Novel hydroxy-6-heteroarylphenanthridines and their use as PDE4 inhibitors

Field of application of the invention

The invention relates to novel hydroxy-6-heteroarylphenanthridine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

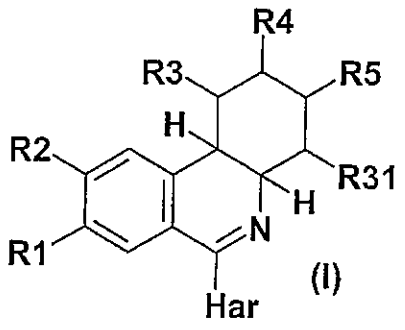
Known technical background

The International Patent applications WO99/57118 and WO02/05616 describe 6-phenylphenanthridines as PDE4 inhibitors.
In the International Patent application WO99/05112 substituted 6-alkylphenanthridines are described as bronchial therapeutics.
In the European Patent application EP 0490823 dihydroisoquinoline derivatives are described which are said to be useful in the treatment of asthma.
The International Patent application WO00/42019 discloses 6-arylphenanthridines as PDE4 inhibitors.
The International Patent application WO02/06270 discloses 6-heteroarylphenanthridines as PDE4 inhibitors.
The International Patent application WO97/35854 discloses phenanthridines substituted in the 6-position as PDE4 inhibitors.
The International Patent applications WO2004/019944 and WO2004/019945 disclose hydroxy-substituted 6-phenylphenanthridines as PDE4 inhibitors.

Description of the invention

It has now been found that the novel 2-hydroxy-6-heteroarylphenanthridines described in greater detail below differ from the previously known compounds by unanticipated and sophisticated structural alterations and have surprising and particularly advantageous properties.

The invention thus relates to a compound of formula I,



(I)

in which

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

Har is substituted by R6 and R7 and is a pyridinyl radical, in which

R6 is 1-4C-alkoxy,

R7 is 1-4C-alkoxy,

or a salt, a N-oxide or a salt of a N-oxide of this compound.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

As completely or predominantly fluorine-substituted 1-2C-alkoxy, for example, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radicals are replaced by fluorine atoms.

As more detailed exemplary suitable Har radicals may be mentioned, pyridinyl, which is substituted by R6 and R7 in which

R6 is 1-4C-alkoxy, particularly 1-2C-alkoxy, and

R7 is 1-4C-alkoxy, particularly 1-2C-alkoxy.

The term pyridyl or pyridinyl includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, at any possible position.

The heterocyclic groups, alone or as part of other groups, mentioned herein may be substituted by their given substituents, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom.

Unless otherwise noted, rings containing quaternizable imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these imino-type ring nitrogen atoms by the mentioned substituents.

Unless otherwise noted, any heteroatom of a heterocyclic ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When any variable occurs more than one time in any constituent, each definition is independent.

As it is known for the person skilled in the art, compounds comprising nitrogen atoms can be form N-oxides. Particularly, imine nitrogen, especially heterocyclic or heteroaromatic imine nitrogen, or pyridine-type nitrogen (=N-) atoms, can be N-oxidized to form the N-oxides comprising the group $=N^{+}(O^{-})$-. Thus, the compounds according to the present invention comprising the imine nitrogen atom in position 5 of the phenylphenanthridine backbone and, optionally (depending on the meaning of the substituents), one or more further nitrogen atoms suitable to exist in the N-oxide state ($=N^{+}(O^{-})$-) may be capable to form (depending on the number of nitrogen atoms suitable to form stabile N-oxides) mono-N-oxides, bis-N-oxides or multi-N-oxides, or mixtures thereof.

The term N-oxide(s) as used in this invention therefore encompasses all possible, and in particular all stabile, N-oxide forms, such as mono-N-oxides, bis-N-oxides or multi-N-oxides, or mixtures thereof in any mixing ratio.

Possible salts for compounds of the formula I -depending on substitution- are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

In the context of the foregoing, as further acids, which may be used in the preparation of possible salts of compounds of formula I, can be mentioned adipic acid, L-ascorbic acid, L-aspartic acid, benzenesulfonic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, caprylic acid (octanoic acid), dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-glucuronic acid, glutamic acid, 2-oxo-glutaric acid, hippuric acid,

lactic acid, malonic acid, mandelic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, palmitic acid, pamoic acid (embonic acid), and pyroglutamic acid.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

A compound of formula I more particular worthy to be mentioned is that in which

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

Har is 2,6-dimethoxypyridin-3-yl,

or a salt, a N-oxide or a salt of a N-oxide of this compound.

A particularly preferred compound of formula I is (2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol or a salt of this compound.

A special interest in the compounds according to this invention relates to those compounds which are included -within the meaning of this invention- by one or, when possible, by more of the following embodiments:

A special embodiment of the compounds of the present invention include those compounds of formula I in which one of R1 and R2 is methoxy, and the other is methoxy, ethoxy, difluoromethoxy or 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is ethoxy or, particularly, methoxy, and R2 is methoxy, or, particularly, ethoxy, difluoromethoxy or 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R2 is methoxy, ethoxy, difluoromethoxy or 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R2 is ethoxy, difluoromethoxy or 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which one of R1 and R2 is 2,2-difluoroethoxy, and the other is different from 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is ethoxy or, particularly, methoxy, and R2 is 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R2 is 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R2 is ethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R2 is difluoromethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I, in which Har is pyridinyl bisubstituted by 1-4C-alkoxy, such as, for example, 2,6-dimethoxypyridinyl (e.g. 2,6-dimethoxypyridin-3-yl).

Another special embodiment of the compounds of the present invention include those compounds of formula I, in which Har is pyridinyl substituted by R6 and R7, in which

R6 is 1-4C-alkoxy, particularly methoxy or ethoxy,

R7 is 1-4C-alkoxy, particularly methoxy or ethoxy,

such as, for example, dimethoxy-pyridinyl or ethoxy-(methoxy-)pyridinyl, e.g. dimethoxy-pyridin-3-yl or dimethoxy-pyridin-4-yl or ethoxy-(methoxy-)pyridine-3-yl, like 2,6-dimethoxy-pyridin-3-yl, 2,6-dimethoxy-pyridin-4-yl, 4,6-dimethoxy-pyridin-3-yl, 5,6-dimethoxy-pyridin-3-yl, 4,6-diethoxy-pyridin-3-yl, or 5-ethoxy-6-methoxy-pyridin-3-yl.

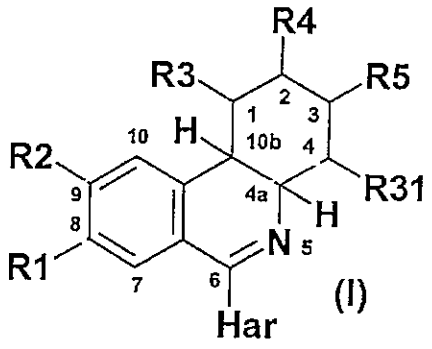
A further special embodiment of the compounds of the present invention include those compounds of formula I, in which Har is pyridinyl substituted by two methoxy radicals, such as, for example, 2,6-dimethoxy-pyridin-3-yl.

Exemplary compounds according to the present invention may include,
compounds selected from the group consisting of those compounds mentioned in the following examples as final compounds, particularly those embodimental examples which are from formula I, in which R3, R31, R41 and R5 are all hydrogen, and/or those compounds listed in the Table A in the appended "Biological Investigations", the enantiomers, as well as the salts, the N-oxides and the salts of the N-oxides of these compounds and enantiomers.

Preferably, any or all of those compounds of formula I, in which R3, R31, R41 and R5 are all hydrogen, which are described by way of example as final compounds in the following examples and, particularly, the enantiomers thereof, particularly those having the formula Ia*****, as well as the salts of these compounds and enantiomers, are to be mentioned as a particular interesting aspect of the present invention.

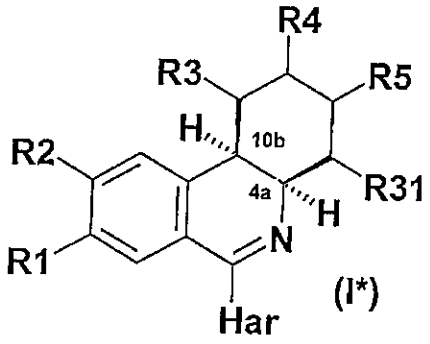
The compounds of formula I are chiral compounds having chiral centers in positions 2, 4a and 10b.

