]^+$)

Example 9

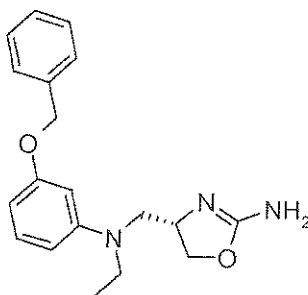
(S)-4-[[(4-Chloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



10 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. White solid. MS
 (ISP): 242.2 ($[^{37}\text{Cl}]M+H^+$), 240.2 ($[^{35}\text{Cl}]M+H^+$)

Example 10

15 (S)-4-[[(3-Benzyloxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



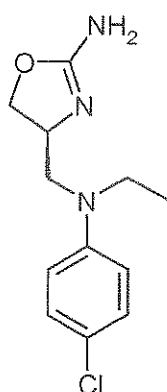
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-benzyloxyaniline.
 Amorphous colorless solid. MS (ISP): 326.3 ($[M+H]^+$)

20

Example 11

(S)-4-[[(4-Chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 30 -

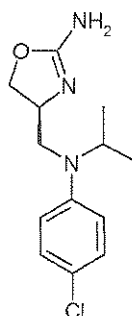


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. Light yellow gum. MS (ISP): 256.3 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 254.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

5

Example 12

(S)-4-[(4-Chloro-phenyl)-isopropyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine

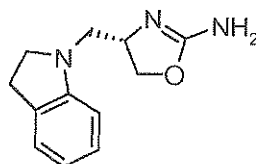


The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. Colourless gum. MS (ISP): 270.3 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 268.3 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

10

Example 13

(S)-4-(2,3-Dihydro-indol-1-ylmethyl)-4,5-dihydro-oxazol-2-ylamine



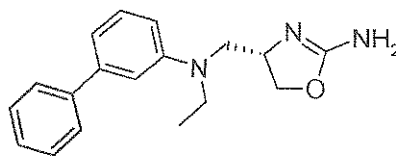
15

In analogy to example 3 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and indoline. White solid. MS (ISP): 218.4 ($[\text{M}+\text{H}]^+$)

Example 14

(S)-4-[(Biphenyl-3-yl-ethyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

20

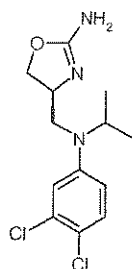


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-aminobiphenyl. Colorless amorphous solid. MS (ISP): 296.5 ($[M+H]^+$)

5

Example 15

(S)-4-[(3,4-Dichloro-phenyl)-isopropyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine

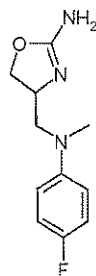


The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. Colourless gum. MS (ISP): 306.2 ($[^{37}\text{Cl}^{37}\text{Cl}]M+H^+$), 304.1 ($[^{37}\text{Cl}^{35}\text{Cl}]M+H^+$), 302.2 ($[^{35}\text{Cl}^{35}\text{Cl}]M+H^+$)

10

Example 16

(S)-4-[(4-Fluoro-phenyl)-methyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine



15

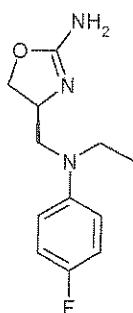
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoroaniline. Light yellow gum. MS (ISP): 224.4 ($[M+H]^+$)

Example 17

(S)-4-[[Ethyl-(4-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

20

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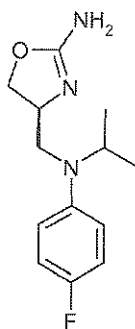


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoroaniline. Light yellow gum. MS (ISP): 238.3 ($[M+H]^+$)

5

Example 18

(S)-4-[[4-(4-Fluoro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

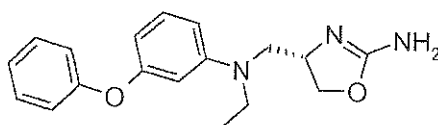


The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoroaniline. Light yellow gum. MS (ISP): 252.1 ($[M+H]^+$)

10

Example 19

(S)-4-[[Ethyl-(3-phenoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-phenoxyaniline. Amorphous yellow solid. MS (ISP): 312.3 ($[M+H]^+$)

15

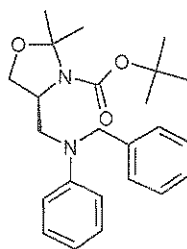
Example 20

(S)-4-[(Benzyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

20

a) (S)-4-[(Benzyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

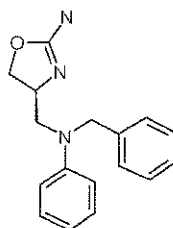
- 33 -



To a stirred solution of (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (495 mg; example 2.a) at r.t. in 1,2-dichloroethane (10 ml) under an argon atmosphere were added benzaldehyde dimethyl acetal (0.37 ml), trifluoroacetic acid (0.13 ml) and sodium triacetoxymethylborohydride (571 mg). The mixture was stirred at room temperature overnight. The mixture was directly adsorbed on silica gel and purified by chromatography (SiO₂; gradient: heptane -> heptane/EtOAc 7:3) to give (S)-4-[(benzyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (492 mg, 77 %) as a colourless viscous oil. MS (ISP): 397.4 ([M+H]⁺)

10

b) (S)-4-[(Benzyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

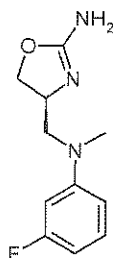


In analogy to example 1.c and 1.d (S)-4-[(benzyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to (S)-4-[(benzyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine. Colorless gum. MS (ISP): 282.1 ([M+H]⁺)

15

Example 21

(S)-4-[(3-Fluoro-phenyl)-methyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine

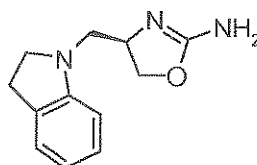


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoroaniline. Light yellow gum. MS (ISP): 224.1 ([M+H]⁺)

20

Example 22

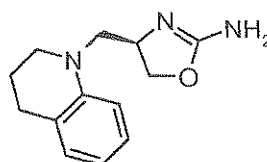
(R)-4-(2,3-Dihydro-indol-1-ylmethyl)-4,5-dihydro-oxazol-2-ylamine



In analogy to example 3 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and indoline. Off-white solid. MS (ISP): 218.4 ([M+H]⁺)

Example 23

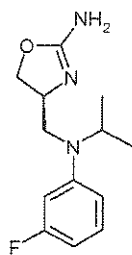
(R)-4-(3,4-Dihydro-2H-quinolin-1-ylmethyl)-4,5-dihydro-oxazol-2-ylamine



In analogy to example 3 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 1,2,3,4-tetrahydro-quinoline. Off-white solid. MS (ISP): 232.1 ([M+H]⁺)

Example 24

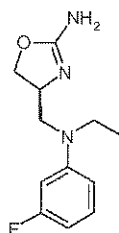
(S)-4-[[(3-Fluoro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoroaniline. Light yellow gum. MS (ISP): 252.4 ([M+H]⁺)

Example 25

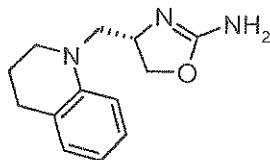
(S)-4-[[Ethyl-(3-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoroaniline. Light yellow gum. MS (ISP): 238.1 ($[M+H]^+$)

Example 26

5 (S)-4-(3,4-Dihydro-2H-quinolin-1-ylmethyl)-4,5-dihydro-oxazol-2-ylamine

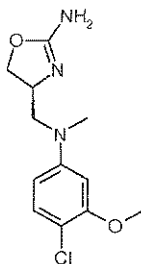


In analogy to example 3 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 1,2,3,4-tetrahydro-quinoline. Off-white solid. MS (ISP): 232.1 ($[M+H]^+$)

10

Example 27

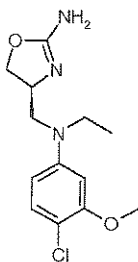
(S)-4-{[(4-Chloro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



15 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-3-methoxyaniline. White solid. MS (ISP): 272.3 ($[^{37}\text{Cl}]M+H]^+$), 270.3 ($[^{35}\text{Cl}]M+H]^+$)

Example 28

20 (S)-4-{[(4-Chloro-3-methoxy-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

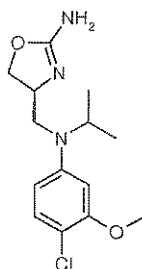


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-3-methoxyaniline. Colourless viscous oil. MS (ISP): 286.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 284.3 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

5

Example 29

(S)-4-[[[(4-Chloro-3-methoxy-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-3-methoxyaniline. Off-white gum. MS (ISP): 300.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 298.3 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

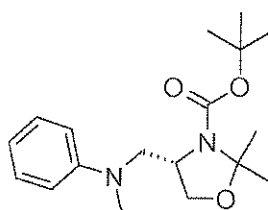
10

Example 30

(S)-4-[(Methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

15

a) (S)-2,2-Dimethyl-4-[(methyl-phenyl-amino)-methyl]-oxazolidine-3-carboxylic acid tert-butyl ester

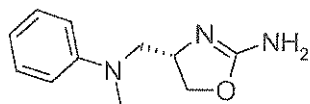


To a stirred solution of (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (500 mg; example 2.a) at r.t. in methanol (10 ml) under an argon atmosphere were added formaldehyde (37 % solution in H_2O ; 0.62 ml), zinc chloride (890 mg) and NaBH_3CN (308 mg). The mixture was heated to 40°C and stirring at that temperature was continued for 2 h. The mixture was concentrated and the residue was taken up in EtOAc/ H_2O . The biphasic mixture was filtered. The aqueous layer from the filtrate was back extracted with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane $\rightarrow$ cyclohexane/EtOAc 85:15) to give

25

(S)-2,2-dimethyl-4-[(methyl-phenyl-amino)-methyl]-oxazolidine-3-carboxylic acid tert-butyl ester (462 mg, 88 %) as colorless viscous oil. MS (ISP): 321.4 ($[M+H]^+$)

b) (S)-4-[(Methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



5

In analogy to example 1.c and 1.d (S)-2,2-dimethyl-4-[(methyl-phenyl-amino)-methyl]-oxazolidine-3-carboxylic acid tert-butyl ester was converted to (S)-4-[(methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine. Colorless gum. MS (ISP): 206.1 ($[M+H]^+$)

10

Example 31

(S)-4-[[4-Bromo-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

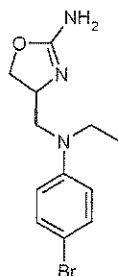


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-bromoaniline. White solid. MS (ISP): 286.1 ($[^{81}\text{Br}]M+H^+$), 284.2 ($[^{79}\text{Br}]M+H^+$)

15

Example 32

(S)-4-[[4-Bromo-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-bromoaniline. Colourless gum. MS (ISP): 300.2 ($[^{81}\text{Br}]M+H^+$), 298.2 ($[^{79}\text{Br}]M+H^+$)

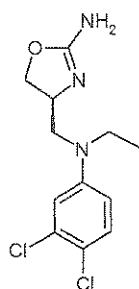
20

Example 33

(S)-4-[[3,4-Dichloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

25

- 38 -

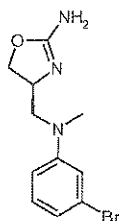


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. Colourless gum. MS (ISP): 292.1 ($[\{^{37}\text{Cl}^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 290.1 ($[\{^{37}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$), 288.1

5 ($[\{^{35}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

Example 34

(S)-4-[[[(3-Bromo-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



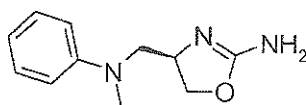
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-

10 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-bromoaniline. Colourless gum.

