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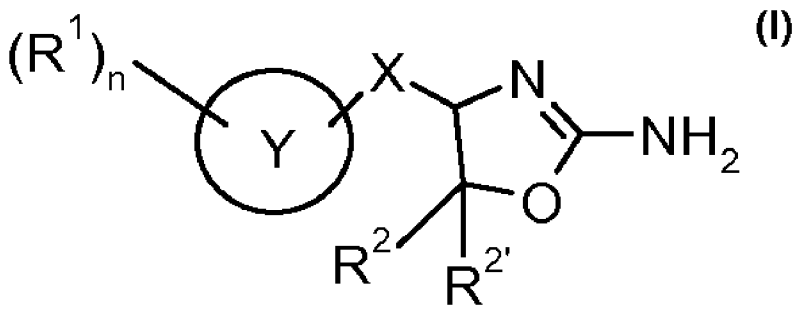
(54) Title: 2-AMINOOXAZOLINES AS TAAR1 LIGANDS

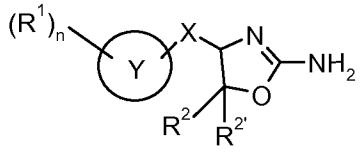


(I)

(57) Abstract: The invention relates to compounds of formula (I) wherein R^1 is halogen; R^2 is lower alkyl or lower alkyl substituted by halogen; $R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen; X is a bond, $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$; Y is phenyl or cyclohexyl; and n is 0, 1 or 2; or to a pharmaceutically suitable acid addition salt thereof. The compounds of formula I are active on the TAAR1 receptor and are therefore suitable for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, substance abuse and metabolic disorders, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

2-AMINOOXAZOLINES AS TAAR1 LIGANDS

The invention relates to compounds of formula



I

wherein

R^1 is halogen;

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

X is a bond, $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

Y is phenyl or cyclohexyl; and

n is 0, 1 or 2;

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 by the present invention.

2-Aminooxazolines are described in the literature as hypertensive agents with good affinity to the adrenergic receptor or as intermediates in processes for preparation of pharmaceutical active agents, for example in EP 0 167 459, US 4,311,840, DE 2,253, 555, Tetrahedron (2001), 57(1), 195 – 200 or in Bioorganic and Medicinal Chemistry Letters (2004), 14(2), 313-316.

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

The compounds may be used for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy,

migraine, hypertension, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

Some of the physiological effects (i.e. cardiovascular effects, hypotension, induction of sedation) which have been reported for compounds which may bind to adrenergic receptors (WO02/076950, WO97/12874 or EP 0717 037) 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 receptors, in particular good selectivity vs the human and rat alpha1 and alpha2 adrenergic 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 and reuptake after release are tightly regulated. An imbalance in the levels of biogenic amines is known to be responsible for the altered brain function under many pathological conditions [2-5]. A second class of endogenous amine compounds, the so-called trace amines (TAs) significantly overlap with the classical biogenic amines regarding structure, metabolism and subcellular localization. The TAs include p-tyramine, β-phenylethylamine, tryptamine and octopamine, and they are present in the mammalian nervous system at generally lower levels than classical biogenic amines [6].

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

For a long time, TA-specific receptors had only been hypothesized based on anatomically discrete high-affinity TA binding sites in the CNS of humans and other mammals [10,11]. Accordingly, the pharmacological effects of TAs were believed to be mediated through the well known machinery of classical biogenic amines, by either triggering their release, inhibiting their reuptake or by "crossreacting" with their receptor systems [9,12,13]. This view changed significantly with the recent identification of several members of a novel family of GPCRs, the trace amine associated receptors (TAARs) [7,14]. There are 9 TAAR genes in human (including 3 pseudogenes) and 16 genes in mouse (including 1 pseudogene). The TAAR genes do not contain introns (with

one exception, TAAR2 contains 1 intron) and are located next to each other on the same chromosomal segment. The phylogenetic relationship of the receptor genes, in agreement with an in-depth GPCR pharmacophore similarity comparison and pharmacological data suggest that these receptors form three distinct subfamilies [7,14]. TAAR1 is in the first subclass of four genes (TAAR1-4) highly conserved between human and rodents. TAs activate TAAR1 via Gαs. Dysregulation of TAs was shown to contribute to the aetiology of various diseases like depression, psychosis, attention deficit hyperactivity disorder, substance abuse, Parkinson's disease, migraine headache, eating disorders, metabolic disorders and therefore TAAR1 ligands have a high potential for the treatment of these diseases.

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

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

Objects of the present invention are novel compounds of formula I and the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to affinity to the trace amine associated receptors, new specific compounds falling into the scope of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

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

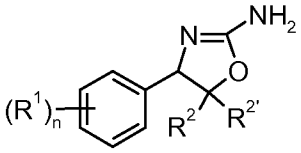
As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon

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

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

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

- Preferred compounds of formula I are those of formulas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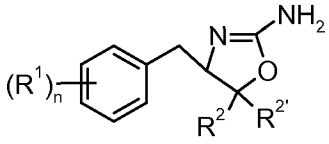
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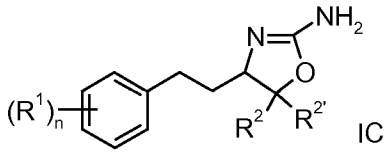
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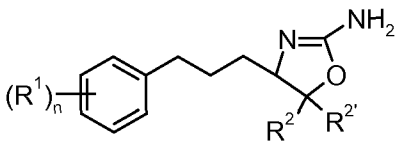

ID

wherein

R^1 is halogen;

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

n is 0, 1 or 2;

The following specific compounds are preferred:

(4R,5S)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine

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

(4S,5R)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine

(4S)-5-ethyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine

(4S,5R)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine

(4S,5S)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine

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

(4S,5R)-4-benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine

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

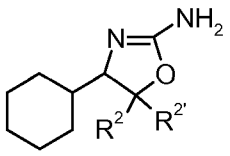
(4S,5S)-4-[2-(4-chloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine

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

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

(4S,5R)-4-[3-(4-chloro-phenyl)-propyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine.

- Preferred compounds of formula I are further those of formulas



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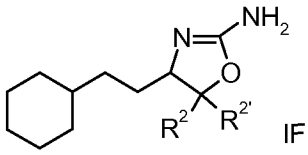


IF

wherein

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

n is 1 or 2;

The following compounds are preferred:

(4-cyclohexyl-5-methyl-4,5-dihydro-oxazol-2-ylamine

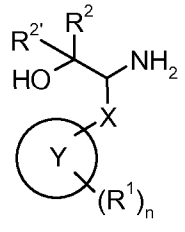
(4S,5S)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine or

(4S,5R)-4-(2-cyclohexyl-ethyl)-5-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, which process comprises

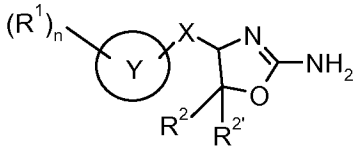
a) Reacting a compound of formula



II

with cyanogen bromide

to a compound of formula



I

wherein the definitions are as described above, or

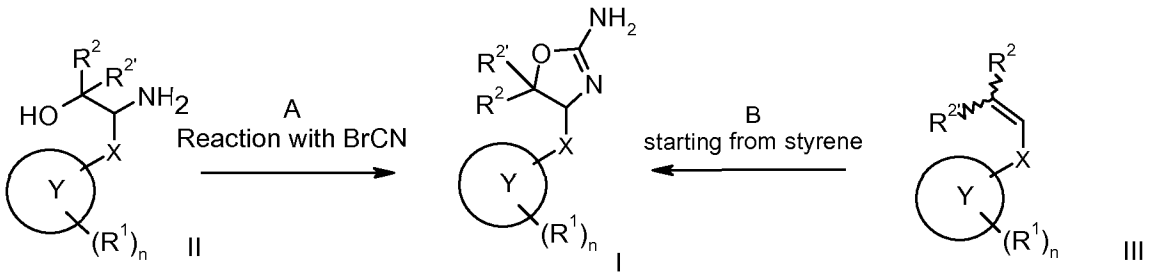
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The preparation of compounds of formula **I** of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following schemes 1-5. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