Numbering



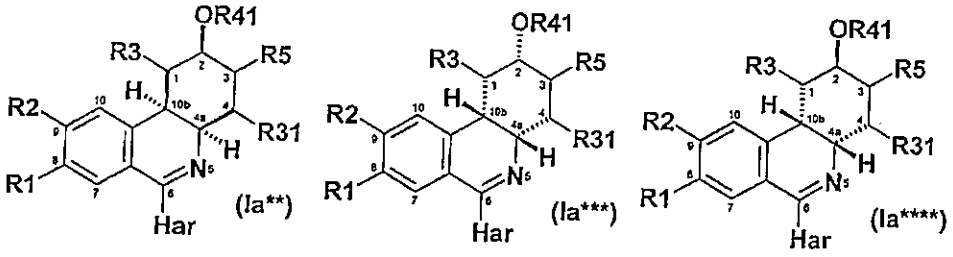
The invention includes all conceivable stereoisomers in pure form as well as in any mixing ratio. Preference is given to compounds of formula I in which the hydrogen atoms in positions 4a and 10b are in the cis position relative to one another. The pure cis enantiomers and their mixtures in any mixing ratio and including the racemates are more preferred in this context.

Particularly preferred in this context are those compounds of formula I, which have with respect to the positions 4a and 10b the configuration shown in formula (I*):



If, for example, in compounds of formula I* R3, R31 and R5 have the meaning hydrogen and R4 has the meaning -OR41, then the configuration – according to the rules of Cahn, Ingold and Prelog – is R in the 4a position and R in the 10b position.

Further preferred compounds of the formula I are those which have, with respect to the positions 2, 4a and 10b, the same configuration as shown in the formulae Ia** and Ia*** and Ia****:

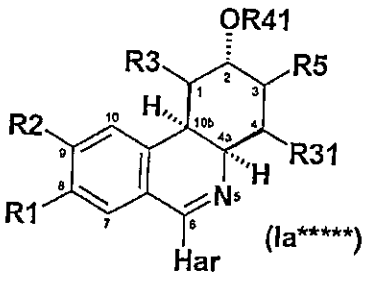


If, for example in compounds of the formula Ia** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 2, R in the position 4a and R in the position 10b.

If, for example in compounds of the formula Ia*** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 2, S in the position 4a and S in the position 10b.

If, for example in compounds of the formula Ia**** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 2, S in the position 4a and S in the position 10b.

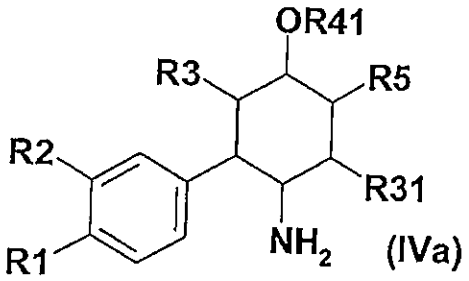
More particular preferred compounds of the formula I are those which have, with respect to the positions 2, 4a and 10b, the same configuration as shown in the formula Ia*****:



(Ia*****)

If, for example in compounds of the formula Ia***** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 2, R in the position 4a and R in the position 10b.

The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereoisomeric compounds). Thus, e.g. an enantiomer separation can be carried out at the stage of the starting compounds having a free amino group such as starting compounds of formula IVa as defined below.



(IVa)

Separation of the enantiomers can be carried out, for example, by means of salt formation of the racemic compounds of the formula IVa with optically active acids, preferably carboxylic acids, subsequent resolution of the salts and release of the desired compound from the salt. Examples of optically active carboxylic acids which may be mentioned in this connection are the enantiomeric forms of mandelic acid, tartaric acid, O,O'-dibenzoyltartaric acid, camphoric acid, quinic acid, glutamic acid, pyroglutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α-methoxyphenylacetic acid, α-methoxy-α-trifluoromethylphenylacetic acid and 2-phenylpropionic acid. Alternatively, enantiomerically pure starting compounds of the formula IVa can be prepared via asymmetric syntheses. Enantiomerically pure starting compounds as well as enantiomerically pure compounds of the formula I can be also obtained by chromatographic separation on chiral separating

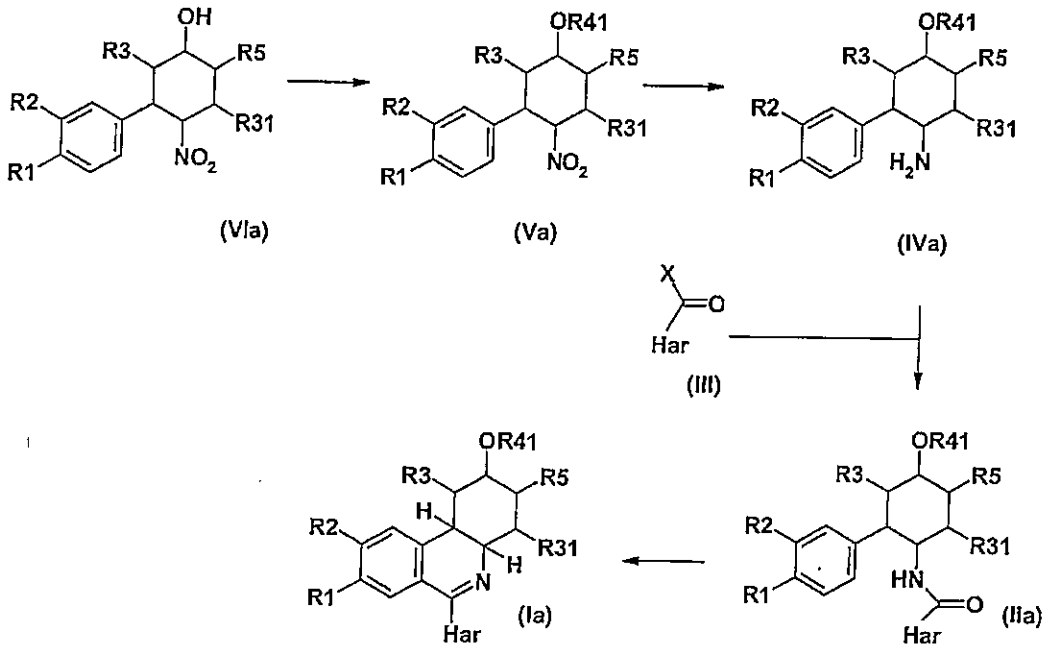
columns; by derivatization with chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by (fractional) crystallization from a suitable solvent.
The compounds according to the invention can be prepared, for example, as shown in the reaction schemes below and according to the following specified reaction steps, or, particularly, in a manner as described by way of example in the following examples, or analogously or similarly thereto according to preparation procedures or synthesis strategies known to the person skilled in the art.

Compounds of formula I, in which R1, R2, R3, R31, R4, R5 and Har have the meanings mentioned above, can be obtained as described as follows.

Compounds of formula Ia, in which R1, R2, R3, R31, R41, R5 and Har have the meanings mentioned above whereby R41 is other than hydrogen (for example, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxyl-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine substituted 1-4C-alkyl), can be prepared as described and shown in reaction scheme 1 below.

In the first reaction step of the synthesis route shown in scheme 1, compounds of the formula Va, in which R1, R2, R3, R31, R41 and R5 have the meanings mentioned above whereby R41 is other than hydrogen, are prepared from the corresponding compounds of the formula VIa by introduction of the group R41 whereby R41 is other than hydrogen (for example, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxyl-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine substituted 1-4C-alkyl). The introduction reaction is carried out in a manner habitual per se for an etherification or esterification reaction, or as described by way of example in the following examples.

Reaction scheme 1:



In the next reaction step of the synthesis route shown in reaction scheme 1, the nitro group of compounds of the formula Va, in which R1, R2, R3, R31, R41 and R5 have the meanings mentioned above whereby R41 is other than hydrogen, is reduced to the amino group of the corresponding compounds of the formula IVa. Said reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4426 or as described in the following examples. In more detail, the reduction can be carried out, for example, by catalytic hydrogenation, e.g. in the presence of Raney nickel or a noble metal catalyst such as palladium on active carbon, in a suitable solvent such as methanol or ethanol at room temperature and under normal or elevated pressure. Optionally, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent. Preferably, however, the reduction is carried out using a hydrogen-producing mixture, for example, metals such as zinc, zinc-copper couple or iron with organic acids such as acetic acid or mineral acids such as hydrochloric acid. More preferably, the reduction is carried out using a zinc-copper couple in the presence of an organic or an inorganic acid. Such a zinc-copper couple is accessible in a way known to the person of ordinary skill in the art.