MS (ISP): 286.1 ($[\{^{81}\text{Br}\}\text{M}+\text{H}]^+$), 284.2 ($[\{^{79}\text{Br}\}\text{M}+\text{H}]^+$)

Example 35

(R)-4-[(Methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



15

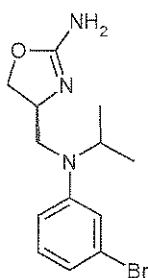
The title compound was prepared in analogy to example 30 starting from (R)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (example 1.a). Colorless gum. MS (ISP): 206.1 ($[\text{M}+\text{H}]^+$)

20

Example 36

(S)-4-[[[(3-Bromo-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 39 -

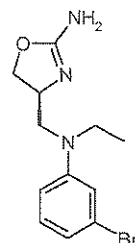


The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-bromoaniline. Colourless gum.
MS (ISP): MS (ISP): 314.2 ($[\{^{81}\text{Br}\}\text{M}+\text{H}]^+$), 312.2 ($[\{^{79}\text{Br}\}\text{M}+\text{H}]^+$)

5

Example 37

(S)-4-[[(3-Bromo-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

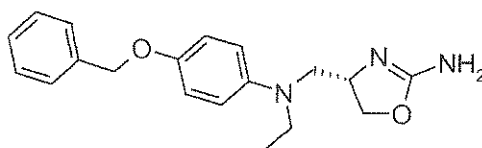


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-bromoaniline. Light yellow viscous oil. MS (ISP): 300.2 ($[\{^{81}\text{Br}\}\text{M}+\text{H}]^+$), 298.2 ($[\{^{79}\text{Br}\}\text{M}+\text{H}]^+$)

10

Example 38

(S)-4-[[(4-Benzyloxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



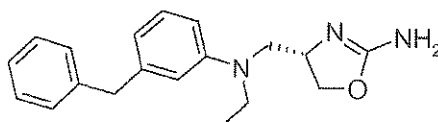
15

In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-benzyloxyaniline. Light brown viscous oil. MS (ISP): 326.3 ($[\text{M}+\text{H}]^+$)

20

Example 39

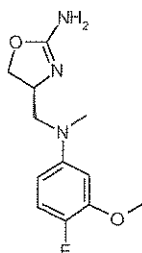
(S)-4-[[(3-Benzyl-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-benzylaniline. Light brown viscous oil. MS (ISP): 310.3 ($[M+H]^+$)

Example 40

- 5 (S)-4-{[(4-Fluoro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

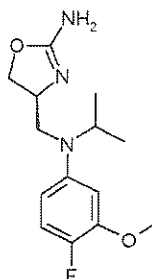


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline.

- 10 Colourless gum. MS (ISP): 254.4 ($[M+H]^+$)

Example 41

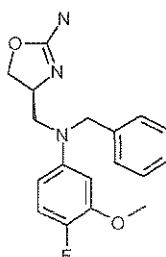
- (S)-4-{[(4-Fluoro-3-methoxy-phenyl)-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



- 15 The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline.
Light yellow gum. MS (ISP): 282.4 ($[M+H]^+$)

Example 42

- 20 (S)-4-{[Benzyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

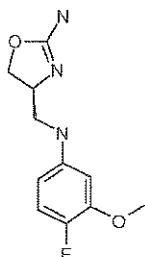


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline. Colourless gum. MS (ISP): 330.4 ($[M+H]^+$)

5

Example 43

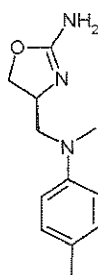
(S)-4-[(4-Fluoro-3-methoxy-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine



To a stirred solution of (S)-4-[[benzyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine (150 mg, example 42) at r.t. in methanol (25 ml) were
10 added ammonium formate (30 mg) and 10% palladium on activated charcoal (48 mg). The resulting suspension was stirred at 75 °C overnight and the mixture was then cooled to room temperature, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂; gradient: dichloromethane -> dichloromethane /methanol 9:1) to give (S)-4-[(4-fluoro-3-methoxy-phenylamino)-
15 methyl]-4,5-dihydro-oxazol-2-ylamine (39 mg, 36 %) as a light yellow gum. MS (ISP): 240.1 ($[M+H]^+$)

Example 44

(S)-4-[(Methyl-p-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

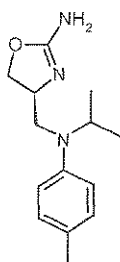


20 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-methylaniline. Colourless gum. MS (ISP): 220.2 ($[M+H]^+$)

Example 45

(S)-4-[(Isopropyl-p-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

- 42 -

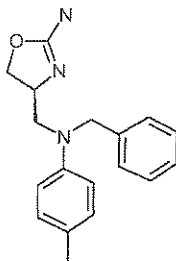


The title compound was prepared in analogy to example 2 starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-methylaniline. Colourless gum.
MS (ISP): 248.4 ($[M+H]^+$)

5

Example 46

(S)-4-[(Benzyl-p-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

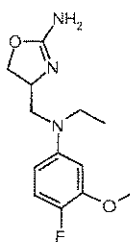


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-methylaniline. Colourless gum.

10 MS (ISP): 296.3 ($[M+H]^+$)

Example 47

(S)-4-[[Ethyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



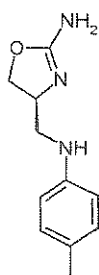
15 In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline.
Light yellow gum. MS (ISP): 268.3 ($[M+H]^+$)

Example 48

20

(S)-4-(p-Tolylamino-methyl)-4,5-dihydro-oxazol-2-ylamine

- 43 -



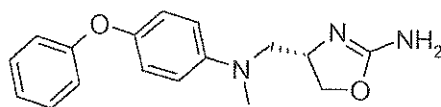
In analogy to example 43 the title compound was prepared starting from (S)-4-[(benzyl-p-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (example 46). Colourless gum.

MS (ISP): 206.3 ($[M+H]^+$)

5

Example 49

(S)-4-[[Methyl-(4-phenoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

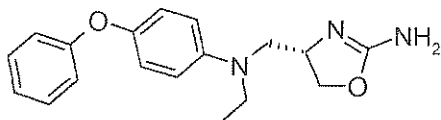


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-phenoxyaniline. Colorless

10 viscous oil. MS (ISP): 298.3 ($[M+H]^+$)

Example 50

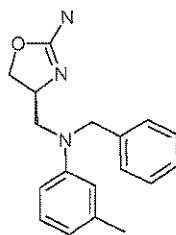
(S)-4-[[Ethyl-(4-phenoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



15 In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-phenoxyaniline. Light yellow viscous oil. MS (ISP): 312.4 ($[M+H]^+$)

Example 51

(S)-4-[(Benzyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

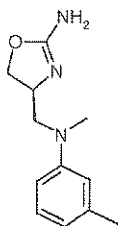


20

In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-methylaniline. Colourless gum.
MS (ISP): 296.4 ($[M+H]^+$)

Example 52

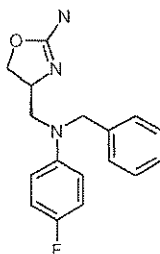
(S)-4-[(Methyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-
 5 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-methylaniline. Colourless gum.
 MS (ISP): 220.3 ($[M+H]^+$)

Example 53

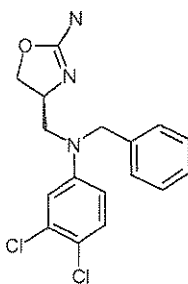
(S)-4-[[Benzyl-(4-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



10 In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoroaniline. Light brown
 gum. MS (ISP): 300.3 ($[M+H]^+$)

Example 54

(S)-4-[[Benzyl-(3,4-dichloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



15

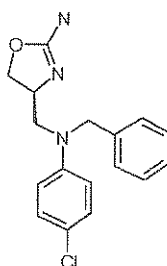
In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. Colourless
 gum. MS (ISP): 354.2 ($[^{37}\text{Cl}^{37}\text{Cl}]M+H^+$), 352.1 ($[^{37}\text{Cl}^{35}\text{Cl}]M+H^+$), 350.3
 ($[^{35}\text{Cl}^{35}\text{Cl}]M+H^+$)

20

Example 55

(S)-4-[[Benzyl-(4-chloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 45 -

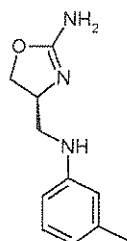


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. Colourless gum.
MS (ISP): 318.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 316.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

5

Example 56

(S)-4-(m-Tolylamino-methyl)-4,5-dihydro-oxazol-2-ylamine

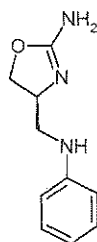


In analogy to example 43 the title compound was prepared starting from (S)-4-[(benzyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (example 51). Colourless gum.
MS (ISP): 206.4 ($[\text{M}+\text{H}]^+$)

10

Example 57

(S)-4-Phenylaminomethyl-4,5-dihydro-oxazol-2-ylamine



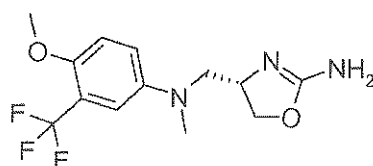
In analogy to example 43 the title compound was prepared starting from (S)-4-[(benzyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (example 20). Colourless gum.
MS (ISP): 192.3 ($[\text{M}+\text{H}]^+$)

15

Example 58

(S)-4-[[[4-Methoxy-3-trifluoromethyl-phenyl]-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

20

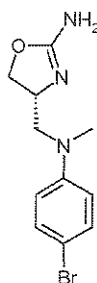


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-methoxy-3-trifluoromethylaniline. Colorless viscous oil. MS (ISP): 304.0 ($[M+H]^+$)

5

Example 59

(R)-4-[[4-Bromo-phenyl]-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



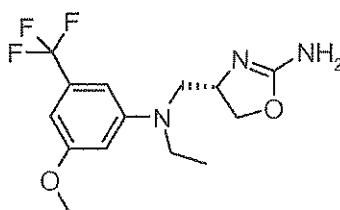
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-bromoaniline. White solid. MS (ISP): 285.9 ($[^{81}\text{Br}\{M+H\}]^+$), 283.9 ($[^{79}\text{Br}\{M+H\}]^+$)

10

Example 60

(S)-4-[[Ethyl-(3-methoxy-5-trifluoromethyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

15



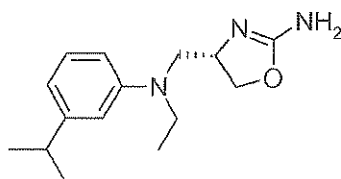
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-methoxy-5-trifluoromethylaniline. Light yellow viscous oil. MS (ISP): 318.1 ($[M+H]^+$)

20

Example 61

(S)-4-[[Ethyl-(3-isopropyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

- 47 -

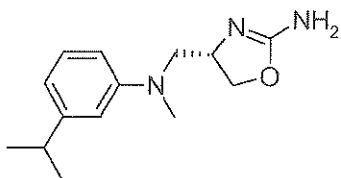


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-isopropylaniline. Light yellow viscous oil. MS (ISP): 262.3 ($[M+H]^+$)

5

Example 62

(S)-4-[[[3-Isopropyl-phenyl]-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



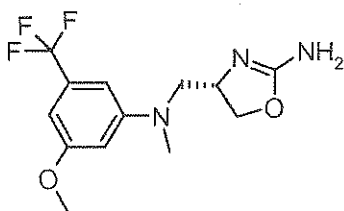
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-isopropylaniline. Colorless viscous oil. MS (ISP): 248.1 ($[M+H]^+$)

10

Example 63

(S)-4-[[[3-Methoxy-5-trifluoromethyl-phenyl]-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

15



In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-methoxy-5-trifluoromethylaniline. Colorless viscous oil. MS (ISP): 304.0 ($[M+H]^+$)

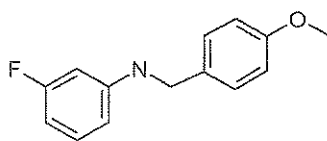
20

Example 64

(S)-4-[[[3-Fluoro-phenyl]-(4-methoxy-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

25 a) (3-Fluoro-phenyl)-(4-methoxy-benzyl)-amine

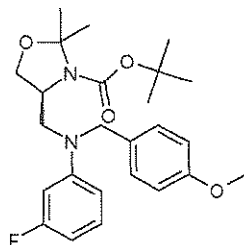
- 48 -



To a stirred solution of anisaldehyde (0.30 ml) at r.t. in methanol (15 ml) under an argon atmosphere were added 3-fluoroaniline (0.22 ml), ZnCl_2 (1.21 g) and NaBH_3CN (0.43 g). The mixture was stirred at 40 °C for 1 h, then cooled to r.t. and concentrated *in vacuo*.

- 5 The residue was purified by column chromatography (SiO_2 ; gradient: heptane -> heptane/EtOAc 7:3) to give (3-fluoro-phenyl)-(4-methoxy-benzyl)-amine (617 mg) as a light yellow oil. MS (ISP): 232.1 ($[\text{M}+\text{H}]^+$)

10 b) (S)-4-[[[(3-Fluoro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

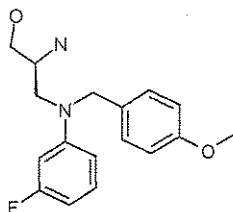


To a stirred solution of tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (600 mg) at r.t. in methanol (15 ml) under an argon atmosphere were added (3-fluoro-phenyl)-(4-methoxy-benzyl)-amine (654 mg), ZnCl_2 (1.44 g) and NaBH_3CN (0.52 g).