In more detail, the compounds of formula **I** can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in schemes 1 to 5, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

GENERAL PROCEDURE

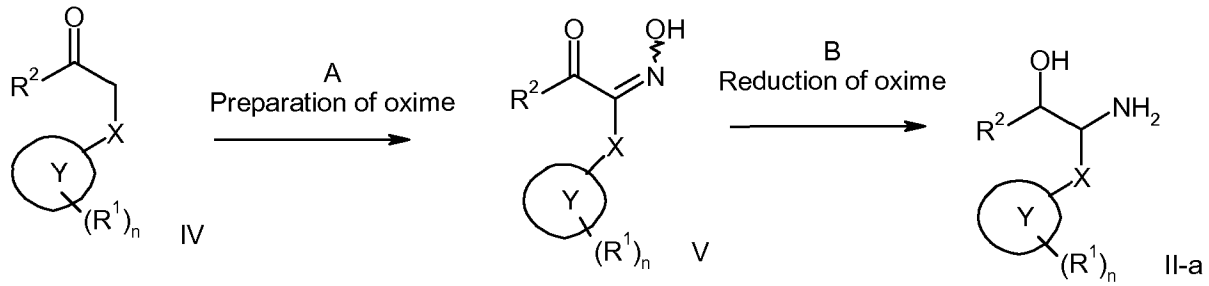
Scheme 1: Cyclization of aminoalcohol



Step A: Cyclisation of the amino alcohol II to the corresponding 2-aminooxazoline I can be accomplished by treatment with cyanogen bromide in THF as solvent and K_2CO_3 as base at r.t. overnight, or by treatment with cyanogen bromide in methanol as solvent and sodium acetate as base at 0 °C to r.t. overnight.

Step B: Amino-oxazoline ring formation can be accomplished by a two-steo procedure comprising treatment of a corresponding alkene with silver cyanate and iodine in a solvent mixture such as ethyl acetate/acetonitrile at temperatures from 0 °C to room temperature for 1 – 18 hrs, followed by reaction with aqueous ammonia at room temperature.

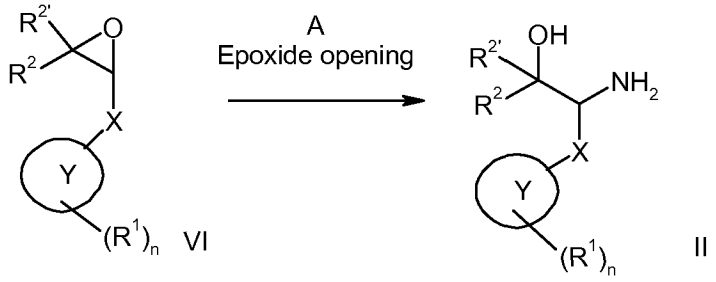
Scheme 2: Preparation of aminoalcohols via alpha-keto-oxime



Step A: Oxime formation V is effected either by treatment of the ketone IV with sodium nitrite in AcOH or tert-butyl nitrite in EtOH in the presence of NaOEt.

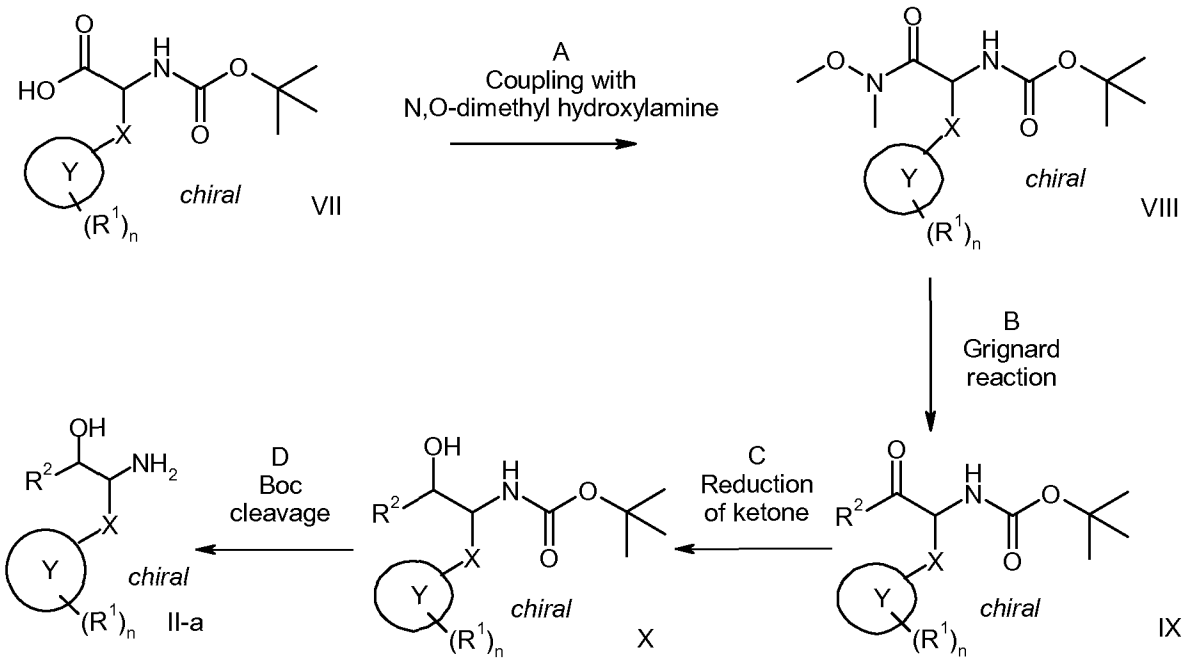
Step B: Reduction of the oxime V to the aminoalcohol II-a is effected either by hydrogenation at elevated pressure (130 bar) in the presence of Raney nickel as catalyst (leaving an aromatic ring Y intact) or by hydrogenation at elevated pressure (2.5 bar) in the presence of PtO_2 as catalyst (leading to saturation of an aromatic ring Y).

Scheme 3: Preparation of aminoalcohols via epoxide opening



Step A: Conversion of epoxide VI to aminoalcohol II is effected by treatment with 25 % aqueous NH_3-solution in the presence of lithium perchlorate at 125°C (autoclave).

Scheme 4: Preparation of aminoalcohols by Weinreb route



Step A: The Weinreb amide VIII is prepared by coupling acid VII with N,O-dimethyl hydroxylamine in a suitable solvent such as CH_2Cl_2, DMF, acetonitrile, THF using activation by an amide coupling reagent such as BOP, BOP-Cl, TBTU, EDCI, EDCI/DMAP in the presence of a base like TEA, DIPEA, N-methylmorpholine etc. at 0 °C to 50 °C. Reaction times range from 1 hr – 72 hrs.

Preferred conditions are CH_2Cl_2, EDCI and N-methyl morpholine at 0 °C for 4 hrs..

Step B: Conversion of the Weinreb amide VIII to the corresponding alkyl ketone IX is accomplished by treatment with an alkyl Grignard reagent in a solvent such as THF, diethylether at -40°C – 40°C for 1 – 8 hrs.

Preferred conditions are methyl magnesium chloride in THF at r.t. for 1.5 hr.