Compounds of the formula IVa, in which R1, R2, R3, R31, R41 and R5 have the meanings indicated above whereby R41 is other than hydrogen and which are sensitive against catalytic hydrogenation, can be prepared from the corresponding compounds of the formula Va by selective reduction of the nitro group in a manner known to the person skilled in the art, for example by hydrogen transfer reaction in the presence of a metal catalyst, for example palladium or, preferably, Raney nickel, in a lower alcohol as solvent using, for example, ammonium formiate or, preferably, hydrazine hydrate as hydrogen donor.

Compounds of the formula IIa, in which R1, R2, R3, R31, R41, R5 and Har have the meanings indicated above whereby R41 is other than hydrogen, are accessible from the corresponding compounds of the formula IVa by reaction with corresponding compounds of the formula III, in which X represents a suitable leaving group, preferably a chlorine atom.

Alternatively, compounds of the formula IIa can also be prepared from the corresponding compounds of the formula IVa and corresponding compounds of the formula III, in which X is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1yl)-N,N,N',N'-tetramthyl-uronium-hexafluorophosphate] and N,N'-carbonyldiimidazole. In the scope of this invention preferred amide bond linking reagents are uronium salts and, particularly, carbodiimides, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Compounds of the formula III are either known or can be prepared in a known manner.

Compounds of the formula Ia, in which R1, R2, R3, R31, R41, R5 and Har have the meanings mentioned above whereby R41 is other than hydrogen, can be obtained by cyclocondensation of corresponding compounds of the formula IIa.

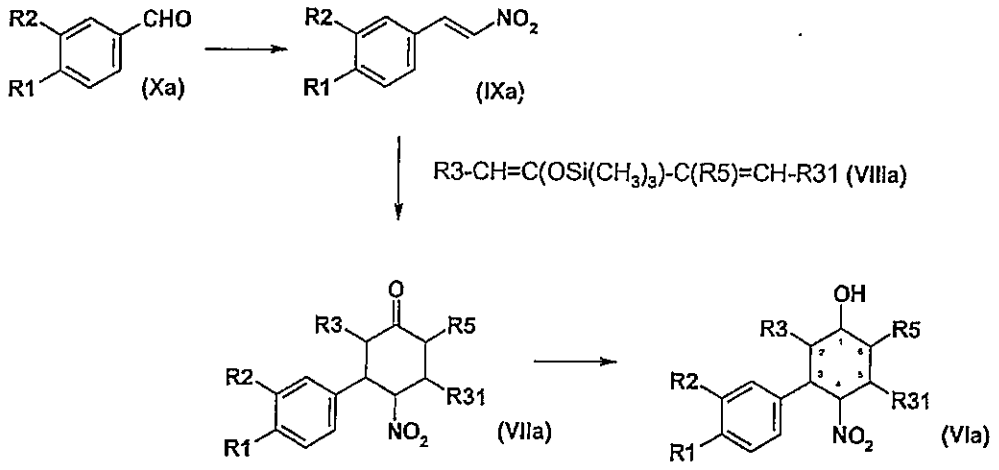
Said cyclocondensation reaction is carried out in a manner known per se to the person skilled in the art or as described by way of example in the following examples, according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., 1956, 4280-4282) in the presence of a suitable condensing agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as isopropyl acetate or acetonitrile, or without further solvent using an excess of condensing agent, at reduced temperature, or at room temperature, or at elevated temperature or at the boiling temperature of the solvent or condensing agent used. If necessary, said cyclocondensation reaction can be carried out in the presence of one or more suitable Lewis Acids such as, for example, suitable metal halogenides (e.g. chlorides) or sulphonates (e.g. triflates), including rare earth metal salts, such as e.g. anhydrous aluminum trichloride, aluminum tribromide, zinc chloride, boron trifluoride ethereate, titanium tetrachloride or, in particular, tin tetrachloride,
Parallel to the cyclization in the presence of a chlorine-containing condensing agent (such as e.g. phosphorus pentachloride), a nucleophilic or electrophilic substitution of the Har moiety giving the corresponding chlorine substituted Har moiety can take place, especially in the case of electron rich

Har groups, such as e.g. the dimethoxypyridinyl radical, like the 2,6-dimethoxypyridin-4-yl or the 2,6-dimethoxy-pyridin-3-yl radical.

Below reaction scheme 2 shows the synthesis of compounds of the formula VIa, in which R1, R2, R3, R31 and R5 have the meanings indicated above, from corresponding compounds of the formula VIIa via reduction reaction of the carbonyl group. Suitable reducing agents for the abovementioned reduction reaction may include, for example, metal hydride compounds such as, for example, diisopropylaluminium hydride, borane, sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, zinc borohydride, potassium tri-sec-butylborohydride, sodium tri-sec-butylborohydride, lithium tri-sec-butylborohydride, β-isopinocampheyl-9-borabicyclo[3.3.1]nonane and the like. The preferred examples of said reducing agents are sodium cyanoborohydride, β-isopinocampheyl-9-borabicyclo[3.3.1]nonane and potassium tri-sec-butylborohydride. The most preferred examples of the abovementioned reducing agents are β-isopinocampheyl-9-borabicyclo[3.3.1]nonane and potassium tri-sec-butylborohydride, which both allow to prepare compounds of the formula VIa stereoselectively. "Stereoselectively" in this connection means that those compounds of the formula VIa, in which the hydrogen atoms in positions 1 and 3 are located at the opposite side of the plane defined by the cyclohexane ring, are obtained preferentially.

The compounds of the formula VIIa, in which R1, R2, R3, R31 and R5 have the meanings mentioned above, are either known or can be obtained by the reaction of compounds of the formula IXa, in which R1 and R2 have the meanings mentioned above, with compounds of the formula VIIIa, in which R3, R31 and R5 have the meanings mentioned above. The cycloaddition reaction is carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or in J. Org. Chem. 1952, 17, 581 or as described in the following examples.

Reaction scheme 2:



Compounds of the formulae VIa or Va, in which the phenyl ring and the nitro group are trans to one another, can be converted in a manner known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or as described in the following examples.

The compounds of the formulae VIIIa and IXa are either known or can be prepared in a known manner. The compounds of the formula IXa can be prepared, for example, in a manner known to the person skilled in the art from corresponding compounds of the formula Xa as described, for example, in J. Chem. Soc. 1951, 2524 or in J. Org. Chem. 1944, 9, 170 or as described in the following examples.

The compounds of the formula Xa, in which R1 and R2 have the meanings indicated above, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Dtsch. Chem. Ges. 1925, 58, 203.

The compounds of formula I, in which R1, R2, R3, R31 and Har have the meanings mentioned above, R4 is –O-R41 and R41 is hydrogen can be obtained from corresponding compounds of formula Ia, in which R41 is an acyl group, such as e.g. acetyl, by deesterfication (e.g. saponification) reactions.

The deesterification (e.g. saponification) is expediently carried out analogously to the methods known to the person skilled in the art or as described by way of example in the following examples.

Optionally, compounds of the formula I can be converted into their salts, or, optionally, salts of the compounds of the formula I can be converted into the free compounds.

In addition, the compounds of the formula I can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The substances according to the invention are isolated and purified in a manner known per se, for example by distilling off the solvent under reduced pressure and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low-molecular-weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted into the free compounds, which can in turn be converted into salts, by alkalization or by acidification. In this manner, pharmacologically unacceptable salts can be converted into pharmacologically acceptable salts.

The solvates or particularly hydrates of the compounds according to this invention can be prepared in a manner known per se, e.g. in the presence of the appropriate solvent. Hydrates may be obtained from water or from mixtures of water with polar organic solvents (for example alcohols, e.g. methanol, ethanol or isopropanol, or ketones, e.g. acetone).

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds of the formula I.

The following examples serve to illustrate the invention. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous or similar manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

Any or all of the compounds which are mentioned as final compounds in the following examples as well as their salts, N-oxides and salts of the N-oxides are a preferred subject of the present invention.