- 15 The mixture was stirred at 50 °C for 16 h, then cooled to r.t. and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 ; gradient: heptane -> heptane/EtOAc 7:3) to give (S)-4-[[[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (191 mg, 17%) as a colourless viscous oil. MS (ISP): 445.5 ($[\text{M}+\text{H}]^+$)

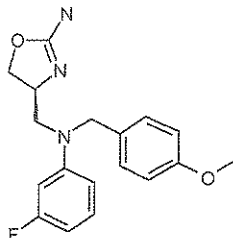
20

c) (S)-2-Amino-3-[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol



- In analogy to example 1.c (S)-4-[[[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to (S)-2-amino-3-[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol. Light yellow viscous oil. MS (ISP): 305.4 ($[\text{M}+\text{H}]^+$)
- 25

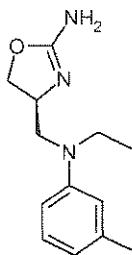
d) (S)-4-[[[(3-Fluoro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- 5 In analogy to example 1.d (S)-2-amino-3-[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol was reacted with cyanogen bromide to give (S)-4-[[[(3-fluoro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine. Light yellow gum. MS (ISP): 330.3 ($[M+H]^+$)

Example 65

- 10 (S)-4-[(Ethyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

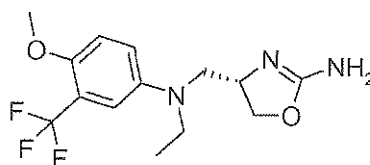


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-methylaniline. Colourless gum. MS (ISP): 234.3 ($[M+H]^+$)

15

Example 66

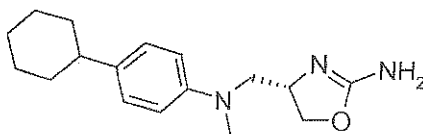
- (S)-4-[[Ethyl-(4-methoxy-3-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-methoxy-3-trifluoromethylaniline. Colorless viscous oil. MS (ISP): 318.1 ($[M+H]^+$)
- 20

Example 67

- (S)-4-[[[(4-Cyclohexyl-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

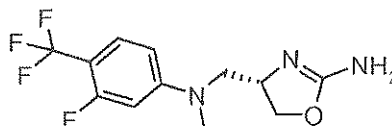


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-cyclohexylaniline. Off-white solid. MS (ISP): 288.0 ([M+H]⁺)

5

Example 68

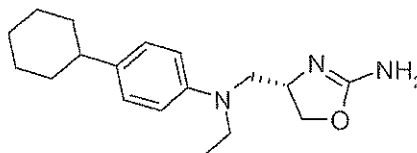
(S)-4-[[[(3-Fluoro-4-trifluoromethyl-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



10 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethylaniline. Light yellow viscous oil. MS (ISP): 292.3 ([M+H]⁺)

Example 69

15 (S)-4-[[[(4-Cyclohexyl-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

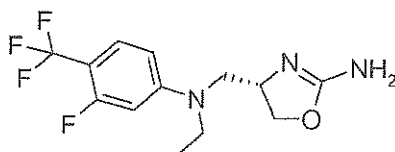


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-cyclohexylaniline. Light brown viscous oil. MS (ISP): 302.3 ([M+H]⁺)

20

Example 70

(S)-4-[[[Ethyl-(3-fluoro-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

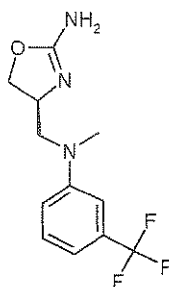


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethylaniline. Off-white solid. MS (ISP): 306.1 ($[M+H]^+$)

5

Example 71

(S)-4-[[Methyl-(3-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

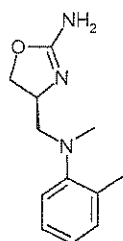


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-trifluoromethylaniline. Light yellow viscous oil. MS (ISP): 273.9 ($[M+H]^+$)

10

Example 72

(S)-4-[(Methyl-o-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



15

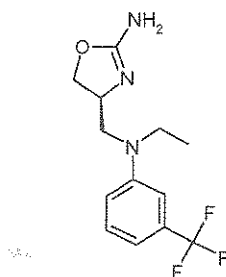
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-methylaniline. Light yellow viscous oil. MS (ISP): 220.3 ($[M+H]^+$)

20

Example 73

(S)-4-[[Ethyl-(3-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 52 -

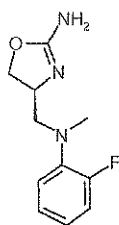


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-trifluoromethylaniline. Light yellow viscous oil. MS (ISP): 288.0 ($[M+H]^+$)

5

Example 74

(S)-4-[[[2-(2-Fluoro-phenyl)-1-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-yl]amine

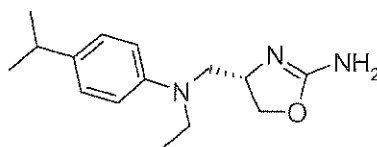


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoroaniline. Light yellow viscous oil. MS (ISP): 224.1 ($[M+H]^+$)

10

Example 75

(S)-4-[[[Ethyl-(4-isopropyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-yl]amine



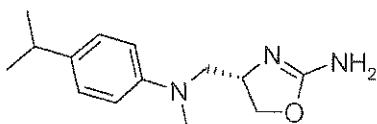
15

In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-isopropylaniline. Off-white waxy solid. MS (ISP): 262.3 ($[M+H]^+$)

20

Example 76

(S)-4-[[[(4-Isopropyl-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-yl]amine

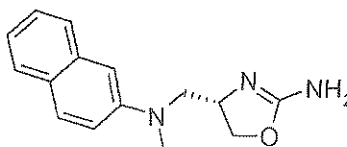


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-isopropylaniline. Light yellow waxy solid. MS (ISP): 248.3 ($[M+H]^+$)

5

Example 77

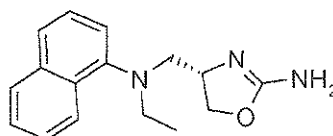
(S)-4-[(Methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and β -naphthyl amine. Off-white
10 solid. MS (ISP): 256.1 ($[M+H]^+$)

Example 78

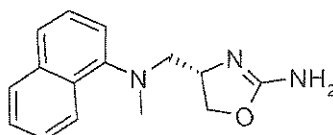
(S)-4-[(Ethyl-naphthalen-1-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



15 In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and α -naphthyl amine. Colorless waxy solid. MS (ISP): 270.4 ($[M+H]^+$)

Example 79

20 (S)-4-[(Methyl-naphthalen-1-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

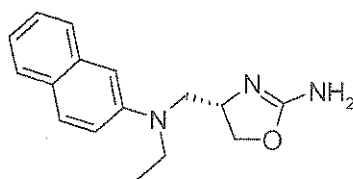


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and α -naphthyl amine. Colorless waxy solid. MS (ISP): 256.1 ($[M+H]^+$)

25

Example 80

(S)-4-[(Ethyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

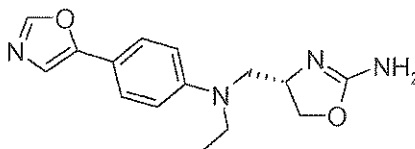


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and β -naphthyl amine. Light brown viscous oil. MS (ISP): 270.1 ($[M+H]^+$)

5

Example 81

(S)-4-[[Ethyl-(4-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

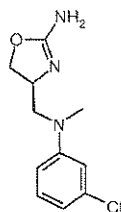


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-oxazol-5-yl-phenylamine. Light brown viscous oil. MS (ISP): 287.1 ($[M+H]^+$)

10

Example 82

(S)-4-[[[(3-Chloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



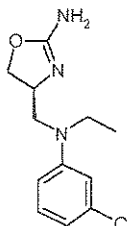
15

In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-chloroaniline. Colourless gum. MS (ISP): 242.2 ($[^{37}\text{Cl}]M+H]^+$), 240.1 ($[^{35}\text{Cl}]M+H]^+$)

20

Example 83

(S)-4-[[[(3-Chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

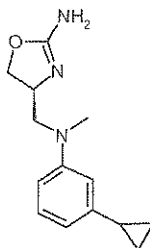


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-chloroaniline. Colourless gum. MS (ISP): 256.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 254.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

5

Example 84

(S)-4-[[[3-Cyclopropyl-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

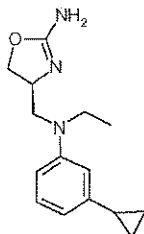


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-cyclopropylaniline. Colourless gum. MS (ISP): 246.2 ($[\text{M}+\text{H}]^+$)

10

Example 85

(S)-4-[[[3-Cyclopropyl-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



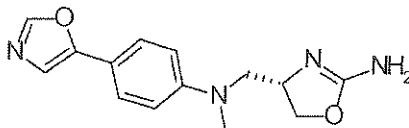
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-cyclopropylaniline. Colourless gum. MS (ISP): 260.2 ($[\text{M}+\text{H}]^+$)

15

Example 86

(S)-4-[[Methyl-(4-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

20



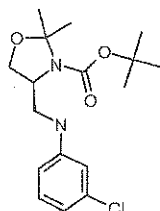
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-oxazol-5-yl-phenylamine. Off-white solid. MS (ISP): 273.0 ($[\text{M}+\text{H}]^+$)

25

Example 87

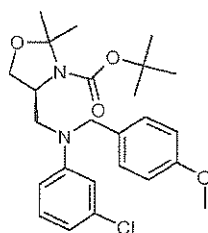
(S)-4-[(3-Chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

- a) (S)-4-[(3-Chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid
 5 tert-butyl ester



- In analogy to example 1.a tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate was reacted with 3-chloroaniline to give (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester. Off-
 10 white solid. MS (ISP): 343.2 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 341.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$)

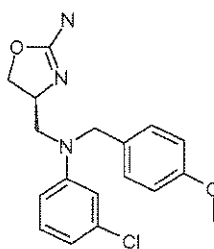
- b) (S)-4-[(3-Chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



- 15 In analogy to example 20.a tert-butyl (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was reacted with p-anisaldehyde dimethyl acetal to give (S)-4-[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester. White solid. MS (ISP): 463.1 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 461.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$)

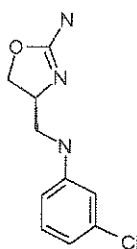
20

- c) (S)-4-[(3-Chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1.c and 1.d (S)-4-[[[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to (S)-4-[[[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine. White solid. MS (ISP): 348.3 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 346.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

d) (S)-4-[(3-Chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

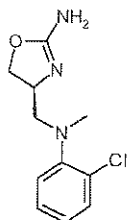


To a stirred solution of (S)-4-[[[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine (97 mg) at r.t. in dichloromethane (10 ml) were added anisole (0.31 ml) and trifluoroacetic acid (2.74 ml). The mixture was stirred at r.t. for 48 h and was then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated aq. sodium bicarbonate solution, the phases were separated, and the organic phase was dried and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 ; gradient: dichloromethane $\rightarrow$ dichloromethane /methanol 85:15) to give (S)-4-[(3-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine (22 mg, 35%) as a white gum. MS (ISP): 228.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 226.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

20

Example 88

(S)-4-[[[(2-Chloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

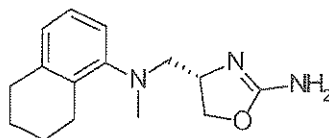


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-chloroaniline. Colourless gum. MS (ISP): 242.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 240.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)

25

Example 89

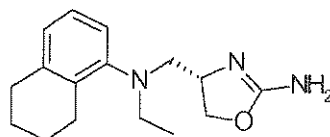
(S)-4-{{Methyl-(5,6,7,8-tetrahydro-naphthalen-1-yl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine



- 5 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 5,6,7,8-tetrahydro-naphthalen-1-ylamine. White solid. MS (ISP): 260.0 ($[M+H]^+$)

Example 90

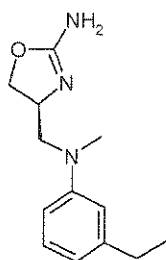
- 10 (S)-4-{{Ethyl-(5,6,7,8-tetrahydro-naphthalen-1-yl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine



- In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 5,6,7,8-tetrahydro-naphthalen-1-ylamine. Yellow viscous oil. MS (ISP): 274.4 ($[M+H]^+$)
- 15

Example 91

(S)-4-{{(3-Ethyl-phenyl)-methyl-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine

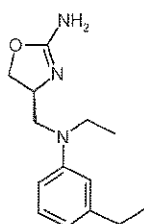


- 20 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-ethylaniline. Colourless gum. MS (ISP): 234.1 ($[M+H]^+$)

Example 92

(S)-4-{{Ethyl-(3-ethyl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine

- 59 -

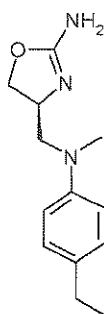


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-ethylaniline. Colourless gum.
MS (ISP): 248.3 ($[M+H]^+$)

5

Example 93

(S)-4-[[[4-Ethyl-phenyl]-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

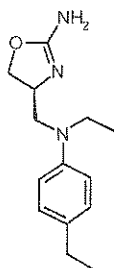


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-ethylaniline. Colourless gum.