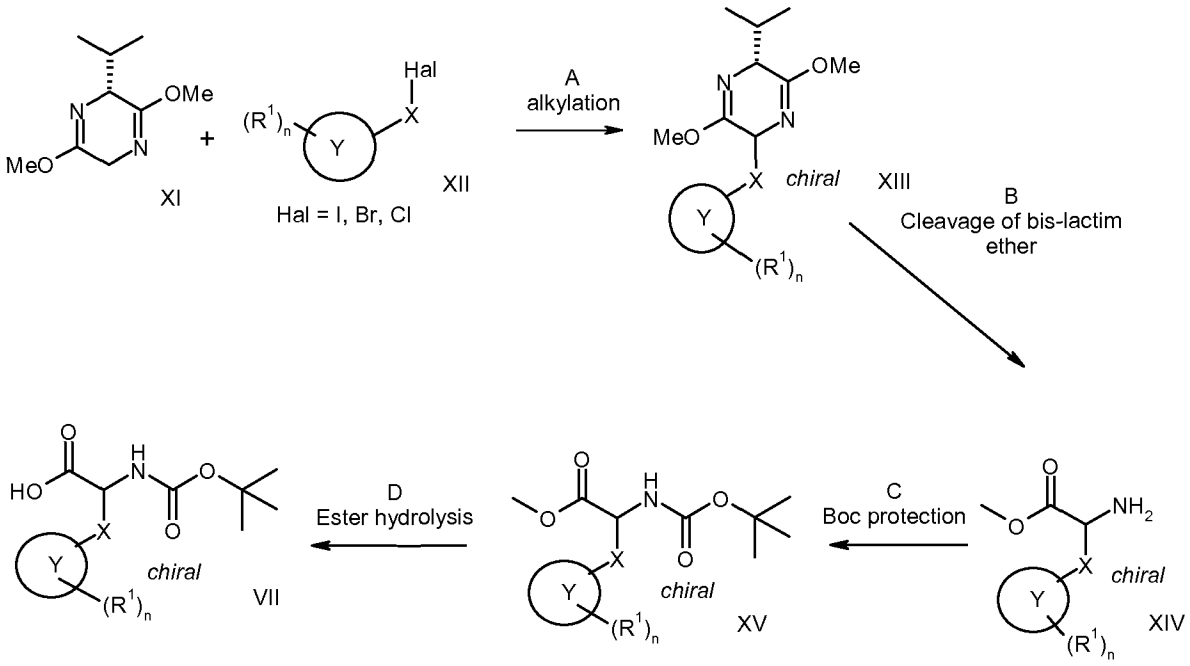
Step C: Reduction of a ketone IX is achieved with a reductant such $NaBH_4$, $LiBH_4$, DIBAH, $LiAlH_4$, BH_3 or BH_3-dimethylsulfide in a solvent such as MeOH, EtOH, THF, diethylether or toluene at -78°C – 50°C for 1 – 24 hrs.

Preferred conditions are $NaBH_4$ in EtOH at r.t. overnight. A mixture of epimers is formed.

Step D: Cleavage of the amino protecting group can be effected with a variety of methods known in the art. The tert-butoxycarbonyl group can be cleaved using a mineral acid such as HCl, H_2SO_4 or H_3PO_4 or a organic acid such as CF_3COOH, $CHCl_2COOH$, HOAc or p-toluonesulfonic acid in a solvent such as CH_2Cl_2, $CHCl_3$, THF, MeOH, EtOH or H_2O at 0 to 60°C.

Preferred conditions are CF_3COOH in dichloromethane at room temperature overnight.

Scheme 5: Preparation of chiral amino acids for Weinreb route by Schöllkopf alkylation



Step A: Deprotonation of bis-lactimether XI (also called "Schöllkopf's chiral auxiliary") with a suitable base such as n-butyl-lithium, tert-butyl-lithium or LiHMDS in an appropriate organic solvent such as tetrahydrofuran, optionally in the presence of an auxiliary such as EDTA, TMEDA, DMI or HMPA at a low temperature followed by addition of the haloalkane XII and reaction for several hours leads to product XIII (Vassiliou, S. *et al Synlett* **2003**, 2398-2400; Schöllkopf, U. *Topics Curr. Chem.* **1983**, *109*, 65).

Preferred conditions are the use of 1.6M n-butyl lithium solution as base with HMPA as additive in THF as solvent at -78 °C and allowing the mixture to reach room temperature overnight.

Step B: Bis-lactim ether product XIII is cleaved under acidic conditions using a mineral acid such as HCl, H_2SO_4 or H_3PO_4 or an organic acid such as CF_3COOH, $CHCl_2COOH$, HOAc or p-toluonesulfonic acid in a solvent such as acetonitrile, CH_2Cl_2, $CHCl_3$, THF, MeOH, EtOH or H_2O at 0 to 60°C.

Preferred conditions are a trifluoroacetic acid in a mixture of water and acetonitrile (1:3 to 6:1) r.t. overnight.

Step C: Boc protection of amino ester XIV is accomplished by treatment with Boc anhydride in a suitable solvent such as acetonitrile, CH_2Cl_2, EtOAc, dioxane, MeOH or THF in the presence of a base such as triethylamine, DIPEA, pyridine, Na_2CO_3, $NaHCO_3$.

Step D: Hydrolysis of ester XV is effected by dissolving it in a suitable solvent like MeOH, EtOH, THF, 1,4-dioxane, water or mixtures thereof and a base like LiOH, NaOH, KOH, Na_2CO_3, K_2CO_3 or Cs_2CO_3. Preferred conditions are NaOH in EtOH/H_2O.

Isolation and purification of the compounds

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

Salts of compounds of formula I

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

between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

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

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

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

Materials and Methods

Construction of TAAR expression plasmids and stably transfected cell lines

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

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

Membrane preparation and radioligand binding

Cells at confluence were rinsed with ice-cold phosphate buffered saline without Ca^{2+} and Mg^{2+} containing 10 mM EDTA and pelleted by centrifugation at 1000 rpm for 5 min at 4 °C. The pellet was then washed twice with ice-cold phosphate buffered saline and cell pellet was frozen immediately by immersion in liquid nitrogen and stored until use at -80 °C. Cell pellet was then suspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing 10 mM EDTA, and homogenized with a Polytron (PT 3000, Kinematica) at 10,000 rpm for 10 s. The homogenate was centrifuged at 48,000×*g* for 30 min at 4 °C and the pellet resuspended in 20 ml HEPES-NaOH (20 mM), pH 7.4 containing 0.1 mM EDTA (buffer A), and homogenized with a Polytron at 10,000 rpm for 10 s. The homogenate was then centrifuged at 48,000×*g* for 30 min at 4 °C and the pellet resuspended in 20 ml buffer A, and homogenized with a Polytron at 10,000 rpm for 10 s. Protein concentration was determined by the method of Pierce (Rockford, IL). The homogenate was then centrifuged at 48,000×*g* for 10 min at 4 °C, resuspended in HEPES-NaOH (20 mM), pH 7.0 including $MgCl_2$ (10 mM) and $CaCl_2$ (2 mM) (buffer B) at 50 ug protein per ml and homogenized with a Polytron at 10,000 rpm for 10 seconds.

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

The preferred compounds show a Ki value (μM) in mouse on TAAR1 in the range of <0.2 μM as shown in the table below.

Example	Ki (μM) mouse	Example	Ki(μM) mouse	Example	Ki (μM) mouse
7	0.0273	11a	0.0058	14	0.0007
8	0.0017	12	0.1594	14a	0.0018
8a	0.0031	12a	0.1751	15	0.0006
9	0.0171	13	0.0133	15a	0.008
11	0.0009	13a	0.0527	17	0.0003

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)

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

Manufacturing Procedure

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

Capsule Formulation

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

Manufacturing Procedure

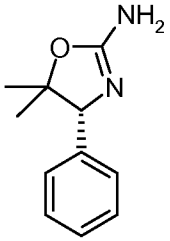
1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Experimental

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

Example 1

(R)-5,5-Dimethyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine



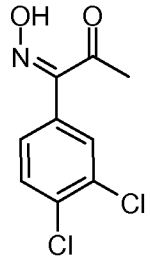
A solution of (R)-1-amino-2-methyl-1-phenyl-propan-2-ol (2.40 g) in THF (20 ml) was treated under an argon atmosphere with K_2CO_3 (2.41 g) and a solution of cyanogen bromide (1.85 g) in

THF (20 ml). The reaction mixture was stirred at r.t. overnight, then filtered. The residue was washed with THF. The filtrate was concentrated. The crude product was purified by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (0.98 g) as off-white solid. MS (ISP): 191.4 ($[M+H]^+$)