In the examples, m.p. stands for melting point, h for hour(s), min for minutes, R_f for rentention factor in thin layer chromatography, s.p. for sintering point, EF for empirical formula, MW for molecular weight, MS for mass spectrum, M for molecular ion, fnd. for found, calc. for calculated, other abbreviations have their meanings customary per se to the skilled person.

According to common practice in stereochemistry, the symbols RS and SR are used to denote the specific configuration of each of the chiral centers of a racemate. In more detail, for example, the term "(2RS,4aRS,10bRS)" stands for a racemate (racemic mixture) comprising the one enantiomer having the configuration (2R,4aR,10bR) and the other enantiomer having the configuration (2S,4aS,10bS).

Examples

Final Compounds

1. (2RS,4aRS,10bRS)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

423 mg of acetic acid (2RS,4aRS,10bRS)-6-(2,6-dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester (Example 1a) dissolved in 1 ml of dichloromethane and 9 ml of methanol are added to 152 mg of cesium carbonate and the solution stirred for 19 h. The reaction mixture is adsorbed to silica gel and purified by flash chromatography to give 229 mg of the title compound as a colourless foam.

EF: $C_{23}H_{28}N_2O_5$; MW: calc.: 412.49

MS: fnd.: 413.3 (MH^+)

Starting from appropriate ester compounds, which are mentioned or described explicitly below (compounds 2a to 13a and 16a) the following compounds 2 to 16 are obtained according to the procedure as in Example 1.

2. (2RS,4aRS,10bRS)-9-(2,2-Difluoro-ethoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

Starting from compound 2a the title compound is obtained in an analogous manner as described for Example 1.

EF: $C_{23}H_{26}F_2N_2O_5$; MW: calc.: 448,47

MS: fnd.: 449,3

3. (2RS,4aRS,10bRS)-8-(2,2-Difluoro-ethoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-9-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

Starting from compound 3a the title compound is obtained in an analogous manner as described for Example 1.

EF: $C_{23}H_{26}F_2N_2O_5$; MW: calc.: 448,47

MS: fnd.: 449,3

4. (2RS,4aRS,10bRS)-6-(2,6-Dimethoxy-pyridin-3-yl)-8,9-dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

Starting from compound 4a the title compound is obtained in an analogous manner as described for Example 1.

EF: $C_{22}H_{26}N_2O_5$; MW: calc.: 398,46

MS: fnd.: 399,4

5. (2RS,4aRS,10bRS)-6-(2,6-Dimethoxy-pyridin-4-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

Starting from compound 5a the title compound is obtained in an analogous manner as described for Example 1.

EF: $C_{23}H_{28}N_2O_5$; MW: calc.: 412.49 MS: fnd.: 413.2

6. (2S,4aS,10bS)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

The title compound can be obtained by chromatographical separation of the corresponding racemate (Example 1) using a column as described below at the end of the chapter "Final compounds".

EF: $C_{23}H_{28}N_2O_5$; MW: calc.: 412,49

MS: fnd.: 413,3

7. (2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

Starting from compound 7a the title compound is obtained in an analogous manner as described for Example 1.

Alternatively, the title compound can be obtained by chromatographical separation of the corresponding racemate (Example 1) using a column as described below at the end of the chapter "Final compounds".

EF: $C_{23}H_{28}N_2O_5$; MW: calc.: 412,49

MS: fnd.: 413,3

8. (2R,4aR,10bR)-6-(4,6-Diethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{25}H_{32}N_2O_5$

Calc.: 440,54

Found (MH^+): 441.3

9. (2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{23}H_{28}N_2O_5$

Calc.: 412,49

Found (MH^+): 413.3

10. (2R,4aR,10bR)-6-(5,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{23}H_{28}N_2O_5$

Calc.: 412.49

11. (2R,4aR,10bR)-9-Ethoxy-6-(5-ethoxy-6-methoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{24}H_{30}N_2O_5$

Calc.: 426.52

12. (2RS,4aRS,10bRS)-9-(1,1-Difluoro-methoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{22}H_{24}F_2N_2O_5$

Calc.: 434,44

Found (MH+): 435.3

13. (2RS,4aRS,10bRS)-8-(1,1-Difluoro-methoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-9-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

$C_{22}H_{24}F_2N_2O_5$

Calc.: 434,44

Found (MH+): 435.2

14. (2S,4aS,10bS)-6-(2,6-Dimethoxy-pyridin-3-yl)-8,9-dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

The title compound can be obtained by chromatographical separation of the corresponding racemate (Example 4) using a column as described below at the end of the chapter "Final compounds".

$C_{22}H_{26}N_2O_5$

Calc.: 398,46

Found (MH+): 399.3

15. (2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-8,9-dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol

The title compound can be obtained by chromatographical separation of the corresponding racemate (Example 4) using a column as described below at the end of the chapter "Final compounds".

$C_{22}H_{26}N_2O_5$

Calc.: 398,46

Found (MH+): 399.2

1a. Acetic acid (2RS,4aRS,10bRS)-6-(2,6-dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

1.67 g of phosphorus pentachloride are suspended in 5 ml of dichloromethane. 1.227 g of crude acetic acid (1RS,3RS,4RS)-4-{[1-(2,6-dimethoxy-pyridin-3-yl)methanoyl]amino)-3-(3-ethoxy-4-methoxyphenyl)cyclohexyl ester (compound A1) dissolved in 15 ml of dichloromethane are added and the reaction mixture stirred at room temperature over night. The reaction mixture is cooled with an ice bath and 20 ml of triethylamine are added, than cautiously 10 ml of water with vigorous stirring. The organic layer is separated, concentrated and the crude product purified by flash chromatography to give 715 mg of the title compound.

EF: $C_{25}H_{30}N_2O_6$; MW: calc.: 454.53

MS: fnd.: 455.2 (MH^+)

Starting from the appropriate starting compounds, which are mentioned or described explicitly below (compounds A2 to A10), or which can be prepared in a manner known to the person skilled in the art or analogously or similarly to the examples described herein, the following compounds 2a to 5a, 7a to 13a and 16a, are obtained according to the procedure as in Example 1a. If necessary, the cyclization reaction can be carried out in the presence of a catalytic amount of a Lewis acid such e.g. tin tetrachloride.

2a. Acetic acid (2RS, 4aRS, 10bRS)-9-(2,2-difluoro-ethoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

EF: $C_{25}H_{28}F_2N_2O_6$; MW: calc.: 490.51

MS: fnd: 491.2

3a. Acetic acid (2RS,4aRS,10bRS)-8-(2,2-difluoro-ethoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-9-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

EF: $C_{25}\ H_{28}\ F_2\ N_2\ O_6$; MW: calc.: 490,51

MS: fnd.: 491,3

4a. Acetic acid (2RS,4aRS,10bRS)-6-(2,6-dimethoxy-pyridin-3-yl)-8,9-dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

EF: $C_{24}\ H_{28}\ N_2\ O_6$; MW: calc.: 440,5

MS: fnd.: 441,3

5a. Acetic acid (2RS,4aRS,10bRS)-6-(2,6-dimethoxy-pyridin-4-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

EF: $C_{25}\ H_{30}\ N_2\ O_6$; MW: calc.: 454,53

MS: fnd.: 455,2

7a. Acetic acid (2R,4aR,10bR)-6-(2,6-dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

Starting from compound A6 the title compound is obtained according to the procedure as in Example 1a. If necessary, the cyclization reaction can be carried out in the presence of a catalytic amount of a Lewis acid such e.g. tin tetrachloride.