10 MS (ISP): 234.1 ($[M+H]^+$)

Example 94

(S)-4-[[[Ethyl-(4-ethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-

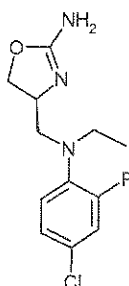
15 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-ethylaniline. Colourless gum.

MS (ISP): 248.2 ($[M+H]^+$)

Example 95

(S)-4-[[[4-Chloro-2-fluoro-phenyl]-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 60 -

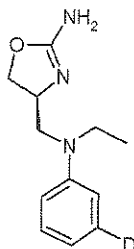


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-2-fluoroaniline. Light yellow viscous oil. MS (ISP): 274.0 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 272.2 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$)

5

Example 96

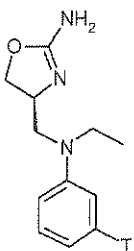
(S)-4-{[Ethyl-(3- ^2H)-phenyl]-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine



5.0 mg of (S)-4-{[(3-bromo-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine (example 37) was dissolved in 0.5 ml of THF and treated with 9.4 μl of triethylamine and 1.8 mg of Pd/C (10 %). After cooling to -78°C the black suspension was evacuated three times and purged with D_2 . After stirring for 1 h at room temperature the black reaction mixture was filtered over Dicalite. The Dicalite-Pd/C-solid was washed with 2x1 ml of CH_2Cl_2 . The clear solution was concentrated and purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 96:4 and 1 % of NH_4OH (25 % in water)). A second purification was necessary in order to obtain product in 98 % purity, which was obtained by an RP-18 column ($\text{H}_2\text{O}/\text{MeCN}$ 9:1 + 1% AcOH).

Example 97

(S)-4-{[Ethyl-(3- ^3H)-phenyl]-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine



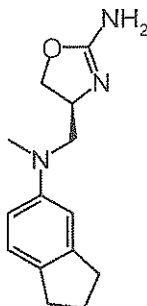
20

In a 1-ml tritiation-flask was added 2.5 mg of Pd/C (10 %). 5.0 mg of (S)-4-[[[3-bromo-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine (example 37) was dissolved in 0.4 ml of THF and treated with 4.7 μ l of triethylamine and 0.4 ml of MeOH. This solution was also added to the tritiation-flask. The black suspension was degassed four
5 times, frozen with liquid N₂ and purged with tritium (13 Ci). The reaction mixture was allowed to warm to RT and a starting pressure of 808 mbar was observed. After 1 h and 20 min, the reaction mixture was cooled with liquid N₂ and the tritium gas was taken back to the waste-storage. The suspension was degassed once and the solvent condensed to an ampoule. The black solid was treated 3 times with 1 ml of MeOH and the solvent
10 back-condensed to the ampoule. The residue was suspended in 10 ml of EtOH and filtered over 0.2 μ m nylon, obtaining a colorless solution of the crude product with an activity of 385 mCi, which was further dissolved with EtOH to 50 ml. The crude product was obtained in 88.3 % purity, which was disclosed by radio-TLC (solid phase: Merck RP-18 F254s, eluent: MeCN/H₂O 1:1 + 1% AcOH, R_f (product): 0.46, R_f (starting
15 material) 0.38).

53.9 mCi (7.7 ml) of the ethanol-solution was concentrated and purified by an RP-18 column chromatography (eluent H₂O/MeCN 9:1 + 1% AcOH). The fractions were analysed by HPLC (see conditions below), and those fractions with a purity of >98 % were adjusted to pH ~10 with NH₄OH (25 % in water). The combined fractions were
20 filtered over an RP-18 plaque and washed with water. This aqueous solution was discarded. The product was eluted from the RP-plaque with EtOH and diluted to 25 ml. 25.0 mCi (46.4 %) of the product having 98.9 % purity were obtained.

Example 98

(S)-4-[(Indan-5-yl-methyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



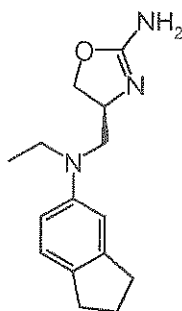
25

In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 5-aminoindane. White solid. MS (ISP): 246.4 ([M+H]⁺)

Example 99

30 (S)-4-[(Ethyl-indan-5-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

- 62 -

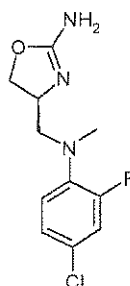


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 5-aminoindane. Off-white solid. MS (ISP): 260.3 ($[M+H]^+$)

5

Example 100

(S)-4-[[[(4-Chloro-2-fluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



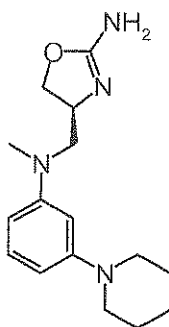
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-2-fluoroaniline. White solid. MS (ISP): 260.1 ($[^{37}\text{Cl}]\{M+H\}^+$), 258.0 ($[^{35}\text{Cl}]\{M+H\}^+$).

10

Example 101

(S)-4-[[Methyl-(3-piperidin-1-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

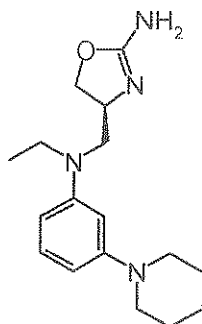
15



In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-piperidin-1-ylaniline. Viscous yellow oil. MS (ISP): 289.3 ($[M+H]^+$)

Example 102

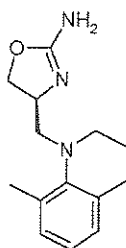
(S)-4-{{[Ethyl-(3-piperidin-1-yl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



- 5 In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-piperidin-1-ylaniline. Viscous colourless oil. MS (ISP): 303.3 ($[M+H]^+$)

Example 103

10 (S)-4-{{[(2,6-Dimethyl-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

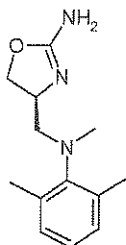


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,6-dimethylaniline. Colourless gum. MS (ISP): 248.1 ($[M+H]^+$).

15

Example 104

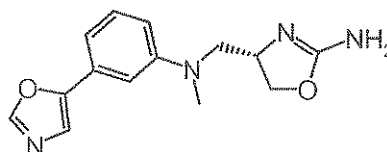
(S)-4-{{[(2,6-Dimethyl-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



- 20 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,6-dimethylaniline. Light yellow gum. MS (ISP): 234.3 ($[M+H]^+$)

Example 105

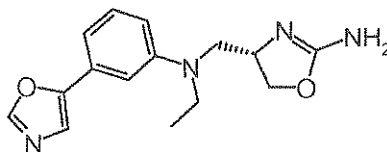
(S)-4-[[Methyl-(3-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-
 5 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-(1,3-oxazol-5-yl)amine. Off-white solid. MS (ISP): 273.3 ($[M+H]^+$)

Example 106

(S)-4-[[Ethyl-(3-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



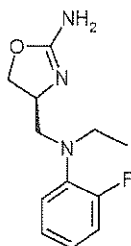
10

In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-(1,3-oxazol-5-yl)amine.
 Viscous yellow oil. MS (ISP): 287.0 ($[M+H]^+$)

15

Example 107

(S)-4-[[Ethyl-(2-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

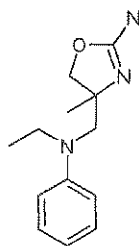


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-
 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoro-aniline. Colourless gum.
 20 MS (ISP): 238.1 ($[M+H]^+$).

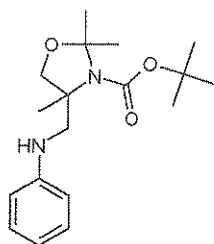
Example 108

(RS)- 4-[(Ethyl-phenyl-amino)-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine

- 65 -



a) (RS)-2,2,4-Trimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester

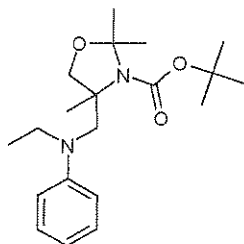


5

To a stirred solution of (RS)-4-formyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (300 mg) at r.t. in methanol (3 ml) was added aniline (132 mg) and the mixture was heated at 80 °C for 3 h. NaBH₄ (93 mg) was then added and the mixture was stirred at 60 °C for 16 h, then cooled to r.t. and concentrated *in vacuo*. The residue was
 10 purified by column chromatography (SiO₂; gradient: heptane/ethyl acetate) to give (RS)-2,2,4-trimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (181 mg, 46%) as a yellow oil. MS (ISP): 321.1 ([M+H]⁺).

b) (RS)-4-[(Ethyl-phenyl-amino)-methyl]-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

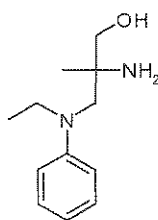
15



In analogy to example 1.b (RS)-2,2,4-trimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester was reacted with acetaldehyde to give (RS)-4-[(ethyl-phenyl-amino)-methyl]-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.
 20 Colourless oil. MS (ISP): 349.5 ([M+H]⁺).

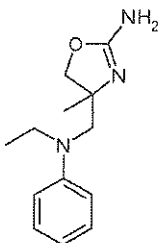
c) (RS)-2-Amino-3-(ethyl-phenyl-amino)-2-methyl-propan-1-ol

- 66 -



In analogy to example 1.c (RS)-4-[(ethyl-phenyl-amino)-methyl]-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was reacted with hydrogen chloride to give (RS)-2-amino-3-(ethyl-phenyl-amino)-2-methyl-propan-1-ol. Colourless oil. MS (ISP):
 5 209.3 ($[M+H]^+$).

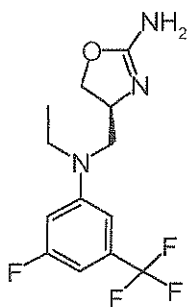
d) (RS)-4-[(Ethyl-phenyl-amino)-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1.d (RS)-2-amino-3-(ethyl-phenyl-amino)-2-methyl-propan-1-ol
 10 was reacted with cyanogen bromide to give (RS)-4-[(ethyl-phenyl-amino)-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine as a colourless gum. MS (ISP): 234.0 ($[M+H]^+$).

Example 109

(S)-4-[[Ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-
 15 2-ylamine



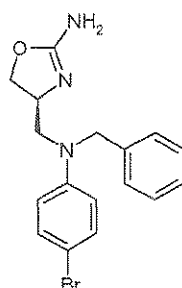
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-5-trifluoromethylaniline. White waxy solid. MS (ISP): 306.1 ($[M+H]^+$)

20

Example 110

(S)-4-[[Benzyl-(4-bromo-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 67 -

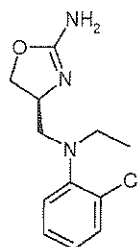


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-bromoaniline. Colourless gum. MS (ISP): 362.2 ($[\{^{81}\text{Br}\}\text{M}+\text{H}]^+$), 360.1 ($[\{^{79}\text{Br}\}\text{M}+\text{H}]^+$).

5

Example 111

(S)-4-[[[(2-Chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

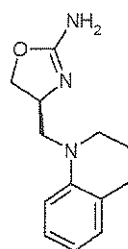


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-chloro-aniline. Colourless gum. MS (ISP): 256.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 254.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

10

Example 112

(S)-4-[(Ethyl-o-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



15

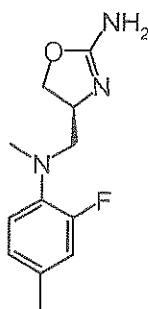
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and o-toluidine. Colourless gum. MS (ISP): 234.3 ($[\text{M}+\text{H}]^+$).

Example 113

(S)-4-[[[(2-Fluoro-4-methyl-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

20

- 68 -

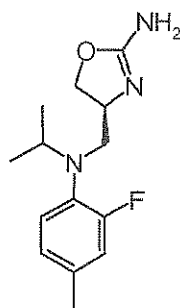


In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoro-4-methylaniline. White waxy solid. MS (ISP): 238.1 ($[M+H]^+$)

5

Example 114

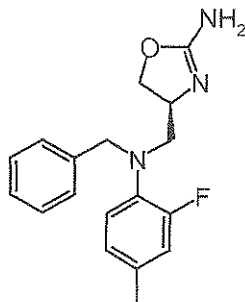
(S)-4-[(2-Fluoro-4-methyl-phenyl)-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



10 In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoro-4-methylaniline. Light yellow waxy solid. MS (ISP): 266.0 ($[M+H]^+$)

Example 115

15 (S)-4-[(Benzyl-(2-fluoro-4-methyl-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



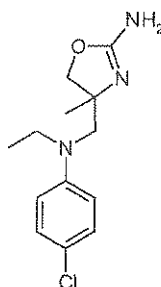
In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoro-4-methylaniline.