Example 2

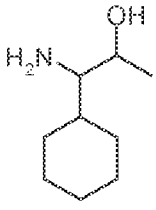
4-Cyclohexyl-5-methyl-4,5-dihydro-oxazol-2-ylamine

a) 1-(3,4-Dichloro-phenyl)-propane-1,2-dione-1-oxime



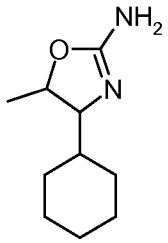
A solution of 3,4-dichlorophenylacetone (5.0 g) in AcOH (7 ml) was cooled to 15 °C and treated dropwise with a solution of sodium nitrite (2.0 g) in AcOH (7 ml). The reaction mixture was maintained at 15 °C for 30 min and then allowed to reach r.t. Water (10 ml) and dioxane (10 ml) were added, and stirring was continued overnight. The reaction mixture was evaporated. The residue was crystallized from EtOH (8 ml) and water (8 ml). The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (1.15 g) as white solid. MS (ISP): 230.0 ($[M+H]^+$)

b) 1-Amino-1-cyclohexyl-propan-2-ol



A solution of 1-(3,4-dichloro-phenyl)-propane-1,2-dione 1-oxime (0.5 g) in EtOH (30 ml) was hydrogenated at 2.5 bar at r.t. overnight in the presence of PtO_2 (50 mg). The catalyst was filtered off and washed with EtOH, the filtrate was concentrated. The crude product was purified by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (218 mg; CAS 90726-26-4) as colorless liquid. MS (ISP): 158.2 ($[M+H]^+$)

c) 4-Cyclohexyl-5-methyl-4,5-dihydro-oxazol-2-ylamine

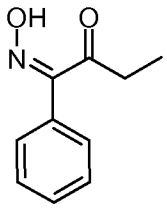


The title compound was prepared in analogy to example 1 from 1-amino-1-cyclohexyl-propan-2-ol. White solid. MS (ISP): 183.3 ($[M+H]^+$)

Example 3

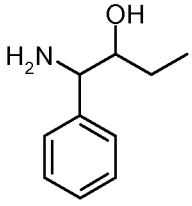
(4R,5S)-5-Ethyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine

a) 1-Phenyl-butane-1,2-dione 1-oxime



A solution of benzyl ethyl ketone (5.0 g) in EtOH (50 ml) was treated dropwise at 0 °C under an argon atmosphere with tert-butyl nitrite (4.3 ml). After 5 min, a solution of NaOEt (2.8 g) in EtOH (50 ml) was added dropwise. The reaction mixture was stirred at r.t. overnight, then concentrated. The residue was dissolved in water and extracted with EtOAc. The organic layers were dried over MgSO4, filtered and evaporated. The crude product was purified by column chromatography (silica gel; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 19:1) to give the title compound (4.04 g) as yellow solid. MS (ISP): 178.3 ($[M+H]^+$)

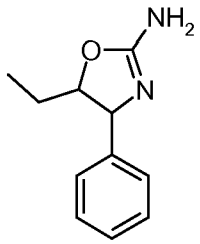
b) 1-Amino-1-phenyl-butan-2-ol



A solution of 1-phenyl-butane-1,2-dione 1-oxime (1.60 g) in EtOH (50 ml) was hydrogenated at 130 bar in the presence of Raney nickel (480 mg; Degussa 46.5 %) at 70 °C. After cooling, the reaction mixture was filtered. The catalyst was washed with EtOH. The filtrated was

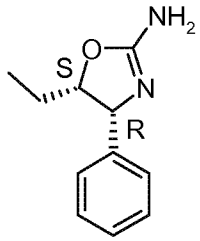
concentrated. The crude product was purified by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (1.26 g) as yellow solid. MS (ISP): 166.4 ($[M+H]^+$)

c) 5-Ethyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 1 from 1-amino-1-phenyl-butan-2-ol. White solid. MS (ISP): 191.4 ($[M+H]^+$)

d) (4R,5S)-5-Ethyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine

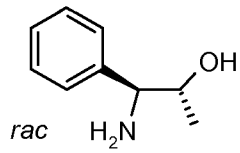


5-Ethyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine (814 mg) was separated by chiral HPLC (Chiralpak AD, EtOH/heptane = 10:90) to yield the title compound (310 mg) as white solid. MS (ISP): 191.4 ($[M+H]^+$)

Example 4

(4R,5S)-5-Methyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine

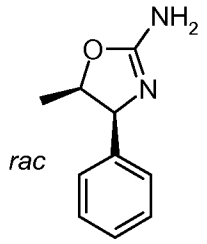
a) (1RS,2SR)-1-Amino-1-phenyl-propan-2-ol



A solution of (2RS,3RS)-2-methyl-3-phenyl-oxirane (2.10 g; CAS 23355-97-7), lithium perchlorate (3.41 g) and 25 % aqueous NH_3-solution (70 ml) in THF (30 ml) were placed in an autoclave and heated to 125 °C (9 bar) for 16 hrs. After cooling, the mixture was taken up in water and CH_2Cl_2. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic

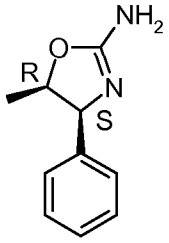
layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: cyclohexane -> CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (1.77 g) as white solid. MS (ISP): 152.2 ($[M+H]^+$)

c) (4RS,5SR)-5-Methyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 1 from (1RS,2SR)-1-amino-1-phenyl-propan-2-ol. White solid. MS (ISP): 177.3 ($[M+H]^+$)

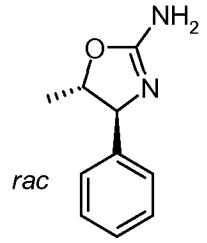
d) (4S,5R)-5-Methyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine



(4RS,5SR)-5-Methyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine (1.7 g) was separated by chiral HPLC (Chiralpak AD, EtOH/heptane = 10:90) to yield the title compound (453 mg) as white solid. MS (ISP): 177.4 ($[M+H]^+$)

Example 5

(4RS,5RS)-5-Methyl-4-phenyl-4,5-dihydro-oxazol-2-ylamine



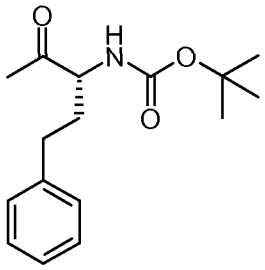
To a stirred solution of trans-β-methyl styrene (1.00 g) at r.t. in acetonitrile (15 ml) under an argon atmosphere were added silver cyanate (1.39 g) and EtOAc (20 ml). The mixture was cooled in an ice bath and a solution of I_2 (2.58 g) in EtOAc (30 ml) (difficult dissolution!) was added dropwise for 15 min. The ice bath was removed and stirring at r.t. was continued

overnight. The mixture was filtered and the cake was washed with EtOAc. The filtrate was concentrated to leave a dark syrup which was taken up in 25 % aqueous NH_3-solution (sticky paste, impossible to stir). The mixture was heated to 85 °C and then stirred for 5 hrs. The mixture was cooled to r.t. and extracted with CH_2Cl_2. The combined organics were washed with brine (30 ml), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: cyclohexane -> CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1). The product fractions were combined and concentrated. The residue was triturated with a mixture of cyclohexane (5 ml) and CH_2Cl_2 (0.5 ml). The product was collected by filtration and washed with cyclohexane. The title compound (188 mg) was obtained as off-white solid. MS (ISP): 177.4 ($[M+H]^+$)

Example 6

(4R,5R)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine

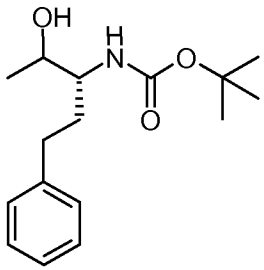
a) ((R)-2-Oxo-1-phenethyl-propyl)-carbamic acid tert-butyl ester