EF: $C_{25}H_{30}N_2O_6$; MW: calc.: 454,53

MS: fnd.: 455,3

8a. Acetic acid (2R,4aR,10bR)-6-(4,6-diethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{27}H_{34}N_2O_6$

Calc.: 482.58

Found (MH^+): 483.3

9a. Acetic acid (2R,4aR,10bR)-6-(4,6-dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{25}H_{30}N_2O_6$

Calc.: 454.53

Found (MH^+): 455.3

10a. Acetic acid (2R,4aR,10bR)-6-(5,6-dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{25}H_{30}N_2O_6$

Calc.: 454.53

11a. Acetic acid (2R,4aR,10bR)-9-ethoxy-6-(5-ethoxy-6-methoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{26}H_{32}N_2O_6$

Calc.: 468.55

12a. Acetic acid (2RS,4aRS,10bRS)-9-(1,1-difluoro-methoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{24}H_{26}F_2N_2O_6$

Calc.: 476,48

Found (MH+): 477.4

13a. Acetic acid (2RS,4aRS,10bRS)-8-(1,1-difluoro-methoxy)-6-(2,6-dimethoxy-pyridin-3-yl)-9-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

$C_{24}H_{26}F_2N_2O_6$

Calc.: 476,48
Found (MH+): 477.3

Starting from the appropriate compounds mentioned above and the appropriate acid the corresponding salts can be obtained, for example, according to the following general procedure, or analogously or similarly thereto:
About 1 g of the free base is solved in about 10 ml of a suitable solvent at room temperature. To this solution 1.1 eq. of the appropriate acid is added in one portion under stirring. The mixture is stirred over night while the salt precipitated. The salt is filtered off, washed with about 2 ml of the suitable solvent and dried over night at about 50 °C in vacuo. Thus, for example, in the case of hydrochloric acid an ether or alcohol solvent (e.g. dioxane, THF, diethylether, methanol, ethanol, or the like), or in the case of organic acids, such as e.g. fumaric, tartaric or oxoglutaric acid, a ketone solvent (e.g. acetone) may be suitable.

The following salts are obtained according to the abovementioned procedure or analogously or similarly thereto:

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol hydrochloride
(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol hydrochloride
(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol sulfate
(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol sulfate
(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol methansulfonate
(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol methansulfonate
(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol citrate
(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol citrate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol L-tartrate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol L-tartrate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-tartrate; m.p.: fnd.: decomposition starting at 107°C

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-tartrate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol *meso*-tartrate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol *meso*-tartrate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-malate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-malate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol L-malate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol L-malate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol fumarate; m.p.: fnd.: decomposition starting at 172°C

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol fumarate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol maleinate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol maleinate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol oxoglutarate; m.p.: fnd.: decomposition starting at 110°C

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol oxoglutarate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol oxalate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol oxalate

(2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-gluconate

(2R,4aR,10bR)-6-(4,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol D-gluconate

Optionally the abovementioned salts can be converted in a suitable solvent with the aid of a suitable base into the free compounds, which can be isolated in a manner known per se.

Chromatographical separation:
Altenatively to the above described synthesis procedures using enantiomerically pure starting compounds, enantiomerically pure final compounds of formual I, in which R41 is hydrogen, can be obtained from the corresponding racemates by chromatographical separation, which can be afforded with one or more of the following chiral columns:
CHIRALPAK® AD-H 5µm (250 x 20 mm), 25°C,
heptane/2-propanol/diethylamine= 90/10/0.1; 20 ml/min, detection at 340 nm;
CHIRALPAK® AD 20 µm (285 x 110 mm), 30 °C, acetonitrile/isopropanol = 95:5; 570 ml/min, detection at 250 nm or 280 nm;
CHIRALPAK® AD 20 µm (250 x 50 mm), ambient temperature, heptane/isopropanol = 95:5, 120 ml/min, detection at 330 nm; or
CHIRALPAK® 50801 20µm (250 x 50 mm), 25 °C, methanol, 120 ml/min, detection at 330 nm.

Starting Materials

A1. Acetic acid (1RS,3RS,4RS)-4-{[1-(2,6-dimethoxy-pyridin-3-yl)methanoyl]amino}-3-(3-ethoxy-4-methoxyphenyl)cyclohexyl ester

555 mg of 2,6-dimethoxynicotinic acid and 581 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride are placed in a flask under nitrogen. 778 mg of acetic acid (1RS,3RS,4RS)-4-amino-3-(3-ethoxy-4-methoxyphenyl)cyclohexyl ester (compound B1) and 2 mg of 4-dimethylaminopyridine both as solution in dichloromethane are added and the solution stirred for 1 h at 40°C, than 42 h at room temperature. The reaction is quenched with 5 ml of water. After phase separation the organic layer is washed with 2.5 ml of saturated potassium hydrogencarbonate solution. After drying the organic layer with magnesium sulfate the solvent is removed to give 1.227 g of the crude title compound which are used for the following step without further purification.

MW: calc.: 472.54 MS: fnd: 473.1

Starting from the appropriate commercially available or art-known heteroaryl carboxylic acids and the appropriate compound B1, B2, B3, B4 or B5 further relevant, non-explicitly described starting compounds analogous to compound A1, which are also used to give via the abovementioned cyclization step the compounds mentioned above, are obtained according to the procedure as in Example A1.

The following compounds can be prepared from the appropriate starting compounds mentioned below and the appropriate commercially available or art-known heteroaryl carboxylic acids in a manner according to Example A1.

A2. Acetic acid (1RS,3RS,4RS)-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-4-{[1-(2,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-cyclohexyl ester

MW calc.: 508.52 MS: fnd: 509.1

A3. Acetic acid (1RS,3RS,4RS)-3-[4-(2,2-difluoro-ethoxy)-3-methoxy-phenyl]-4-{[1-(2,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-cyclohexyl ester

MW calc.: 508.52 MS: fnd: 509.2

A4. Acetic acid (1RS,3RS,4RS)-3-(3,4-dimethoxy-phenyl)-4-{[1-(2,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-cyclohexyl ester

MW calc.: 458.52 MS: fnd: 459.1

A5. Acetic acid (1RS,3RS,4RS)-4-{[1-(2,6-dimethoxy-pyridin-4-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

MW calc.: 472.54 MS: fnd: 473.1

A6. Acetic acid (1R,3R,4R)-4-{[1-(2,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester
MW calc.: 472.54 MS: fnd: 473.2

A7. Acetic acid (1R,3R,4R)-4-{[1-(4,6-diethoxy-pyridin-3-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

A8. Acetic acid (1R,3R,4R)-4-{[1-(4,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

A9. Acetic acid (1R,3R,4R)-4-{[1-(5,6-dimethoxy-pyridin-3-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

A10. Acetic acid (1R,3R,4R)-4-{[1-(5-ethoxy-6-methoxy-pyridin-3-yl)-methanoyl]-amino}-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

Further relevant starting compounds for the final examples mentioned above can be prepared from the appropriate starting compounds mentioned below and the appropriate commercially available or art-known heteroaryl carboxylic acids in a manner according to Example A1.

B1. Acetic acid (1RS,3RS,4RS)-4-amino-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester
Starting from compound C1 mentioned below, the title compound is obtained analogously to the procedure as in Example B2.
EF: $C_{17}H_{25}NO_4$; MW: 307.39
MS: 308.0 (MH^+)

B1a. Acetic acid (1R,3R,4R)-4-amino-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester
24.0 g (55.0 mmol) of the pyroglutamate of the title compound (compound B1b) are suspended in 150 ml of water, 100 ml of dichloromethane are added, then saturated $KHCO_3$-solution until the gas evolution ceased. After phase separation, reextraction of the water layer and drying the combined organic layers with sodium sulfate the solvent is removed to give 16.9 g of the salt-free title compound.
Analytical Column Chromatography (CHIRALPAK AD-H 250 x 4.6 mm 5 µ No.ADH0CE-DB030, Eluent: n-Hexan/iPrOH = 80/20 (v/v) + 0.1 % Diethylamine): Retention Time: 6.54 min

B1b. Acetic acid (1R,3R,4R)-4-amino-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester, 24ome with L-pyroglutamic acid
Solution A: 55.2 g (180 mmol) of racemic acetic acid (1RS,3RS,4RS)-4-amino-3-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester (compound B1) are dissolved in 540 ml of isopropyl acetate.