Viscous colorless oil. MS (ISP): 314.1 ($[M+H]^+$)

5

Example 116

(RS)-4-[[[(4-Chloro-phenyl)-ethyl-amino]-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine



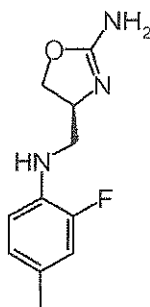
In analogy to example 109 the title compound was prepared starting from (RS)-4-formyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester and 4-chloro-aniline.

10

Colourless gum. MS (ISP): 270.3 ($[^{37}\text{Cl}]M+H^+$), 268.2 ($[^{35}\text{Cl}]M+H^+$).

Example 117

(S)-4-[(2-Fluoro-4-methyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine



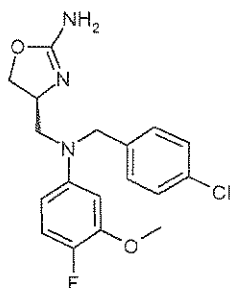
15

In analogy to examples 20 and 43 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-fluoro-4-methylaniline. Waxy white solid. MS (ISP): 224.4 ($[M+H]^+$)

20

Example 118

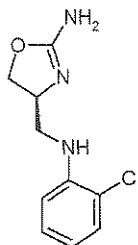
(S)-4-[[[(4-Chloro-benzyl)-(4-fluoro-3-methoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



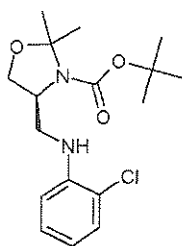
In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-fluoro-3-methoxyaniline and 4-chlorobenzaldehyde dimethyl acetal. Light yellow gum. MS (ISP): 366.1 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$),
 5 364.2 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

Example 119

(S)-4-[(2-Chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

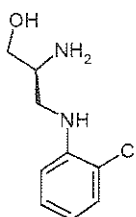


10 a) (S)-4-[(2-Chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



In analogy to example 1.a tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate was reacted with 2-chloroaniline to give (S)-4-[(2-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.
 15 White solid. MS (ISP): 343.2 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 341.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

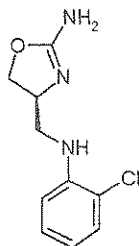
b) (S)-2-Amino-3-(2-chloro-phenylamino)-propan-1-ol



In analogy to example 1.c (S)-4-[(2-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was reacted with hydrogen chloride to give (S)-2-amino-3-(2-chloro-phenylamino)-propan-1-ol. White solid. MS (ISP): 203.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 201.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

5

c) (S)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



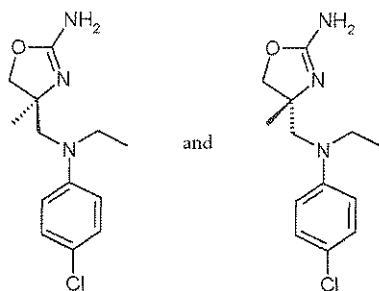
In analogy to example 1.d (S)-2-amino-3-(2-chloro-phenylamino)-propan-1-ol was reacted with cyanogen bromide to give (S)-4-[(isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine as a colourless gum. MS (ISP): 228.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 226.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

10

Examples 120 & 121

(S)-4-[(4-Chloro-phenyl)-ethyl-amino]-methyl}-4-methyl-4,5-dihydro-oxazol-2-ylamine and (R)-4-[(4-Chloro-phenyl)-ethyl-amino]-methyl}-4-methyl-4,5-dihydro-oxazol-2-ylamine

15



(RS)-4-[(4-Chloro-phenyl)-ethyl-amino]-methyl}-4-methyl-4,5-dihydro-oxazol-2-ylamine (example 116) was separated by chiral column chromatography (Chiralpak AD, EtOH/heptane = 1:10) to yield (S)-4-[(4-chloro-phenyl)-ethyl-amino]-methyl}-4-methyl-4,5-dihydro-oxazol-2-ylamine (white solid; MS (ISP): 270.3 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 268.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)) and (R)-4-[(4-chloro-phenyl)-ethyl-amino]-methyl}-4-methyl-4,5-dihydro-oxazol-2-ylamine (white solid; MS (ISP): 270.3 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 268.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$)).

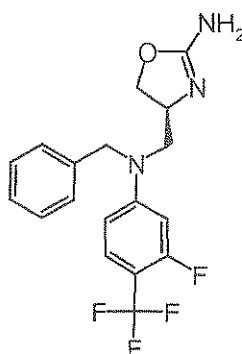
20

Example 122

(S)-4-[(Benzyl-(3-fluoro-4-trifluoromethyl-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

25

- 72 -

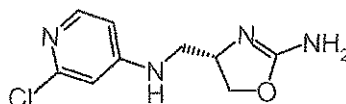


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethylaniline. Viscous colorless oil. MS (ISP): 368.1 ($[M+H]^+$)

5

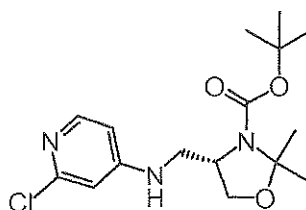
Example 123

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(2-chloro-pyridin-4-yl)-amine



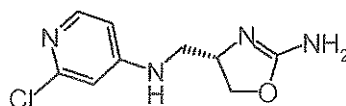
a) ((S)-4-[(2-Chloro-pyridin-4-ylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

10



To a stirred solution of tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (500 mg) at r.t. in 1,2-dichloroethane (10 ml) under an argon atmosphere was added 2-chloro-4-aminopyridine (255 mg). After 30 min stirring at r.t. were added sodium tri-
 15 acetoxymethylborohydride (523 mg) and acetic acid (0.11 ml). The reaction mixture was stirred overnight at 60 °C, then cooled to r.t., diluted with CH_2Cl_2 and washed with 10 % aqueous Na_2CO_3 . The aqueous phase was back extracted with CH_2Cl_2 . The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2 ; gradient: cyclohexane -> cyclo-
 20 hexane/EtOAc 3:2) to give (S)-4-[(2-chloro-pyridin-4-ylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (179 mg, 26%) as colorless amorphous solid. MS (ISP): 342.1 ($[M+H]^+$)

b) ((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(2-chloro-pyridin-4-yl)-amine

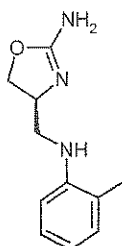


In analogy to example 1.c and 1.d (S)-4-[(2-chloro-pyridin-4-ylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to the title compound. White solid. MS (ISP): 227.3 ($[M+H]^+$)

5

Example 124

(S)-4-(o-Tolylamino-methyl)-4,5-dihydro-oxazol-2-ylamine

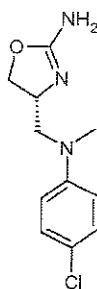


In analogy to example 119 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and o-toluidine. Light yellow gum. MS (ISP): 206.1 ($[M+H]^+$).

10

Example 125

(R)-4-[(4-Chloro-phenyl)-methyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine



In analogy to example 3 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-N-methylaniline. Colourless gum. MS (ISP): 242.1 ($[^{37}\text{Cl}]M+H^+$), 240.1 ($[^{35}\text{Cl}]M+H^+$).

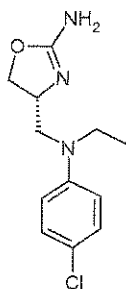
15

Example 126

(R)-4-[(4-Chloro-phenyl)-ethyl-amino]-methyl-4,5-dihydro-oxazol-2-ylamine

20

- 74 -



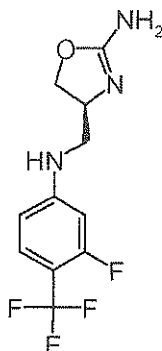
In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. Light yellow gum.

MS (ISP): 256.2 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 254.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

5

Example 127

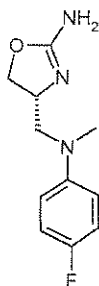
(S)-4-[(3-Fluoro-4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine



10 In analogy to examples 20 and 43 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethyl-aniline. Viscous colorless oil. MS (ISP): 278.1 ($[\text{M}+\text{H}]^+$)

Example 128

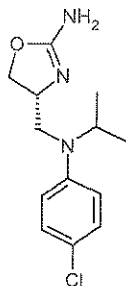
15 (R)-4-[[4-Fluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 3 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-N-methylaniline. Light yellow gum. MS (ISP): 224.4 ($[\text{M}+\text{H}]^+$).

Example 129

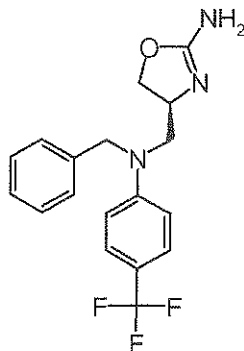
(R)-4-[[(4-Chloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- 5 The title compound was prepared in analogy to example 2 starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloroaniline. Colourless gum.
MS (ISP): 270.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 268.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

Example 130

- 10 (S)-4-[[Benzyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



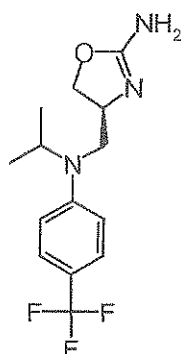
In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-trifluoromethylaniline.

- 15 Viscous colorless oil. MS (ISP): 350.3 ($[\text{M}+\text{H}]^+$)

Example 131

(S)-4-[[Isopropyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

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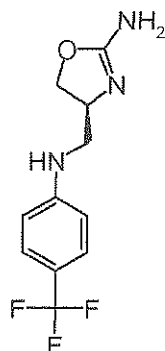
In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-trifluoromethylaniline.

Viscous colorless oil. MS (ISP): 302.1 ($[M+H]^+$)

5

Example 132

(S)-4-[(4-Trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine



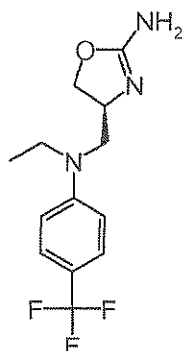
In analogy to examples 20 and 43 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-trifluoromethylaniline. Waxy white solid. MS (ISP): 260.1 ($[M+H]^+$)

10

Example 133

(S)-4-[[Ethyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

15



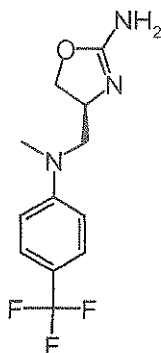
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-trifluoromethyl-aniline.

Viscous colorless oil. MS (ISP): 288.0 ($[M+H]^+$)

5

Example 134

(S)-4-{[Methyl-(4-trifluoromethyl-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



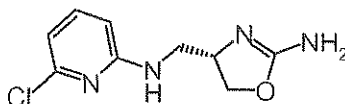
In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-trifluoromethyl-aniline.

10

Viscous colorless oil. MS (ISP): 274.0 ($[M+H]^+$)

Example 135

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-chloro-pyridin-2-yl)-amine



15

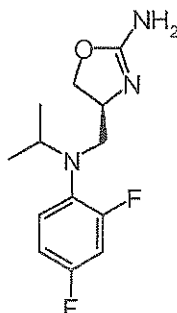
In analogy to example 123 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-amino-6-chloropyridine.

Colorless viscous oil. MS (ISP): 227.4 ($[M+H]^+$)

20

Example 136

(S)-4-{[(2,4-Difluoro-phenyl)-isopropyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

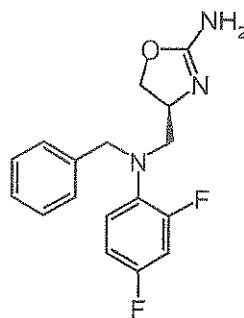


In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,4-difluoroaniline. Viscous colorless oil. MS (ISP): 270.4 ($[M+H]^+$)

5

Example 137

(S)-4-{[Benzyl-(2,4-difluoro-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

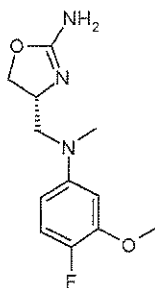


In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,4-difluoroaniline. Viscous colorless oil. MS (ISP): 318.3 ($[M+H]^+$)

10

Example 138

(R)-4-{[(4-Fluoro-3-methoxy-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



15

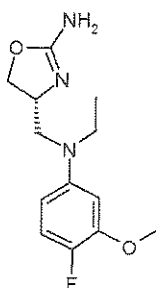
In analogy to example 30 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline. Off-white solid. MS (ISP): 254.1 ($[M+H]^+$).

20

Example 139

(R)-4-{[Ethyl-(4-fluoro-3-methoxy-phenyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

- 79 -

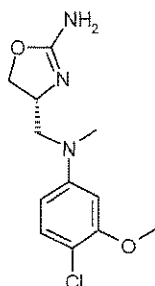


In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-fluoro-3-methoxyaniline. Light yellow gum. MS (ISP): 268.4 ($[M+H]^+$).