To a stirred, cooled (0 °C) solution of [(R)-1-(methoxy-methyl-carbamoyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (4.06 g; CAS 171357-71-4) in THF (30 ml) under an argon atmosphere was added dropwise 3M MeMgCl in THF (16.8 ml) over 10 min. The ice bath was removed and the clear brown solution was stirred at r.t. for 1 hr. The mixture was cooled in an ice bath and carefully treated with 30 ml of 2 N HCl (strong bubbling!). Then it was extracted with EtOAc. The combined organics were washed with brine (30 ml), dried over $MgSO_4$, filtered and concentrated to leave the title compound as a light brown viscous oil. MS (ISP): 300.4 ($[M+Na]^+$)

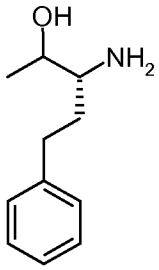
The crude product was used in the next reaction step without further purification.

b) ((R)-2-Hydroxy-1-phenethyl-propyl)-carbamic acid tert-butyl ester



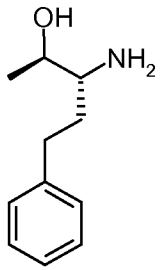
To a stirred solution of ((R)-2-oxo-1-phenethyl-propyl)-carbamic acid tert-butyl ester at 0 °C in ethanol (50 ml) under an argon atmosphere was added carefully $NaBH_4$ (827 mg). The ice bath was removed and stirring at r.t. was continued for 4 h. The clear colorless solution was concentrated to leave a white sticky solid which was taken up in CH_2Cl_2 (50ml) and 1 N NaOH (50 ml). The aqueous phase was back extracted with CH_2Cl_2 (50 ml). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to leave the title compound (2.89 g) as 3:1 mixture of epimers. White solid. MS (ISP): 302.3 ($[M+Na]^+$)
The crude product was used in the next reaction step without further purification.

c) (R)-3-Amino-5-phenyl-pentan-2-ol



To a stirred solution of ((R)-2-hydroxy-1-phenethyl-propyl)-carbamic acid tert-butyl ester (2.88 g) at r.t. in dioxane (20 ml) under an argon atmosphere was added 4 M HCl solution in dioxane (25.8 ml). Stirring at r.t. was then continued for 4 hrs. The mixture (clear colorless solution) was concentrated to leave a light yellow gum. The residue was taken up in 1 N HCl (50 ml) and washed with EtOAc (50 ml). The aqueous phase was brought to pH 12 by the addition of 4 N NaOH. The product was extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to leave the title compound (1.69 g) as a 3:1 mixture of epimers. Light yellow viscous oil. MS (ISP): 180.2 ($[M+H]^+$)
The crude product was used in the next reaction step without further purification.

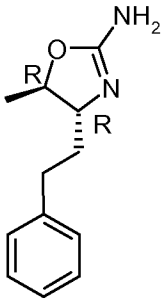
d) (2R,3R)-Amino-5-phenyl-pentan-2-ol



(R)-3-Amino-5-phenyl-pentan-2-ol (1.69 g) was separated by chiral HPLC (Chiralpak AD, EtOH/heptane = 15:85) to yield the first eluting (2R,3R)-amino-5-phenyl-pentan-2-ol (318 mg) as viscous, light yellow oil. MS (ISP): 180.2 ($[M+H]^+$)

The second eluting epimer (2S,3R)-amino-5-phenyl-pentan-2-ol (857 mg) was isolated as viscous, light yellow oil. MS (ISP): 180.2 ($[M+H]^+$)

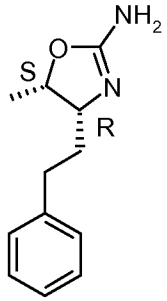
e) (4R,5R)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 1 from (2R,3R)-amino-5-phenyl-pentan-2-ol. Off-white solid. MS (ISP): 205.3 ($[M+H]^+$)

Example 7

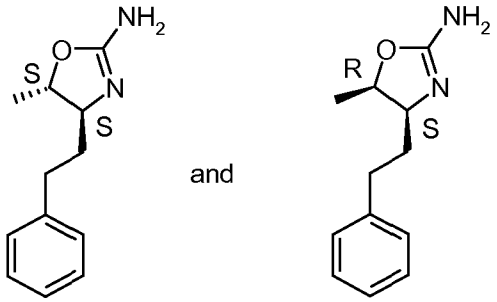
(4R,5S)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine



The title compound was prepared in analogy to example 1 from (2S,3R)-amino-5-phenyl-pentan-2-ol (example 6.d). White solid. MS (ISP): 205.3 ($[M+H]^+$)

Example 8

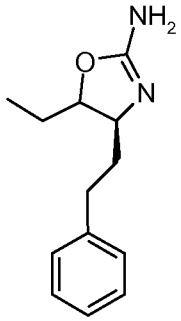
(4S,5S)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine and (4S,5R)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine



The title compounds were prepared in analogy to example 6/7 from [(S)-1-(methoxy-methyl-carbamoyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (CAS 183444-03-3). (4S,5S)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine : off-white solid. MS (ISP): 205.3 ($[M+H]^+$) (4S,5R)-5-Methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine: white solid.MS (ISP): 205.3 ($[M+H]^+$)

Example 9

(S)-5-Ethyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine

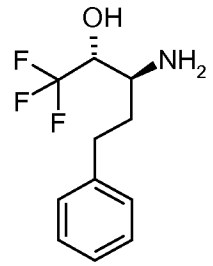


The title compound was prepared in analogy to example 6 starting from [(S)-1-(methoxy-methyl-carbamoyl)-3-phenyl-propyl]-carbamic acid tert-butyl ester (CAS 183444-03-3) and ethylmagnesium chloride. Colorless oil. MS (ISP): 219.4 ($[M+H]^+$)

Example 10

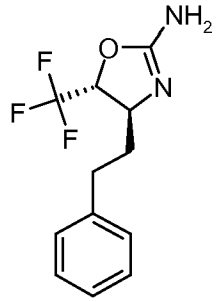
(4S,5R)-4-Phenethyl-5-trifluoromethyl-4,5-dihydro-oxazol-2-ylamine

a) (2R,3S)-3-Amino-1,1,1-trifluoro-5-phenyl-pentan-2-ol



To a stirred solution of (2S,3S)-3-dibenzylamino-1,1,1-trifluoro-5-phenyl-pentan-2-ol (134 mg; *Eur. J. Org. Chem.* **2004**, 1558 - 1566), at r.t. in MeOH (5 ml) under an argon atmosphere was added $Pd(OH)_2$ (20% Pd on C; 14 mg). The black suspension was stirred at r.t. under a hydrogen atmosphere overnight. The catalyst was filtered off and the cake was washed with methanol.The filtrate was concentrated to leave a light yellow solid. The crude product was isolated by column chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: cyclohexane -> CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give the title compound (47 mg; CAS 402733-46-4) as viscous brown oil. MS (ISP): 234.2 ($[M+H]^+$)

b) (4S,5R)-4-Phenethyl-5-trifluoromethyl-4,5-dihydro-oxazol-2-ylamine

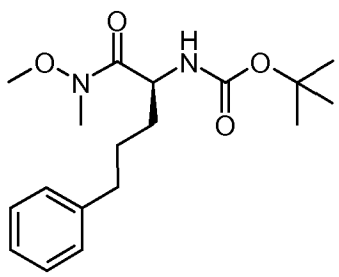


The title compound was prepared in analogy to example 1 from (2S,3S)-3-amino-1,1,1-trifluoro-5-phenyl-pentan-2-ol. Colorless viscous oil. MS (ISP): 259.2 ($[M+H]^+$)

Example 11

(4S,5R)-5-Methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine and (4S,5S)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine

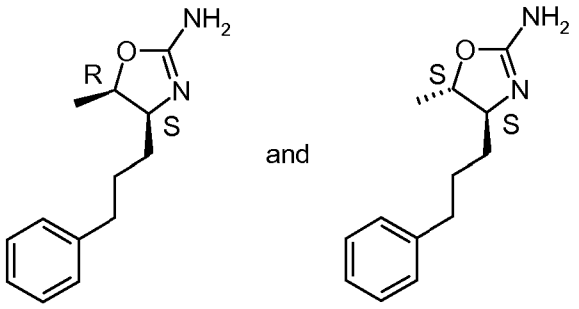
a) [(S)-1-(Methoxy-methyl-carbamoyl)-4-phenyl-butyl]-carbamic acid tert-butyl ester



To a stirred, cooled (-15 to -20 °C) solution of (S)-2-tert-butoxycarbonylamino-5-phenyl-pentanoic acid (8.17 g; CAS 98628-27-4) in dichloromethane under an argon atmosphere were added N-methyl morpholine (3.4 ml) and N,O-dimethylhydroxylamine hydrochloride (2.99 g). N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI; 5.87 g) was then added portionwise over a period of 5 min and stirring at -15 °C to -20 °C was continued for 1 h. CH_2Cl_2 (65 ml) was added to the mixture. The layers were separated and the aqueous phase was back extracted with CH_2Cl_2 (65 ml). The combined organics were washed with brine (65 ml), dried over $MgSO_4$, filtered and concentrated to leave the title compound (8.20 g) as an orange viscous oil.

The crude product was used in the next reaction step without further purification.

b) (4S,5R)-5-Methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine and (4S,5S)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine



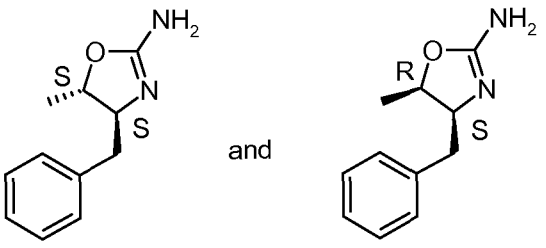
The title compounds were prepared in analogy to example 6/7 from [(S)-1-(methoxy-methyl-carbamoyl)-4-phenyl-butyl]-carbamic acid tert-butyl ester.

(4S,5R)-5-Methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine: light yellow solid. MS (ISP): 219.1 ($[M+H]^+$)

(4S,5S)-5-Methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine: colorless viscous oil. MS (ISP): 219.1 ($[M+H]^+$)

Example 12

(4S,5S)-4-Benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine and (4S,5R)-4-benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine



The title compounds were prepared in analogy to example 6/7 from [(S)-1-(methoxy-methyl-carbamoyl)-2-phenyl-ethyl]-carbamic acid tert-butyl ester (CAS 87694-53-9).

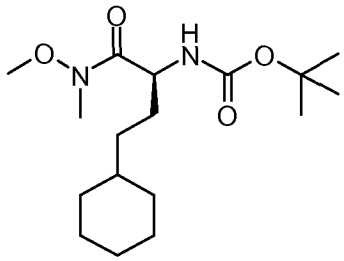
(4S,5S)-4-Benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine: colorless viscous solid. MS (ISP): 191.4 ($[M+H]^+$)

(4S,5R)-4-Benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine: off-white solid. MS (ISP): 191.4 ($[M+H]^+$)

Example 13

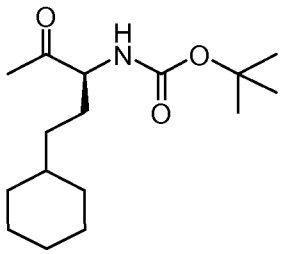
(4S,5S)-4-(2-Cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine

a) [(S)-3-Cyclohexyl-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid tert-butyl ester



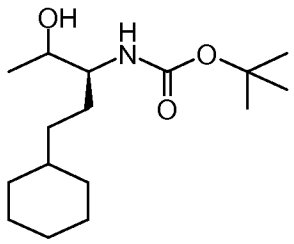
To a stirred, cooled (0 °C) solution of (S)-2-tert-butoxycarbonylamino-4-cyclohexyl-butyric acid (5.73 g; CAS 143415-51-4) in dichloromethane (75 ml) under an argon atmosphere were added N-methyl morpholine (2.43 ml) and N,O-dimethylhydroxylamine hydrochloride (2.15 g). To the reaction mixture was then added portionwise over a period of 5 min N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (4.23 g) and stirring at 0 °C was continued for 3 h 30. Aqueous 1 N HCl (75 ml) was added, followed by CH_2Cl_2 (75 ml). The layers were separated, and the aqueous phase was back extracted with CH_2Cl_2 (75 ml). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to leave [(S)-3-cyclohexyl-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid tert-butyl ester (6.30 g) as a light yellow viscous oil. MS (ISP): 351.4 ($[M+Na]^+$)

b) [(S)-1-(2-Cyclohexyl-ethyl)-2-oxo-propyl]-carbamic acid tert-butyl ester



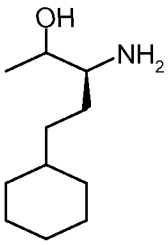
To a stirred, cooled (0 °C) solution of [(S)-3-cyclohexyl-1-(methoxy-methyl-carbamoyl)-propyl]-carbamic acid tert-butyl ester (6.30 g) in THF under an argon atmosphere was added dropwise over 10 min a solution of methyl magnesium chloride (3 M in THF; 25.6 ml). The ice bath was removed and the clear brown solution was stirred at r.t. for 1 h 30. The mixture was cooled in an ice bath and carefully treated with 60 ml of 2 N HCl (60 ml; strong bubbling!), then extracted with EtOAc. The aqueous phase was back extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated to leave [(S)-1-(2-cyclohexyl-ethyl)-2-oxo-propyl]-carbamic acid tert-butyl ester (5.23 g) as a light yellow viscous oil. MS (ISP): 284.2 ($[M+H]^+$)

c) [([(S)-1-(2-Cyclohexyl-ethyl)-2-hydroxy-propyl]-carbamic acid tert-butyl ester



To a stirred solution of [(S)-1-(2-cyclohexyl-ethyl)-2-oxo-propyl]-carbamic acid tert-butyl ester (5.22 g) at 0 °C in ethanol (75 ml) under an argon atmosphere was added carefully $NaBH_4$ (1.39 g). The ice bath was removed and stirring at r.t. was continued overnight. The mixture was concentrated to leave an off-white paste which was taken up in CH_2Cl_2. The insoluble material was filtered off and washed with CH_2Cl_2. The filtrate was concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane -> cyclohexane/EtOAc 3:7) to give [(S)-1-(2-cyclohexyl-ethyl)-2-hydroxy-propyl]-carbamic acid tert-butyl ester (4.32 g; 3:1 mixture of epimers) as white solid. MS (ISP): 308.2 ($[M+Na]^+$)

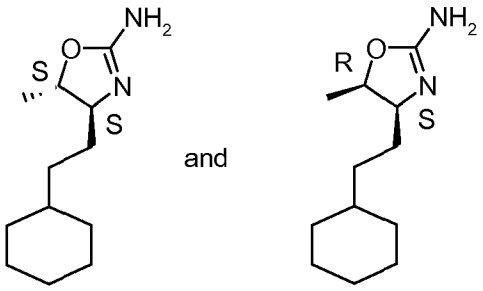
d) (S)-3-Amino-5-cyclohexyl-pentan-2-ol



To a stirred solution of [(S)-1-(2-cyclohexyl-ethyl)-2-hydroxy-propyl]-carbamic acid tert-butyl ester (4.32 g) at r.t. in dioxane (37 ml) under an argon atmosphere was added 4 M HCl solution in dioxane (37.8 ml). The mixture was stirred at r.t. overnight and concentrated to leave an off-

white sticky solid which was dissolved in 50 ml H_2O. The pH of the solution was brought to ~ 1 by the addition of 3 N HCl. It was washed with EtOAC (50 ml). The aqueous phase was brought to pH >12 by the addition of 4 N NaOH. The resulting white slurry was extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to leave (S)-3-amino-5-cyclohexyl-pentan-2-ol (2.76 g; 3:1 mixture of epimers) as a light yellow viscous oil. MS (ISP): 186.3 ($[M+H]^+$)

e) (4S,5S)-4-(2-Cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine and (4S,5R)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine

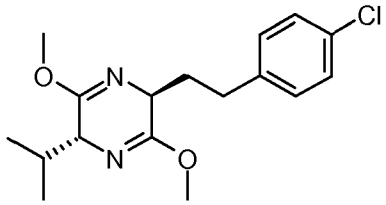


In analogy to example 1 (S)-3-amino-5-cyclohexyl-pentan-2-ol was converted to (S)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine. Epimers were separated by chromatography (silica gel: Isolute® Flash-NH_2 from Separtis; gradient: CH_2Cl_2 -> CH_2Cl_2/MeOH 9:1) to give (4S,5S)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine (42 mg) as colorless viscous oil, MS (ISP): 211.1 ($[M+H]^+$), and (4S,5R)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine (215 mg) as white solid, MS (ISP): 211.1 ($[M+H]^+$).

Example 14

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

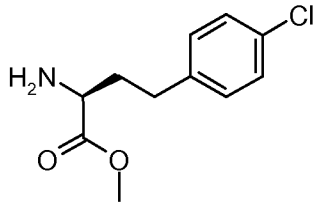
a) (2S,5R)-2-[2-(4-Chloro-phenyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine



To a stirred, cooled (-78 °C) solution of (2R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (3.22 g) in THF (25 ml) under an argon atmosphere was added dropwise n-buthyl lithium 1.6 M in hexane (12.0 ml). The temperature was kept below -70 °C during the addition. When addition

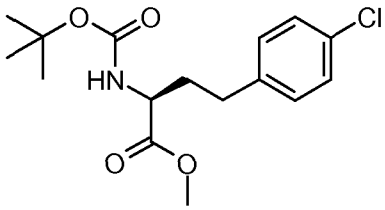
was complete, the mixture was stirred at -78 °C for 1 h, then a solution of 4-chlorophenethyl bromide (5.14 g) in THF (45 ml) was added dropwise. The reaction mixture was stirred overnight, slowly warming up to r.t.. Then, the mixture was diluted with Et_2O (70 ml) and sat. aq. NH_4Cl (70 ml). The aqueous phase was extracted with Et_2O. 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 -> cyclohexane/EtOAc 4:1) to give the title compound (3.09 g) as light yellow viscous oil. MS (ISP): 323.2 ($[M+H]^+$)

b) (S)-2-Amino-4-(4-chloro-phenyl)-butyric acid methyl ester



To a stirred solution of (2S,5R)-2-[2-(4-chloro-phenyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine (3.09 g) at r.t. in acetonitrile (36 ml) under an argon atmosphere were added H_2O (12 ml) and TFA (4.4 ml). The mixture was then stirred overnight at r.t..
The pH was brought to ~ 11 by the addition of 10 % Na_2CO_3. The mixture was 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 -> EtOAc -> EtOAc/MeOH 85:15) to give the title compound (1.86 g) as viscous light yellow oil. MS (ISP): 228.2 ($[M+H]^+$)

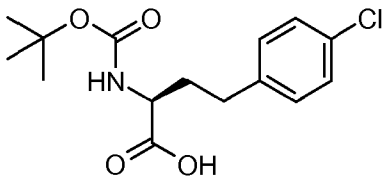
c) (S)-2-tert-Butoxycarbonylamino-4-(4-chloro-phenyl)-butyric acid methyl ester



To a stirred solution of (S)-2-amino-4-(4-chloro-phenyl)-butyric acid methyl ester (1.85 g) at r.t. in acetonitrile (20 ml) under an argon atmosphere were added triethylamine (1.2 ml), $NaHCO_3$ (1.03 g) and Boc_2O (1.95 g). The suspension was stirred at r.t. for overnight. The solids were removed by filtration and the filtrate was concentrated. The residue was taken up in EtOAc, washed with 1 N HCl, H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (silica gel; gradient: cyclohexane ->

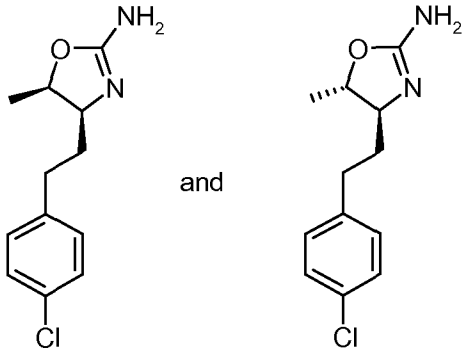
cyclohexane/EtOAc 3:1) to give the title compound (2.35 g) as light yellow viscous oil. MS (ISP): 328.3 ([M+H]$^+$)

d) (S)-2-tert-Butoxycarbonylamino-4-(4-chloro-phenyl)-butyric acid



To a stirred solution of (S)-2-tert-butoxycarbonylamino-4-(4-chloro-phenyl)-butyric acid methyl ester at r.t. (2.34 g) in methanol (10 ml) under an argon atmosphere was added 1 N NaOH (10.3 ml). The suspension was stirred at r.t. for 3 h, soon turning again to a clear light yellow solution. The methanol was distilled off. The aqueous residue was brought to pH ~ 1 by the addition of 5 N HCl. The product was extracted with EtOAc. The combined organics were washed with brine, dried over MgSO4, filtered and concentrated. The resulting gum was triturated in a mixture of n-heptane (20 ml) and EtOAc (2 ml). The suspension was stirred at r.t. for 30 min. The solid was collected by filtration, washed with n-heptane and dried to give the title compound (1.29 g) as white solid. MS (ISN): 312.1 ([M-H]$^-$)

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



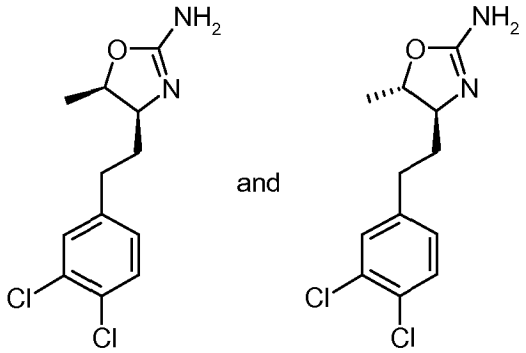
In analogy to example 11 (S)-2-tert-Butoxycarbonylamino-4-(4-chloro-phenyl)-butyric acid was converted to the title compounds.

(4S,5R)-4-[2-(4-Chloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine: off-white solid. MS (ISN): 239.0 ([M+H]$^+$)

(4S,5S)-4-[2-(4-Chloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine: viscous colorless oil. MS (ISN): 239.0 ([M+H]$^+$)

Example 15

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



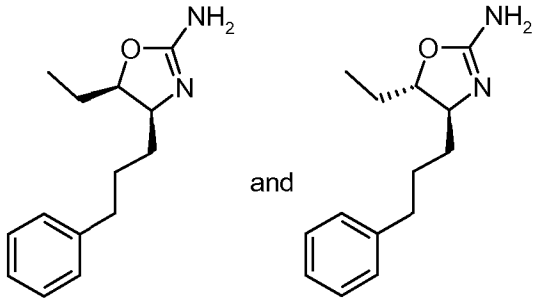
The title compounds were prepared in analogy to example 14, using 4-(2-bromo-ethyl)-1,2-dichloro-benzene as alkylating agent in the first step.

(4S,5R)-4-[2-(3,4-Dichloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine: off-white solid. MS (ISP): 273.2 ($[M+H]^+$)

(4S,5S)-4-[2-(3,4-Dichloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine: light-brown viscous solid. MS (ISP): 273.2 ($[M+H]^+$)

Example 16

(4S,5R)-5-Ethyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine and (4S,5S)-5-ethyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine



The title compounds were prepared in analogy to example 6/7, starting from [(S)-1-(methoxy-methyl-carbamoyl)-4-phenyl-butyl]-carbamic acid tert-butyl ester (example 11.a) and ethylmagnesium chloride.