Solution B: 18.6 g (144 mmol) of L-pyroglutamic acid are dissolved in 260 ml of isopropanol under heating, then 290 ml of isopropyl acetate is added carefully.
Solution B is added to solution A and left for 48 hours. The solid is filtered off and washed with a little isopropyl acetate to give after drying 32.48 g colorless crystals with a ratio of the enantiomers of 97:3 in favour of the title compound.
M.p.: 165-167° C

B2. Acetic acid (1RS,3RS,4RS)-4-amino-3-(3,4-dimethoxyphenyl)cyclohexyl ester

A solution of 10.37 g of acetic acid (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexyl ester (compound C2) in 240 ml of ethanol is added to a zinc-copper couple, prepared from 16.8 g of zinc powder and 920 mg of copper (II) acetate monohydrate in acetic acid, the resulting suspension is refluxed and treated with 26 ml of acetic acid, 3.2 ml of water and 26 ml of ethanol. The resulting mixture is refluxed for further 15 min. The precipitate is filtered off with suction and the solvent is removed. Chromatographical purification on silica gel using a mixture of petroleum ether/ethyl acetate/triethylamine in the ratio 2/7/1 and concentration of the corresponding eluate fractions afford 5.13 g (55 % of theory) of the title compound as a pale brown oil.
R_f = 0.35 (petroleum ether/ethyl acetate/triethylamine = 2/7/1)

B3. Acetic acid (1RS,3RS,4RS)-4-amino-3-[4-(1,1-difluoro-methoxy)-3-methoxy-phenyl]-cyclohexyl ester

Starting from compound C3 mentioned below, the title compound is obtained analogously to the procedure as in Example B2.
EF: $C_{16}H_{21}F_2NO_4$; MW: 329.35
MS: 330.0 (MH^+)

B4. Acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(1,1-difluoro-methoxy)-4-methoxy-phenyl]-cyclohexyl ester

Starting from compound C4 mentioned below, the title compound is obtained analogously to the procedure as in Example B2.
EF: $C_{16}H_{21}F_2NO_4$; MW: 329.35
MS: 330.0 (MH^+)

B5. Acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester

Starting from compound C5 mentioned below, the title compound is obtained analogously to the procedure as in Example B2.

B5a. Acetic acid (1R,3R,4R)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester

The title compound is obtained from its pyroglutamate salt (compound B5b) analogously as described for compound B1a using sodium hydrogencarbonate solution.

B5b. Acetic acid (1R,3R,4R)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester, salt with L-pyroglutamic acid

343 mg (1.00 mmol) of acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester (compound B5) are dissolved in 3 ml of isopropanol. A solution of 103 mg (0.80 mmol) of L-pyroglutamic acid in 2 ml of isopropanol is added. After filtering and drying 162 mg of the pyroglutamate are isolated with an enantiomeric ratio of 97 : 3 in favour of the title compound.

B6. Acetic acid (1SR,3RS,4RS)-3-amino-4-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

3.0 g (7.36 mmol) of acetic acid (1SR,3RS,4RS)-3-tert-butoxycarbonylamino-4-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester (compound C6) are dissolved in 6 ml of 4 M HCl in dioxane and stirred for 30 min. After removal of the solvent the residue is dissolved in dichloromethane and 25 ml of sat. $NaHCO_3$ solution are added carefully. After phase separation, reextraction of the water layer and drying of the combined organic layers (Na_2SO_4) the solvent is removed to give 2.25 g of the title compound.
EF: C17 H25 N O4; MW: 307.39
MS: 308.1 (MH^+)

B7. Acetic acid (1SR,3RS,4RS)-3-amino-4-(3,4-dimethoxy-phenyl)-cyclohexyl ester

The title compound can be obtained from compound C7 analogously as described for compound B6.

C1. Acetic acid (1RS,3RS,4RS)-3-(3-ethoxy-4-methoxy-phenyl)-4-nitrocyclohexyl ester

Starting from compound D1 mentioned below, the title compound is obtained according to the procedure as in Example C2.

C2. Acetic acid (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexyl ester

10.18 g of (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanol (compound D2) are dissolved in 100 ml of acetic anhydride and the solution is heated to 100°C for 1-2 h. After removal of the solvent, the residue is chromatographed on silica gel using a mixture of petroleum ether/ethyl acetate in the ratio 2/1. Concentration of the corresponding eluate fractions furnish 10.37 g (89 % of theory) of the title compound as an oil.
R_f = 0.32 (petroleum ether/ethyl acetate = 2/1)

Starting from the starting compounds mentioned below, the following are obtained according to the procedure as in Example C2:

C3. Acetic acid (1RS,3RS,4RS)-3-[4-(1,1-difluoro-methoxy)-3-methoxy-phenyl]-4-nitrocyclohexyl ester

C4. Acetic acid (1RS,3RS,4RS)-3-[3-(1,1-difluoro-methoxy)-4-methoxy-phenyl]-4-nitrocyclohexyl ester

C5. Acetic acid (1RS,3RS,4RS)-3-(3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-4-nitrocyclohexyl ester

C6. Acetic acid (1SR,3RS,4RS)-3-tert-butoxycarbonylamino-4-(3-ethoxy-4-methoxy-phenyl)-cyclohexyl ester

22.64 g (65 mmol) of [(1RS,6RS)-6-(3-ethoxy-4-methoxy-phenyl)-cyclohex-3-enyl]-carbamic acid tert-butyl ester (compound D6) are dissolved in 180 ml of THF and 50 ml of BH_3 (1 M solution in THF) are added dropwise (30 min). After stirring for 2 h the mixture is cooled using an ice bath and a mixture of 30 ml of H_2O_2 (30%) and 60 ml of aqueous NaOH (3 M) is added. The mixture is stirred for 30 min at room temperature. 400 ml of water and 200 ml of dichloromethane are added. After phase separation, reextraction of the water layer and drying of the combined organic layers (Na_2SO_4) the solvent is removed and the crude product (23.42 g, mixture of the two mentioned regioisomers ~ 2:1 in favour of the title compound) is used directly without further purification.

The crude material from above then is dissolved in 50 ml of pyridine. 50 mg of 4-dimethylaminopyridine and 60 ml of acetic anhydride are added and the mixture stirred for 90 min at 100°C. The solvents and the acetic anhydride are removed (sat. $NaHCO_3$ solution). Purification by means of chromatography yields 9.4 g of the title compound as colorless foam.
EF: C22 H33 N O6; MW: 407.51
MS: 308.1 (MH^+-Boc), 407.8 (MH^+), 430.1 (Mna^+)

C7. Acetic acid (1SR,3RS,4RS)-3-tert-butoxycarbonylamino-4-(3,4-dimethoxy-phenyl)-cyclohexyl ester

The title compound can be obtained from compound D7 analogously as described for compound C6.

D1. (1RS,3RS,4RS)-3-(3-Ethoxy-4-methoxy-phenyl)-4-nitrocyclohexanol

Starting from compound E1 mentioned below, the title compound is obtained according to the procedure as in Example D2.

D2. (1RS,3RS,4RS)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanol

10 g of (1RS,3RS,4SR)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanol (compound E2) are dissolved in 170 ml of absolute 1,2-dimethoxyethane. 14.3 ml of a 30 % solution of sodium methanolate in methanol are added dropwise. After complete addition, stirring is continued for 10 min and a mixture consisting of 85 % phosphoric acid and methanol is added to pH 1. By adding of saturated potassium hydrogencarbonate solution the resulting suspension is neutralized. The mixture is diluted with water

and dichloromethane, the organic layer is separated and extracted with dichloromethane. The solvents are removed under reduced pressure to yield the title compound as a pale yellow oil, which crystallizes. The title compound is used without further purification in the next step.
R_f = 0.29 (petroleum ether/ethyl acetate = 1/1)
M.p.: 126-127°C

Starting from the appropriate starting compounds mentioned below, the following are obtained according to the procedure as in Example D2:

D3. (1RS,3RS,4RS)-3-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-4-nitrocyclohexanol

D4. (1RS,3RS,4RS)-3-[3-(1,1-Difluoro-methoxy)-4-methoxy-phenyl]-4-nitrocyclohexanol

D5. (1RS,3RS,4RS)-3-(3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl)-4-nitrocyclohexanol

D6. [(1RS,6RS)-6-(3-Ethoxy-4-methoxy-phenyl)-cyclohex-3-enyl]-carbamic acid tert-butyl ester
Starting from (1RS,6RS)-6-(3-ethoxy-4-methoxy-phenyl)-cyclohex-3-enylamine (compound E6) the title compound is obtained analogously as described for compound D7.
EF: C20 H29 N O4; MW: 347.46,
MS: 370.1 (Mna^+)

D7. [(1RS,6RS)-6-(3,4-Dimethoxy-phenyl)-cyclohex-3-enyl]-carbamic acid tert-butyl ester
15.18 g (65.06 mmol) of (±)-cis-6-(3,4-dimethoxyphenyl)-cyclohex-3-enylamine (compound E7) and 14.21 g (65.11 mmol) of Boc_2O are stirred in dichloromethane for 2.5 h, then the solvent is removed and the residue crystallized from ethylacetate/n-heptane to give 19.1 g of the title compound.
EF: C19 H27 N O4; MW: 333.43,
MS: 334.2 (MH^+)

E1. (1RS,3RS,4SR)-3-(3-Ethoxy-4-methoxy-phenyl)-4-nitrocyclohexanol
Starting from compound F1 mentioned below, the title compound is obtained according to the procedure as in Example E2.