5

Example 140

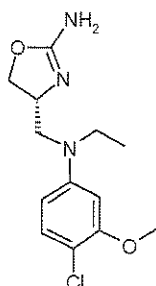
(R)-4-[[4-(4-Chloro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- 10 In analogy to example 30 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-3-methoxyaniline. White solid. MS (ISP): 272.3 ($[^{37}\text{Cl}]M+H^+$), 270.3 ($[^{35}\text{Cl}]M+H^+$).

Example 141

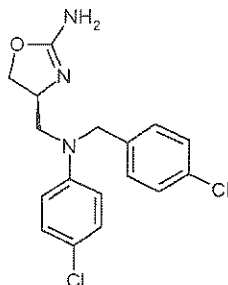
- 15 (R)-4-[[4-(4-Chloro-3-methoxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-3-methoxyaniline. Off-white solid. MS (ISP): 286.1 ($[^{37}\text{Cl}]M+H^+$), 284.3 ($[^{35}\text{Cl}]M+H^+$).
- 20

Example 142

(S)-4-[[(4-Chloro-benzyl)-(4-chloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

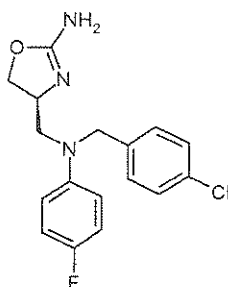


- 5 In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-chloroaniline and 4-chlorobenzaldehyde dimethyl acetal. White gum. MS (ISP): 354.1 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 352.2 ($[^{37}\text{Cl}^{35}\text{Cl}]\text{M}+\text{H}^+$), 350.2 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

10

Example 143

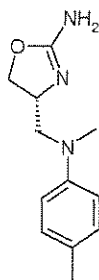
(S)-4-[[(4-Chloro-benzyl)-(4-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-
15 (+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-fluoroaniline and 4-chlorobenzaldehyde dimethyl acetal. Colourless gum. MS (ISP): 336.2 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 334.2 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

Example 144

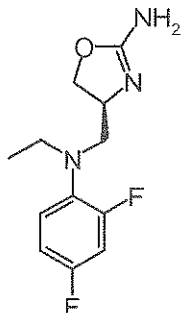
(R)-4-[(Methyl-p-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 3 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and N-methyl-p-toluidine. Colourless gum. MS (ISP): 220.1 ($[M+H]^+$).

Example 145

5 (S)-4-[[(2,4-Difluoro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

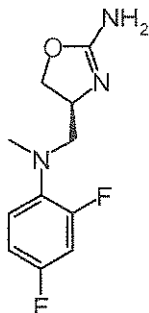


In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,4-difluoroaniline. Viscous colorless oil. MS (ISP): 256.1 ($[M+H]^+$)

10

Example 146

(S)-4-[[(2,4-Difluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

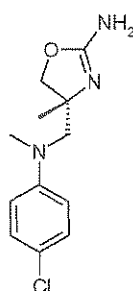


15 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,4-difluoroaniline. Waxy white solid. MS (ISP): 242.1 ($[M+H]^+$)

Example 147

(R)-4-[[(4-Chloro-phenyl)-methyl-amino]-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine

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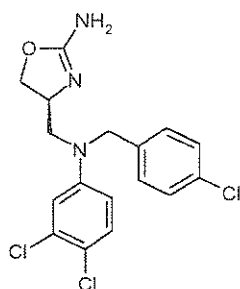


In analogy to example 109 the title compound was prepared starting from (S)-4-formyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester, 4-chloro-aniline and formaldehyde. White solid. MS (ISP): 256.1 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 254.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

5

Example 148

(S)-4-[[4-(4-Chloro-benzyl)-(3,4-dichloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

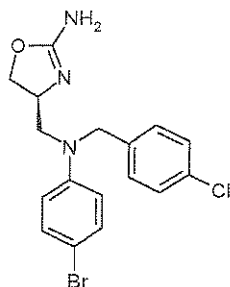


10 In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 3,4-dichloroaniline and 4-chlorobenzaldehyde dimethyl acetal. White solid. MS (ISP): 390.0 ($[^{37}\text{Cl}]\text{M}+\text{H}^+$), 388.1 ($[^{37}\text{Cl}^{35}\text{Cl}]\text{M}+\text{H}^+$), 386.0 ($[^{37}\text{Cl}^{35}\text{Cl}]\text{M}+\text{H}^+$), 384.1 ($[^{35}\text{Cl}]\text{M}+\text{H}^+$).

15

Example 149

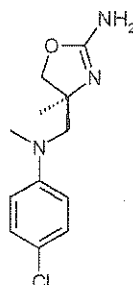
(S)-4-[[4-(4-Bromo-phenyl)-(4-chloro-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



20 In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-bromoaniline and 4-chlorobenzaldehyde dimethyl acetal. White solid. MS (ISP): 398.0 ($[^{37}\text{Cl}^{81}\text{Br}]\text{M}+\text{H}^+$), 396.0 ($[^{37}\text{Cl}^{79}\text{Br}, ^{35}\text{Cl}^{81}\text{Br}]\text{M}+\text{H}^+$), 394.0 ($[^{35}\text{Cl}^{79}\text{Cl}]\text{M}+\text{H}^+$).

Example 150

(S)-4-[[[(4-Chloro-phenyl)-methyl-amino]-methyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine



5

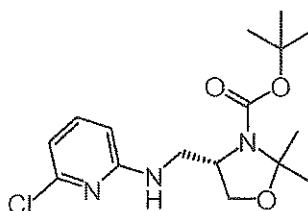
In analogy to example 109 the title compound was prepared starting from (R)-4-formyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid tert-butyl ester, 4-chloro-aniline and formaldehyde. White solid. MS (ISP): 256.1 ([^{37}Cl]M+H) $^{+}$), 254.1 ([^{35}Cl]M+H) $^{+}$.

10

Example 151

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-chloro-pyridin-2-yl)-ethyl-amine

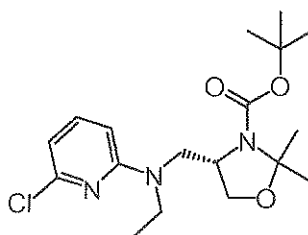
a) (S)-4-[(6-Chloro-pyridin-2-ylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



15

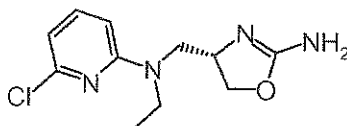
In analogy to example 123.a tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate was reacted with 2-amino-6-chloropyridin. Light yellow solid. MS (ISP): 342.3 ([M+H] $^{+}$)

20 b) ((S)-4-[[[(6-Chloro-pyridin-2-yl)-ethyl-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-4-[(6-chloro-pyridin-2-ylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (528 mg) at r.t. in 1,2-dichloroethane (20 ml) under an argon atmosphere were added molecular sieves 4 A (~ 2 g) and acetaldehyde (0.44 ml). After 30 min stirring at r.t., sodium triacetoxyborohydride (1.02 g) was added, followed by acetic acid (0.13 ml). The mixture was stirred for at r.t. over night, then diluted with CH₂Cl₂ and washed with sat. aq. Na₂CO₃. The biphasic mixture was filtered. The aqueous phase of the filtrate was back extracted with CH₂Cl₂. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂; gradient: cyclohexane -> cyclohexane/EtOAc 85:15) to give (S)-4-[[[(6-chloro-pyridin-2-yl)-ethyl-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (244 mg, 43 %) as viscous yellow oil. MS (ISP): 370.3 ([M+H]⁺)

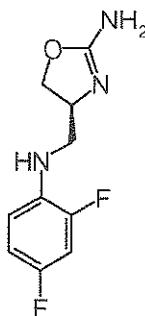
c) ((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-chloro-pyridin-2-yl)-ethyl-amine



In analogy to example 1.c and 1.d (S)-4-[[[(6-chloro-pyridin-2-yl)-ethyl-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester was converted to the title compound. Light yellow viscous oil. MS (ISP): 255.1 ([M+H]⁺)

Example 152

(S)-4-[(2,4-Difluoro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine



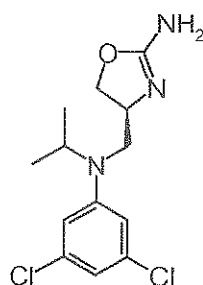
In analogy to examples 20 and 43 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2,4-difluoroaniline.

Waxy colorless solid. MS (ISP): 228.1 ([M+H]⁺)

Example 153

(S)-4-[[[(3,5-Dichloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 85 -

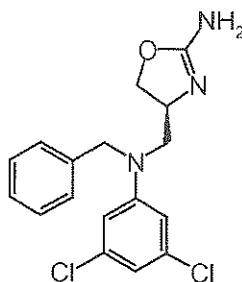


In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,5-dichloroaniline. Viscous colorless oil. MS (ISP): 302.1 ($[M+H]^+$)

5

Example 154

(S)-4-[[Benzyl-(3,5-dichloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



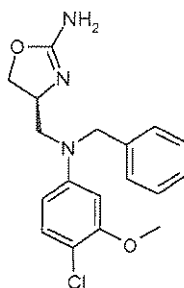
In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,5-dichloroaniline. Viscous colorless oil. MS (ISP): 350.1 ($[M+H]^+$)

10

Example 155

(S)-4-[[Benzyl-(4-chloro-3-methoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

15

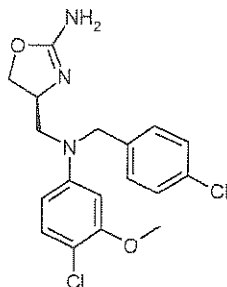


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-chloro-3-methoxyaniline and benzaldehyde dimethyl acetal. White solid. MS (ISP): 348.1 ($[^{37}\text{Cl}]M+H^+$),

20 346.0 ($[^{35}\text{Cl}]M+H^+$).

Example 156

(S)-4-[[(4-Chloro-benzyl)- (4-chloro-3-methoxy-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

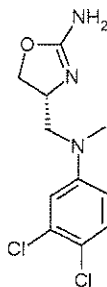


- 5 In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-chloro-3-methoxyaniline and 4-chlorobenzaldehyde dimethyl acetal. Colourless gum. MS (ISP): 384.2 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 382.3 ($[\{^{37}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$), 380.2 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

10

Example 157

(R)-4-[[(3,4-Dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

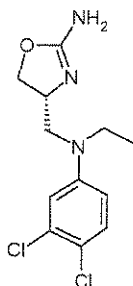


In analogy to example 30 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline.

- 15 Colourless gum. MS (ISP): 278.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 276.1 ($[\{^{37}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$), 274.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

Example 158

(R)-4-[[(3,4-Dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

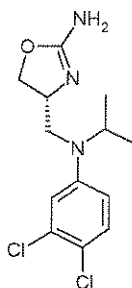


In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. Colourless gum. MS (ISP): 292.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 290.0 ($[\{^{37}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$), 288.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

5

Example 159

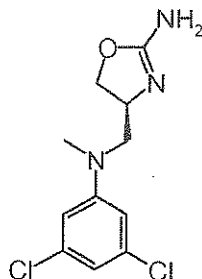
(R)-4-[[[(3,4-Dichloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 2 starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,4-dichloroaniline. Colourless
10 gum. MS (ISP): 306.1 ($[\{^{37}\text{Cl}\}\text{M}+\text{H}]^+$), 304.1 ($[\{^{37}\text{Cl}^{35}\text{Cl}\}\text{M}+\text{H}]^+$), 302.1 ($[\{^{35}\text{Cl}\}\text{M}+\text{H}]^+$).

Example 160

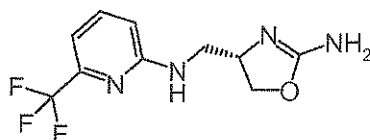
(S)-4-[[[(3,5-Dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



15 In analogy to example 30 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,5-dichloroaniline. White solid. MS (ISP): 274.0 ($[\text{M}+\text{H}]^+$)

Example 161

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-trifluoromethyl-pyridin-2-yl)-amine

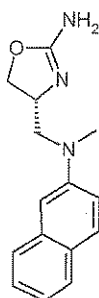


20

In analogy to example 123 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-amino-6-trifluoromethyl-pyridine. Colorless viscous oil. Light yellow viscous oil. MS (ISP): 261.5 ($[\text{M}+\text{H}]^+$)

Example 162

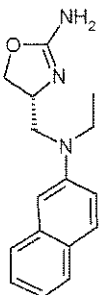
(R)-4-[(Methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 30 the title compound was prepared starting from tert-butyl
 5 (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-aminonaphthalene. White
 solid. MS (ISP): 256.3 ($[M+H]^+$).