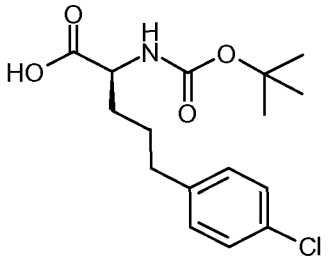
(4S,5R)-5-Ethyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine: white solid. MS (ISP): 233.2 ($[M+H]^+$)

(4S,5S)-5-Ethyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine: orange viscous solid. MS (ISP): 233.2 ($[M+H]^+$)

Example 17

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

a) (S)-2-tert-butoxycarbonylamino-5-(4-chloro-phenyl)-pentanoic acid

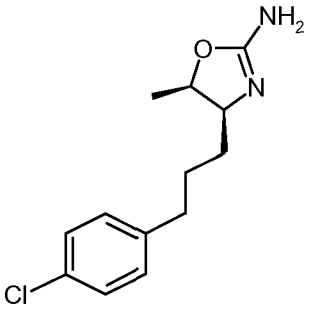


The title compound was prepared in analogy to example 14a-d starting from 1-chloro-4-(3-iodo-propyl)-benzene (CAS 90562-26-8) in place of 4-chlorophenethyl bromide.

(S)-2-tert-butoxycarbonylamino-5-(4-chloro-phenyl)-pentanoic acid: light yellow viscous oil.

MS (ISP): 326.1 ($[M-H]^-$).

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



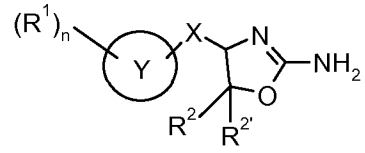
The title compound was prepared in analogy to example 11 starting from (S)-2-tert-butoxycarbonylamino-5-(4-chloro-phenyl)-pentanoic acid in place of (S)-2-tert-butoxycarbonylamino-5-phenyl-pentanoic acid.

(4S,5R)-4-[3-(4-Chloro-phenyl)-propyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine: off-white solid.

MS (ISP): 253.1 ($[M+H]^+$).

Claims

1. A compound of formula



I

wherein

R^1 is halogen;

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

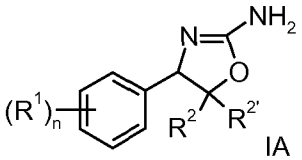
X is a bond, $-CH_2-$, $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$;

Y is phenyl or cyclohexyl; and

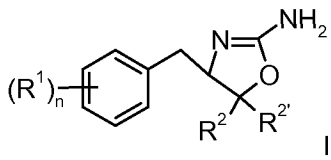
n is 0, 1 or 2;

or a pharmaceutically suitable acid addition salt thereof.

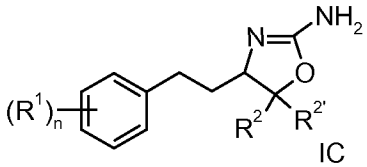
2. A compound of formula IA, IB, IC or ID, encompassed by formula I according to claim 1,



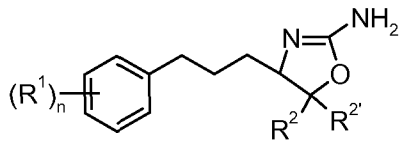
IA



IB



IC



ID

wherein

R^1 is halogen;

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

n is 0, 1 or 2;

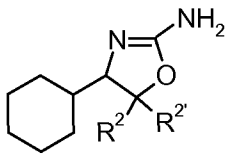
or a pharmaceutically suitable acid addition salt thereof.

3. A compound of formula IB according to claim 2, wherein the compound is
(4S,5S)-4-benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine or
(4S,5R)-4-benzyl-5-methyl-4,5-dihydro-oxazol-2-ylamine.

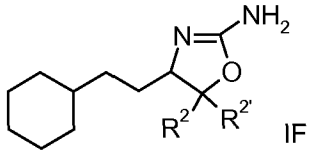
4. A compound of formula IC according to claim 2, wherein the compound is
(4R,5S)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine
(4S,5S)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine
(4S,5R)-5-methyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine
(S)-5-ethyl-4-phenethyl-4,5-dihydro-oxazol-2-ylamine
(4S,5R)-4-[2-(4-chloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine
(4S,5S)-4-[2-(4-chloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine
(4S,5R)-4-[2-(3,4-dichloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine or
(4S,5S)-4-[2-(3,4-dichloro-phenyl)-ethyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine.

5. A compound of formula ID according to claim 2, wherein the compound is
(4S,5R)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine
(4S,5S)-5-methyl-4-(3-phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine
(4S,5R)-4-[3-(4-chloro-phenyl)-propyl]-5-methyl-4,5-dihydro-oxazol-2-ylamine

6. A compound of formulas IE and IF encompassed by formula I according to claim 1



IE



IF

wherein

R^2 is lower alkyl or lower alkyl substituted by halogen;

$R^{2'}$ is hydrogen, lower alkyl or lower alkyl substituted by halogen;

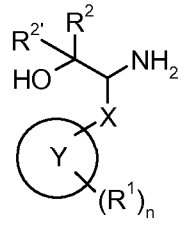
or a pharmaceutically suitable acid addition salt thereof.

7. A compound of formula IE according to claim 6, wherein the compound is

(4-cyclohexyl-5-methyl-4,5-dihydro-oxazol-2-ylamine.

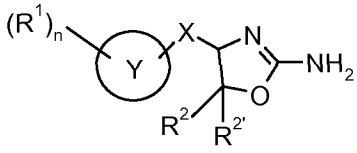
8. A compound of formula IF according to claim 6, wherein the compound is (4S,5S)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine or (4S,5R)-4-(2-cyclohexyl-ethyl)-5-methyl-4,5-dihydro-oxazol-2-ylamine.

9. A process for preparation of a compound of formula I, which process comprises a) reacting a compound of formula



II

with cyanogen bromide to a compound of formula



I

wherein the definitions are as described in claim 1, or

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

10. A medicament containing one of the compounds of formula I according to claim 1 and pharmaceutically acceptable excipients.

11. A medicament as claimed in claim 10 for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder, stress-related disorders, psychotic disorders, schizophrenia, neurological diseases, Parkinson's disease, neurodegenerative disorders, Alzheimer's disease, epilepsy, migraine, substance abuse and metabolic disorders, eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

12. A medicament according to claim 11, containing one or more compounds as claimed in claim 1 for the treatment of depression, psychosis, Parkinson's disease, diabetes, anxiety and attention deficit hyperactivity disorder (ADHD).

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/057669

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/28 A61K31/421 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/092785 A1 (HOFFMANN LA ROCHE [CH]; GALLEY GUIDO [DE]; GROEBKE ZBINDEN KATRIN [CH]) 7 August 2008 (2008-08-07) claim 1	1-13
X	TANAKA CHIAKI ET AL: "Syntheses of oxazolecarboxylic acid derivatives. XIII. Hydrogenolysis of aminooxazoles. (6). Syntheses and hydrogenolysis of 2-amino-2-oxazolines" YAKUGAKU ZASSHI - JOURNAL OF THE PHARMACEUTICAL SOCIETY OF JAPAN, JAPAN SCIENCE AND TECHNOLOGY INFORMATION AGGREGATOR, ELECTRONIC, JP, vol. 97, no. 2, 1 January 1977 (1977-01-01), pages 157-164, XP009136920 ISSN: 0031-6903 Table 1	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2010	10/08/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/057669

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CR 10926 A	12-08-2009
		EC SP099551 A	28-08-2009
		EP 2114906 A1	11-11-2009
		JP 2010517953 T	27-05-2010
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