E2. (1RS,3RS,4SR)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanol
Under nitrogen atmosphere 16.76 g of (3RS,4SR)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanone (compound F2) are dissolved in 300 ml of tetrahydrofurane, the solution is cooled to –78°C, and 75 ml of 1 M solution of potassium tri-sec-butylborohydride in tetrahydrofurane is added dropwise. After stirring for further 1 h, a mixture consisting of 30% hydrogeneperoxide solution and phosphate buffer solution is added. Stirring is continued for further 10 min, the reaction mixture is diluted with 400 ml of ethyl acetate and the aqueous layer is extracted with ethyl acetate, the combined organic phases are

concentrated to give a foam, which is purified by chromatography on silica gel using a mixture of petroleum ether/ethyl acetate in the ratio 1/1 to furnish 10.18 g (60 % of theory) of the title compound.
EF: $C_{14}H_{19}NO_5$; MW: 281.31
MS: 299.1 (MNH_4^+)
R_f = 0.29 (petroleum ether/ethyl acetate = 1/1)
M.p.: 139-141°C

Starting from the appropriate starting compounds mentioned below, the following are obtained according to the procedure as in Example E2:

E3. (1RS,3RS,4SR)-3-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-4-nitrocyclohexanol

E4. (1RS,3RS,4SR)-3-[3-(1,1-Difluoro-methoxy)-4-methoxy-phenyl]-4-nitrocyclohexanol

E5. (1RS,3RS,4SR)-3-(3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl)-4-nitrocyclohexanol

E6. (1RS,6RS)-6-(3-Ethoxy-4-methoxy-phenyl)-cyclohex-3-enylamine
Starting from 2-ethoxy-1-methoxy-4-((1RS,6RS)-6-nitro-cyclohex-3-enyl)-benzene (compound F6) the title compound is obtained analogously as described for compound E7.

E7. (±)-cis-6-(3,4-Dimethoxyphenyl)-cyclohex-3-enylamine
40 g of (±)-cis-1,2-dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene (compound F7) are dissolved in 400 ml of ethanol and 40 g of zinc powder are added. After heating to boiling temperature, 65 ml of glacial acetic acid are added dropwise. Afterwards, the reaction mixture is filtrated and concentrated. The residue is redissolved in diluted hydrochloric acid and extraxted with toluene. The aqueous layer is alkalized using 6 N solution of sodium hydroxide and extracted several times with toluene. The combined organic phases of the alkalic extraction are dried using sodium sulfate and concentrated. The residue is chromatographed on silica gel. 11.5 g of the title compound are obtained.

F1. (3RS,4SR)-3-(3-Ethoxy-4-methoxy-phenyl)-4-nitrocyclohexanone
Starting from compound G1 mentioned below, the title compound is obtained according to the procedure as in Example F2.

F2. (3RS,4SR)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanone
90.0 g of 3,4-dimethoxy-ω-nitrostyrene (compound G2), 90 ml of 2-trimethylsilyloxy-1,3-butadiene and 180 ml of abs. Toluene are put in an autoclave, where the mixture is stirred at 140°C for 2 days and then cooled. After addition of 1000 ml of ethyl acetate, 300 ml of a 2 N solution of hydrochloric acid are dropped under stirring. The phases are separated and the aqueous layer is extracted three times with dichloromethane. The combined organic extracts are washed with saturated sodium

hydrogencarbonate solution, dried over magnesium sulfate and the solvents are removed under reduced pressure to give 150 g of the crude title compound. Further purification is carried out by chromatography on silica gel using petroleum ether/ethyl acetate in the ratio 1/1 as eluent to give 81.5 g (67 % of theory) of the pure title compound.
EF: $C_{14}H_{17}NO_5$; MW: 279.30
MS: 279 (M^+), 297.1 (MNH_4^+)
R_f = 0.47 (petroleum ether/ethyl acetate = 1/1)
M.p.: 147-148°C

Starting from the appropriate starting compounds mentioned below, the following are obtained according to the procedure as in Example F2:

F3. (3RS,4SR)-3-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-4-nitrocyclohexanone

F4. (3RS,4SR)-3-[3-(1,1-Difluoro-methoxy)-4-methoxy-phenyl]-4-nitrocyclohexanone

F5. (3RS,4SR)-3-(3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl)-4-nitrocyclohexanone

F6. 2-Ethoxy-1-methoxy-4-((1RS,6RS)-6-nitro-cyclohex-3-enyl)-benzene
Starting from 2-ethoxy-1-methoxy-4-((1RS,6SR)-6-nitro-cyclohex-3-enyl)-benzene (compound G6) the title compound is obtained analogously as described for compound F7.

F7. (±)-cis-1,2-Dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene
10.0 g of (±)-trans-1,2-dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene (compound G7) and 20.0 g of potassium hydroxide are dissolved in 150 ml of ethanol and 35 ml of dimethylformamide. A solution of 17.5 ml of conc. Sulfuric acid in 60 ml of ethanol is then added dropwise such that the internal temperature does not exceed 4°C. After stirring for 1 h, the mixture is added to 1 l of ice water, the precipitate is filtered off with suction, washed with water and dried, and the crude product is recrystallized in ethanol. 8.6 g of the title compound of m.p. 82.5-84°C are obtained.

G1. 3-Ethoxy-4-methoxy-ω-nitrostyrene
Starting from art-known starting compounds, the title compound is obtained according to the procedure as in Example G2:

G2. 3,4-Dimethoxy-ω-nitrostyrene
207.0 g of 3,4-dimethoxybenzaldehyde, 100.0 g of ammonium acetate and 125 ml of nitromethane are heated to boiling for 3-4 h in 1.0 l of glacial acetic acid. After cooling in an ice bath, the precipitate is

filtered off with suction, rinsed with glacial acetic acid and petroleum ether and dried. M.p.: 140-141°C. Yield: 179.0 g.

Starting from starting compounds, which are art-known or which can be obtained analogously to art-known compounds or according to art-known procedures (such as e.g. as described in WO 95/01338 or analogously or similarly thereto) the following compounds are obtained according to the procedure as in Example G2:

G3. 4-(1,1-Difluoro-methoxy)-3-methoxy-ω-nitrostyrene

G4. 3-(1,1-Difluoro-methoxy)-4-methoxy-ω-nitrostyrene

G5. 3-(2,2-Difluoro-ethoxy-4)-methoxy-ω-nitrostyrene

The title compound is obtained starting from 3-(2,2-difluoro-ethoxy)-4-methoxy-benzaldehyde (compound H1) according to the procedure as in Example G2.
M.p.: 164-165°C

G6. 2-Ethoxy-1-methoxy-4-((1RS,6SR)-6-nitro-cyclohex-3-enyl)-benzene

Starting from 3-ethoxy-4-methoxy-ω-nitrostyrene (compound G1) the title compound is obtained analogously as described for compound G7.

G7. (±)-trans-1,2-Dimethoxy-4-(2-nitrocyclohex-4-enyl)benzene

50.0 g of 3,4-dimethoxy-ω-nitrostyrene (compound G2), and 1.0 g (9.1 mmol) of hydroquinone are suspened in 200 ml of abs. Toluene and treated at –70° C with 55.0 g (1.02 mol) of liquid 1,3-butadiene. The mixture is stirred at 160°C for 6 days in an autoclave and then cooled. Some of the solvent is removed on a rotary evaporator, and the resulting precipitate is filtered off with suction and recrystallized in ethanol. M.p.: 113.5-115.5°C.

H1. 3-(2,2-Difluoro-ethoxy)-4-methoxy-benzaldehyde

10.04 g of isovanillin and 15.5 g of potassium carbonate are placed in an autoclave. 50 ml of DMF are added as well as 12.44 g of 2-bromo-1,1-difluoroethane. The autoclave is closed and heated at 60°C for 20 h. Then the solids are filtered off and washed with 120 ml of DMF. About 120 ml of the solvent are distilled off and the residue poured on 200 ml of ice/water, where the product precipitates. After stirring the slurry for 30 minutes the product is filtered off and dried to give 13.69 g of the desired product.
M.p.: 66-68°C

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral

senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia; as well as for enhancing cognition. Yet in addition, the compounds of the invention are useful in the treatment of diabetes mellitus, leukaemia and osteoporosis.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions for treating disorders which are mediated by phosphodiesterases, in particular PDE4-mediated disorders, such as, for example, those mentioned in the specification of this invention or those which are apparent or known to the skilled person.