Example 163

(R)-4-[(Ethyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



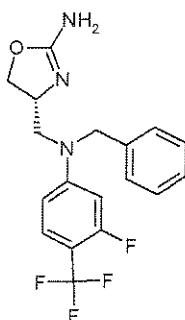
10

In analogy to example 1 the title compound was prepared starting from tert-butyl
 (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-aminonaphthalene. Off-
 white solid. MS (ISP): 270.4 ($[M+H]^+$).

15

Example 164

(R)-4-[[Benzyl-(3-fluoro-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

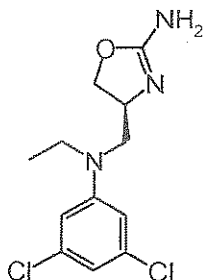


In analogy to example 20 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-amino-2-fluorobenzonitrile and benzaldehyde dimethyl acetal. Colourless gum. MS (ISP): 368.1 ($[M+H]^+$).

5

Example 165

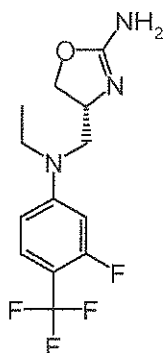
(S)-4-[[(3,5-Dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3,5-dichloroaniline. Light yellow
10 viscous oil. MS (ISP): 288.0 ($[M+H]^+$)

Example 166

(R)-4-[[Ethyl-(3-fluoro-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



15

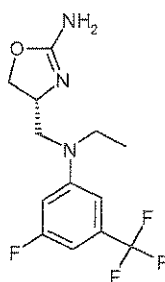
In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethylaniline. Waxy white solid. MS (ISP): 306.0 ($[M+H]^+$)

20

Example 167

(R)-4-[[Ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 90 -

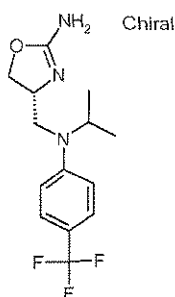


In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-amino-5-fluorobenzotrifluoride. Colourless gum. MS (ISP): 306.3 ($[M+H]^+$).

5

Example 168

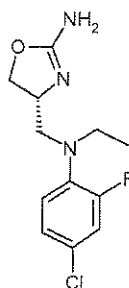
(R)-4-[[Isopropyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- 10 The title compound was prepared in analogy to example 2 starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-amino-benzotrifluoride. Colourless gum. MS (ISP): 302.4 ($[M+H]^+$).

Example 169

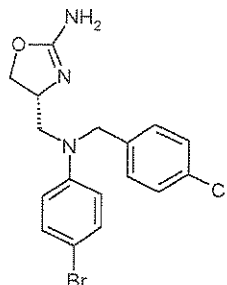
- 15 (R)-4-[[[(4-Chloro-2-fluoro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



- In analogy to example 1 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 4-chloro-2-fluoro-aniline. Colourless
20 gum. MS (ISP): 274.2 ($[^{37}\text{Cl}]M+H]^+$), 272.3 ($[^{35}\text{Cl}]M+H]^+$).

Example 170

(R)-4-[[[(4-Bromo-phenyl)-(4-chloro-benzyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

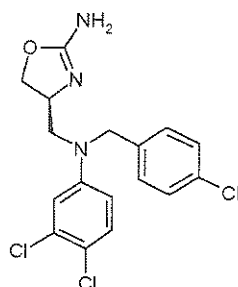


- 5 In analogy to example 20 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-bromoaniline and 4-chlorobenzaldehyde dimethyl acetal. Yellow gum. MS (ISP): 398.1([$^{37}\text{Cl}^{81}\text{Br}$]M+H)⁺, 396.0([$^{37}\text{Cl}^{79}\text{Br}$, $^{35}\text{Cl}^{81}\text{Br}$]M+H)⁺, 394.0([$^{35}\text{Cl}^{79}\text{Cl}$]M+H)⁺.

10

Example 171

(R)-4-[[[(4-Chloro-benzyl)-(3,4-dichloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

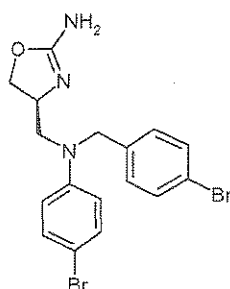


- In analogy to example 20 the title compound was prepared starting from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 3,4-dichloroaniline and 4-chlorobenzaldehyde dimethyl acetal. White solid. MS (ISP): 390.0([^{37}Cl]M+H)⁺, 388.1([$^{37}\text{Cl}^{35}\text{Cl}$]M+H)⁺, 386.0([$^{37}\text{Cl}^{35}\text{Cl}$]M+H)⁺, 384.0([^{35}Cl]M+H)⁺.
- 15

Example 172

- 20 (S)-4-[[[(4-Bromo-benzyl)-(4-bromo-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

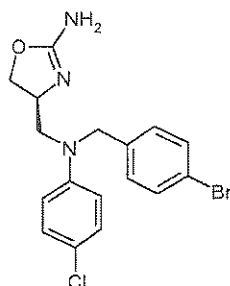
- 92 -



In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-bromoaniline and 4-bromobenzaldehyde dimethyl acetal. Colourless gum. MS (ISP): 442.0 ($[^{81}\text{Br}]\text{M}+\text{H}^+$),
 5 440.1 ($[^{81}\text{Br}^{79}\text{Br}]\text{M}+\text{H}^+$), 438.0 ($[^{79}\text{Br}]\text{M}+\text{H}^+$).

Example 173

(S)-4-[[[4-Bromo-benzyl)-(4-chloro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



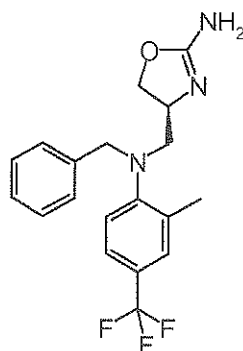
10

In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate, 4-chloroaniline and 4-bromobenzaldehyde dimethyl acetal. Colourless gum. MS (ISP):
 398.1 ($[^{81}\text{Br}^{37}\text{Cl}]\text{M}+\text{H}^+$), 395.9 ($[^{79}\text{Br}^{37}\text{Cl}, ^{81}\text{Br}^{35}\text{Cl}]\text{M}+\text{H}^+$), 394.0 ($[^{79}\text{Cl}^{35}\text{Cl}]\text{M}+\text{H}^+$).

15

Example 174

(S)-4-[[[Benzyl-(2-methyl-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

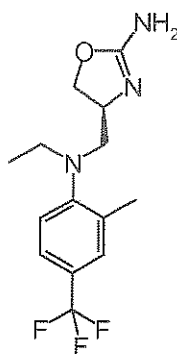


In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-methyl-4-trifluoromethylaniline. Viscous colorless oil. MS (ISP): 364.3 ($[M+H]^+$)

5

Example 175

(S)-4-[[Ethyl-(2-methyl-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



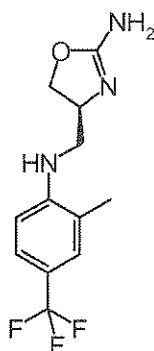
In analogy to example 1 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-methyl-4-trifluoromethylaniline. Viscous colorless oil. MS (ISP): 302.4 ($[M+H]^+$)

10

Example 176

(S)-4-[(2-Methyl-4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

15



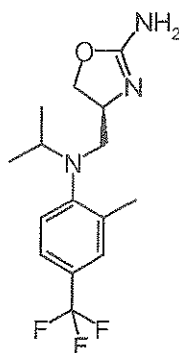
In analogy to examples 20 and 43 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-methyl-4-trifluoromethylaniline. Viscous colorless oil. MS (ISP): 274.4 ($[M+H]^+$)

20

Example 177

(S)-4-[[Isopropyl-(2-methyl-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

- 94 -

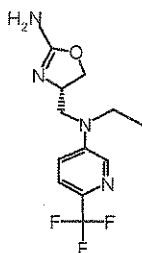


In analogy to example 2 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 2-methyl-4-trifluoromethylaniline. Viscous colorless oil, MS (ISP): 316.4 ($[M+H]^+$)

5

Example 178

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-ethyl-(6-trifluoromethyl-pyridin-3-yl)-amine



- 10 a) (R)-2,2-Dimethyl-4-(6-trifluoromethyl-pyridin-3-ylcarbamoyl)-oxazolidine-3-carboxylic acid tert-butyl ester

To a solution of (4S)-3-(tert.-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylic acid (0.49 g, 2 mmol) in dichloromethane (6 ml) was added 3-amino-6-(trifluoromethyl)pyridine (0.324 mg, 2 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.764 g, 3 mmol) and N,N-diisopropylethylamine (0.388g, 3 mmol). The mixture was stirred overnight at room temperature. For workup sodium bicarbonate solution (5 ml) was added and the mixture was extracted with dichloromethane twice. The combined organic layers were dried (MgSO₄) and filtered. After removal of the solvent the residue was purified by column chromatography (SiO₂, heptane/EtOAc= 4:1) to yield a white solid (0.36 g, 46 %), MS (ISP): 390.3 ($[M+H]^+$).

- b) (R)-4-[Ethyl-(6-trifluoromethyl-pyridin-3-yl)-carbamoyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

To a stirred solution of (R)-2,2-dimethyl-4-(6-trifluoromethyl-pyridin-3-ylcarbamoyl)-oxazolidine-3-carboxylic acid tert-butyl ester (0.20 g, 0.51 mmol) in dimethylsulfoxide (4

25

ml) under an argon atmosphere was added sodium hydride (0.028 g, 0.59 mmol) and the mixture was stirred for 20 min. Iodoethane (0.05 ml, 0.61 mmol) was added and the mixture was stirred overnight at room temperature. Water (20 ml) was added and the mixture was extracted three times with ethyl acetate. The combined organic layers were
5 dried (MgSO_4) and filtered. After removal of the solvent the residue was purified by column chromatography (SiO_2 , heptane/ EtOAc = 1:1) to yield a light yellow oil (0.15 g, 70%), MS (ISP): 418.2 ($[\text{M}+\text{H}]^+$).

c) (S)-2-Amino-3-[ethyl-(6-trifluoromethyl-pyridin-3-yl)-amino]-propan-1-ol

10 To a stirred solution of (S)-4-[(isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.15 g, 0.36 mmol) in tetrahydrofuran (4 ml) under an argon atmosphere was added borane-tetrahydrofuran complex (1 M solution, 1.8 ml, 1.8 mmol). The mixture was stirred at 60 °C for 2 hours. After cooling to room temperature hydrochloric acid (4N in water, 2 ml) was added carefully and the
15 mixture was stirred again at 60 °C for 2 hours. After cooling aqueous sodium hydroxide solution (1M) was added until basic pH and the mixture was extracted three times with ethyl acetate. The combined organic layers were dried (MgSO_4) and filtered. After removal of the solvent the residue was purified by column chromatography (SiO_2 , dichloromethane/ MeOH = 9:1) to yield a white solid (0.04 g, 42 %), MS (ISP): 264.2
20 ($[\text{M}+\text{H}]^+$).

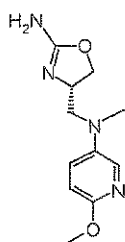
d) ((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-ethyl-(6-trifluoromethyl-pyridin-3-yl)-amine

To a stirred mixture of (S)-2-amino-3-[ethyl-(6-trifluoromethyl-pyridin-3-yl)-amino]-
25 propan-1-ol (0.04 g, 0.15 mmol) and K_2CO_3 (0.025 g, 0.18 mmol) in THF (2 ml) under an argon atmosphere was added a solution of cyanogen bromide (0.025 g, 0.18 mmol) in THF (1 ml). The mixture was stirred for 1 hour, then ethylacetate and water were added. The aqueous phase was back extracted with EtOAc . The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified
30 by column chromatography (SiO_2 , EtOAc/MeOH = 9:1) to give the title compound as white solid (0.02 g, 46 %), MS (ISP): 289.0 ($[\text{M}+\text{H}]^+$).

Example 179

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-methoxy-pyridin-3-yl)-methyl-amine

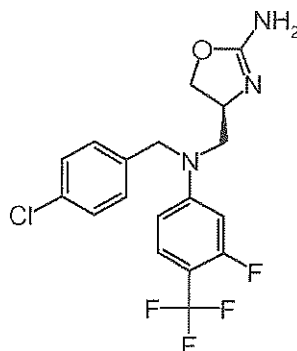
- 96 -



The title compound, MS (ISP): 236.9 ($(M+H)^+$) was obtained in comparable yield analogous to the procedure described for Example 178 using 5-amino-2-methoxypyridine instead of 3-amino-6-(trifluoromethyl)pyridine in step a) and
5 iodomethane instead of iodoethane in step b).