The invention also relates to the use of the compounds according to the invention for the manufacture of pharmaceutical compositions having PDE4 inhibitory activity.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned comprising one or more of the compounds according to the invention.

The invention yet furthermore relates to compositions comprising one or more compounds according to this invention and a pharmaceutically acceptable carrier. Said compositions can be used in therapy, such as e.g. for treating, preventing or ameliorating one or more of the abovementioned diseases.

The invention still yet furthermore relates to pharmaceutical compositions according to this invention having PDE, particularly PDE4, inhibitory activity.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries, excipients, carriers, vehicles, diluents or adjuvants which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example,

powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarly between 0.01 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.003 and 3 mg/kg per day. In another embodiment, the dose for administration by inhalation is between 0.1 and 3 mg per day, and the dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors", 21-40, „The Handbook of Immunopharmacology", Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (MM Teixeira, TiPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor-α in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

Methods for measuring inhibition of PDE4 activity

The PDE4B2 (GB no. M97515) was a gift of Prof. M. Conti (Stanford University, USA). It was amplified from the original plasmid (pCMV5) via PCR with primers Rb9 (5'- GCCAGCGTGCAAATAATGAAGG – 3') and Rb10 (5'- AGAGGGGGATTATGTATCCAC –3') and cloned into the pCR-Bac vector (Invitrogen, Groningen, NL).

The recombinant baculovirus was prepared by means of homologous recombination in SF9 insect cells. The expression plasmid was cotransfected with Bac-N-Blue (Invitrogen, Groningen, NL) or Baculo-Gold DNA (Pharmingen, Hamburg) using a standard protocol (Pharmingen, Hamburg). Wt virus-free recombinant virus supernatant was selected using plaque assay methods. After that, high-titre virus supernatant was prepared by amplifying 3 times. PDE was expressed in SF21 cells by infecting 2×10^6 cells/ml with an MOI (multiplicity of infection) between 1 and 10 in serum-free SF900 medium (Life Technologies, Paisley, UK). The cells were cultured at 28°C for 48 – 72 hours, after which they were pelleted for 5-10 min at 1000 g and 4°C.

The SF21 insect cells were resuspended, at a concentration of approx. 10^7 cells/ml, in ice-cold (4°C) homogenization buffer (20 mM Tris, pH 8.2, containing the following additions: 140 mM NaCl, 3.8 mM KCl, 1 mM EGTA, 1 mM $MgCl_2$, 10 mM β-mercaptoethanol, 2 mM benzamidine, 0.4 mM Pefablock, 10 µM leupeptin, 10 µM pepstatin A, 5 µM trypsin inhibitor) and disrupted by ultrasonication. The homogenate was then centrifuged for 10 min at 1000×g and the supernatant was stored at –80°C until subsequent use (see below). The protein content was determined by the Bradford method (BioRad, Munich) using BSA as the standard.

PDE4B2 activity is inhibited by the said compounds in a modified SPA (scintillation proximity assay) test, supplied by Amersham Biosciences (see procedural instructions "phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtiter plates (MTP's). The test volume is 100 µl and contains 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM Mg^{2+}, 0.5 µM cAMP (including about 50,000 cpm of [3H]cAMP), 1 µl of the respective substance dilution in DMSO and sufficient recombinant PDE (1000×g supernatant, see above) to ensure that 10-20% of the cAMP is converted under the said experimental conditions. The final concentration of DMSO in the assay (1 % v/v) does not substantially affect the activity of the PDE investigated. After a preincubation of 5 min at 37°C, the reaction is started by adding the substrate (cAMP) and the assay is incubated for a further 15 min; after that, it is stopped by adding SPA beads (50 µl). In accordance with the manufacturer's instructions, the SPA beads had previously been resuspended in water, but were then diluted 1:3 (v/v) in water; the diluted solution also contains 3 mM IBMX to ensure a complete PDE activity stop. After the beads have been sedimented (> 30 min), the MTP's are analyzed in commercially available luminescence detection devices. The corresponding IC_{50} values of the compounds for the inhibition of PDE activity are determined from the concentration-effect curves by means of non-linear regression.

Representative inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the Examples.

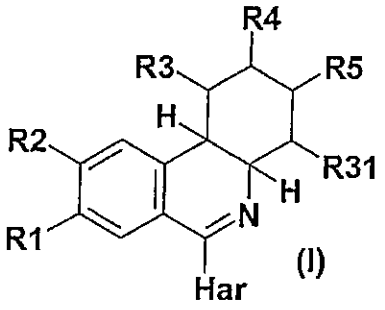
Table A

Inhibition of the PDE4 activity

Compound	-logIC_{50} (mol/l)
1	The inhibitory value of this listed compound is in the range from 7.24 to 9.32
2	The inhibitory values of these listed compounds 2 and 7 are in the range from 6.91 to 9.17
7	
12	The inhibitory values of these listed compounds 12 and 15 are in the range from 7.02 to 9.4
15	

Claims:

1. A compound of formula I



in which

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

Har is substituted by R6 and R7 and is a pyridinyl radical, in which

R6 is 1-4C-alkoxy,

R7 is 1-4C-alkoxy,

or a salt, a N-oxide or a salt of a N-oxide of this compound.

2. A compound of formula I according to claim 1 in which

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

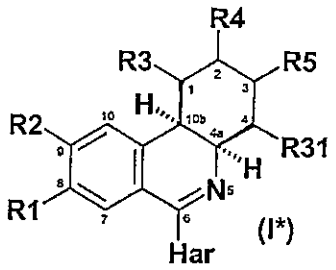
R41 is hydrogen,

R5 is hydrogen,

Har is 2,6-dimethoxypyridin-3-yl,

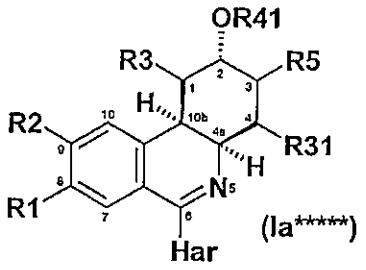
or a salt, a N-oxide or a salt of a N-oxide of this compound.

3. A compound of formula I according to any one of the preceding claims, which has with respect to the positions 4a and 10b the configuration shown in formula I*:



or a salt, a N-oxide or a salt of a N-oxide of this compound.

4. A compound of formula I according to any one of the preceding claims, which has with respect to the positions 2, 4a and 10b the configuration shown in formula Ia*****:



or a salt, a N-oxide or a salt of a N-oxide of this compound.

5. A compound or a N-oxide, salt or salt of a N-oxide of this compound as claimed in any one of the preceding claims for the treatment of diseases.

6. A pharmaceutical composition comprising one or more compounds or N-oxides, salts or salts of a N-oxide of these compounds as claimed in any one of the preceding claims together with customary pharmaceutical excipients and/or vehicles.

7. Use of a compound or a N-oxide, salt or salt of a N-oxide of this compound as claimed in any one of the preceding claims for the production of pharmaceutical compositions for the treatment of a PDE4-mediated disease selected from bronchial asthma, COPD, psoriasis, atopic eczema and diabetes mellitus.

8. A compound of formula I according to claim 1 which is selected from (2R,4aR,10bR)-6-(2,6-Dimethoxy-pyridin-3-yl)-9-ethoxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-ol and the salts of this compound.

9. The compound or a salt of the compound as claimed in claim 8 for use in the treatment of diseases.

10. A pharmaceutical composition comprising the compound or a salt of the compound as claimed in claim 8 together with customary pharmaceutical excipients and/or vehicles.

11. Use of the compound or a salt of the compound as claimed in claim 8 for the production of pharmaceutical compositions for the treatment of PDE4-mediated diseases selected from bronchial asthma, COPD, psoriasis and atopic eczema.

12. Use of the compound or a salt of the compound as claimed in claim 8 for the production of pharmaceutical compositions for the treatment of diabetes mellitus.