Example 180

(S)-4-[[(4-Chloro-benzyl)-(3-fluoro-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine



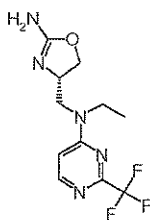
10

In analogy to example 20 the title compound was prepared starting from tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate and 3-fluoro-4-trifluoromethylaniline, using 4-chlorobenzaldehyde dimethylacetal in the second reaction step. Viscous colorless oil. MS (ISP): 401.2 ($[M+H]^+$)

15

Example 181

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amine



20 a) (S)-4-Ethylaminomethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

To a solution of tert-butyl (R)-(+)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (2.29 g, 10 mmol) in methanol (10 ml) were added a solution of ethylamine in methanol (2M,

15 ml, 30 mmol) and molecular sieves 4Å. After stirring at room temperature for 90 min molecular sieves were filtered off and palladium on charcoal was added (0.3 g). The mixture was hydrogenated overnight at atmospheric pressure and room temperature. The catalyst was filtered off, the filtrate was evaporated and the residue purified by column chromatography (SiO₂, EtOAc/MeOH = 95:5) to yield a colourless liquid (2.45 g, 95 %), MS (ISP): 259.0 ([M+H]⁺).

b) (S)-4-[[Ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amino]-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

10 A solution of (S)-4-ethylaminomethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.310 g, 1.2 mmol), 4-chloro-2-(trifluoromethyl)pyrimidine (0.183 g; 1.0 mmol) and N,N-diisopropyl ethyl amine (0.34 ml, 2.0 mmol) in isopropanol (3 ml) was heated in a sealed vessel in a microwave oven for 30 min at 180 °C. Ethyl acetate (20 ml) and silicagel (1 g) was added and the mixture was evaporated. The residue was purified by
15 flash chromatography, column: Isolute® Flash-NH₂ (Separtis); eluent: EtOAc/MeOH = 95:5) to yield a light yellow oil, (0.362 g, 90 %); MS (ISP): 405.5 ((M+H)⁺).

c) (S)-2-Amino-3-[ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amino]-propan-1-ol
(S)-4-[[Ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amino]-methyl]-2,2-dimethyl-

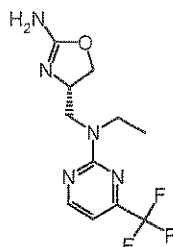
20 oxazolidine-3-carboxylic acid tert-butyl ester (0.339 g, 0.84 mmol) was dissolved in dioxane (6 ml), aqueous hydrochloric acid (4N, 6 ml) was added and the mixture was stirred at 60 °C for 3 hours. The solvent was evaporated and the residue was dissolved in dichloromethane. A solution of ammonia in methanol (2N, 2 ml) was added and the mixture was evaporated over Isolute® Flash-NH₂ silicagel. Chromatography (column:
25 Isolute® Flash-NH₂ from Separtis; eluent: ethyl acetate/ MeOH = 95:5) yielded a light yellow liquid, (0.19 g, 86 %); MS (ISP): 265.3 ((M+H)⁺).

d) ((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amine

30 To a stirred mixture of (S)-2-amino-3-[ethyl-(2-trifluoromethyl-pyrimidin-4-yl)-amino]-propan-1-ol (0.185 g, 0.7 mmol) and K₂CO₃ (0.145 g, 1.05 mmol) in THF (5 ml) under an argon atmosphere was added a solution of cyanogen bromide (0.111 g, 1.05 mmol) in THF (1 ml). The mixture was stirred for 2 hours, then methanol (1 ml) was added. The solution was evaporated over Isolute® Flash-NH₂ silicagel. Chromatography
35 (column: Isolute® Flash-NH₂ from Separtis; eluent: ethyl acetate/ MeOH = 95:5) yielded the title compound as light yellow oil, (0.084 g, 42 %); MS (ISP): 290.0 ((M+H)⁺).

Example 182

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-ethyl-(4-trifluoromethyl-pyrimidin-2-yl)-amine

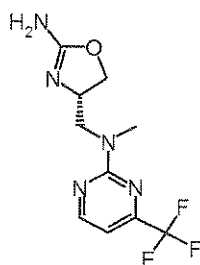


- 5 The title compound, MS (ISP): 290.0 ((M+H)⁺) was obtained in comparable yield analogous to the procedure described for Example 181 using 2-chloro-4-(trifluoromethyl)pyrimidine instead of 4-chloro-2-(trifluoromethyl)pyrimidine in step b).

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Example 183

((S)-2-Amino-4,5-dihydro-oxazol-4-ylmethyl)-methyl-(4-trifluoromethyl-pyrimidin-2-yl)-amine



- The title compound, MS (ISP): 276.0 ((M+H)⁺) was obtained in comparable yield analogous to the procedure described for Example 181 using methylamine instead of ethylamine in step a) and 2-chloro-4-(trifluoromethyl)pyrimidine instead of 4-chloro-2-(trifluoromethyl)pyrimidine in step b).

HPLC conditions:

- 20 Solid phase: Zorbax XDB C18, 150x4.6 mm, 5 μm
Eluent: [A]: 50 mmol ammonium formate/formic acid pH=3, [B]: MeCN, [C]: water with 5 % of B

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Gradient:	min	[A]	[B]	[C]
	0	10	10	80
	2	10	10	80
	10	10	70	20

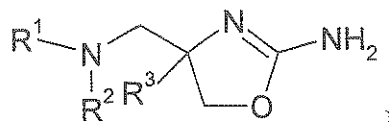
post time: 3 min

5 Detection: 250 nm

Oven: 25 °C

Flow: 1.2 ml/min Retention time: Starting Material: 6.8 min, Product 6.5 min

1. A compound of formula



5 wherein

R¹ is aryl or heteroaryl, wherein the aryl and heteroaryl groups may be unsubstituted or substituted by one to three substituents, selected from the group consisting of cycloalkyl, phenyl, phenoxy, benzyl, benzyloxy, halogen, C₁₋₇-alkyl, C₁₋₇-alkoxy, heteroaryl, piperidin-1-yl or by C₁₋₇-alkyl substituted by halogen, or is aryl or
10 heteroaryl wherein at least one hydrogen atom is replaced by deuterium or tritium;

R² is hydrogen, C₁₋₇-alkyl or is benzyl unsubstituted or substituted by C₁₋₇-alkoxy or halogen; or

R¹ and R² form together with the N-atom to which they are attached 2,3-dihydroindol-1-yl or 3,4-dihydro-quinolin-1-yl;

15 R³ is hydrogen or C₁₋₇-alkyl

or a pharmaceutically suitable acid addition salt thereof.

2. A compound of formula I according to claim 1, wherein R¹ is unsubstituted phenyl and R² is C₁₋₇-alkyl.

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3. A compound of formula I according to claim 2, which compounds are (R)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (S)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or (S)-4-[(methyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

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4. A compound of formula I according to claim 1, wherein R¹ is phenyl substituted by halogen and R² is C₁₋₇-alkyl.

5. A compound of formula I according to claim 4, which compounds are

- (S)-4-[[[(3,4-dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(4-chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3,4-dichloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(4-bromo-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(4-bromo-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3,4-dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3-bromo-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3-bromo-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3-chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(4-chloro-2-fluoro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(4-chloro-2-fluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[ethyl-(2-fluoro-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(2-chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(4-chloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(4-chloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(4-fluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(4-chloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(2,4-difluoro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(2,4-difluoro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(3,4-dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(3,4-dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (R)-4-[[[(3,4-dichloro-phenyl)-isopropyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[[[(3,5-dichloro-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine
 or
 (S)-4-[[[(3,5-dichloro-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

6. A compound of formula I according to claim 1, wherein R¹ is phenyl substituted by halogen or CF₃, and R² is hydrogen.

7. A compound of formula I according to claim 6, which compounds are
 (S)-4-[(3-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine
 (S)-4-[(2-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[(4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine or
(S)-4-[(2,4-difluoro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

8. A compound of formula I according to claim 1, wherein R¹ is phenyl substituted by halogen and C₁₋₇-alkyl, and R² is hydrogen.

9. A compound of formula I according to claim 8, which compound is (S)-4-[(2-fluoro-4-methyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

10. A compound of formula I according to claim 1, wherein R¹ is phenyl substituted by CF₃ and C₁₋₇-alkyl or CF₃ alone and R² is C₁₋₇-alkyl.

11. A compound of formula I according to claim 10, which compounds are

(S)-4-[[ethyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[[methyl-(4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine or

(S)-4-[[ethyl-(2-methyl-4-trifluoromethyl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

12. A compound of formula I according to claim 1, wherein R¹ is pyridine-2-yl and R² is C₁₋₇-alkyl.

13. A compound of formula I according to claim 12, which compound is ((S)-2-amino-4,5-dihydro-oxazol-4-ylmethyl)-(6-chloro-pyridin-2-yl)-amine.

14. A compound of formula I according to claim 1, wherein R¹ is phenyl, substituted simultaneously by halogen and methoxy.

15. A compound of formula I according to claim 14, which compounds are (S)-4-[[[(4-chloro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[[[(4-chloro-3-methoxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[[(4-fluoro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

(R)-4-[[(4-fluoro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine

(R)-4-[[(ethyl-(4-fluoro-3-methoxy-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(R)-4-[[(4-chloro-3-methoxy-phenyl)-methyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine or

(R)-4-[[(4-chloro-3-methoxy-phenyl)-ethyl-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

16. A compound of formula I according to claim 1, wherein R¹ is phenyl, substituted simultaneously by halogen and methoxy or by halogen and R² is benzyl.

17. A compound of formula I according to claim 16, which compounds are (S)-4-[[(benzyl-(4-fluoro-3-methoxy-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[[(benzyl-(4-fluoro-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

(S)-4-[[(benzyl-(4-chloro-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

18. A compound of formula I according to claim 1, wherein R¹ is phenyl, substituted by C₁₋₇-alkyl and R² is C₁₋₇-alkyl.

19. A compound of formula I according to claim 18, wherein the compounds are

(S)-4-[[(ethyl-m-tolyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(S)-4-[[(ethyl-(3-ethyl-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

(S)-4-[[(ethyl-(4-ethyl-phenyl)-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

20. A compound of formula I according to claim 1, wherein R¹ is naphthyl and R² is C₁₋₇-alkyl.

21. A compound of formula I according to claim 20, wherein the compounds are

(S)-4-[[(methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

(R)-4-[[(methyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

(R)-4-[[(ethyl-naphthalen-2-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

22. A compound of formula I according to claim 1, wherein R¹ is phenyl substituted by halogen and CF₃.

23. A compound of formula I according to claim 22, wherein the compounds are

(S)-4-{{ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine

(S)-4-[(3-fluoro-4-trifluoromethyl-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine or

(R)-4-{{ethyl-(3-fluoro-5-trifluoromethyl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine.

24. A compound of formula I according to claim 1, wherein R¹ is indanyl, and R² is C₁₋₇-alkyl.

25. A compound of formula I according to claim 24, wherein the compound is

(S)-4-[(ethyl-indan-5-yl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine.

26. A compound of formula I according to claim 1, wherein R¹ is phenyl, substituted by heteroaryl.

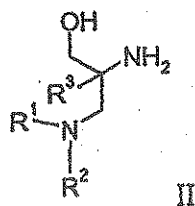
27. A compound of formula I according to claim 24, wherein the compounds are

(S)-4-{{methyl-(3-oxazol-5-yl-phenyl)-amino}-methyl}-4,5-dihydro-oxazol-2-ylamine or

(S)-4-[[ethyl-(3-oxazol-5-yl-phenyl)-amino]-methyl]-4,5-dihydro-oxazol-2-ylamine.

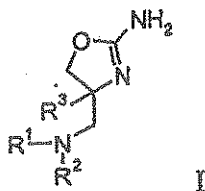
28. A process for preparation of compounds of formula I, which process comprises

a) reacting a compound of formula



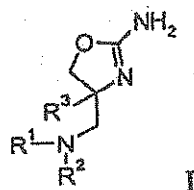
with cyanogen bromide

to a compound of formula



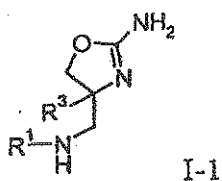
wherein the definitions are as described in claim 1, or

b) deprotecting a compound of formula



for R² being benzyl or benzyl substituted by alkoxy

to a compound of formula



wherein the definitions are as described in claim 1, or

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

29. A medicament containing one or more compounds of formula I and pharmaceutically acceptable excipients.

30. A medicament as claimed in claim 29 for the treatment of anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders and malfunction of body temperature homeostasis and disorders of sleep and circadian rhythm.

31. A medicament according to claim 30, containing one or more compounds as claimed in claims 1-27 for the treatment of depression, psychosis, Parkinson's disease, anxiety and attention deficit hyperactivity disorder (ADHD).

32. The use of a compound of formula I according to claim 1 for the preparation of a medicament for the treatment of anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders and malfunction of body temperature homeostasis and disorders of sleep and circadian rhythm.