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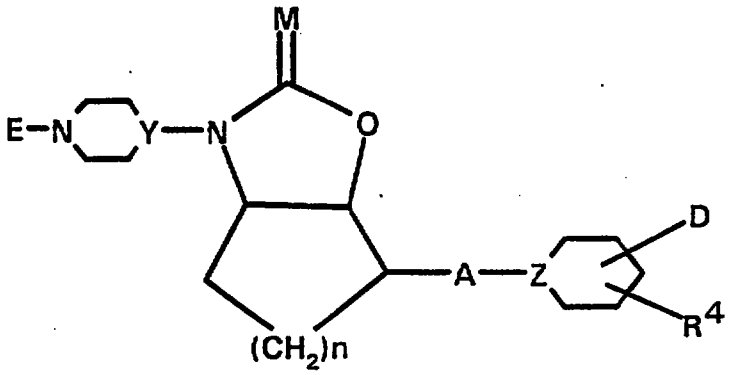
New oxazolidine derivatives, processes for their production and pharmaceutical agents containing these compounds

It is known that compounds which carry a basic and an acidic group are able to inhibit blood platelet aggregation when there is a very particular distance between the basic and acidic group (Drugs of the Future 19(2):135-159 (1994). Compounds with an anti-aggregatory effect on blood platelets are described in the patent documents WO 93/14077, EP-A-0 537-980, EP-A-0 542 363, WO 94/22834, WO 94/22835 and EP 0623615A1.

The present invention concerns new oxazolidine derivatives, processes for their production as well as pharmaceutical agents containing these substances.

It has now been found that oxazolidine derivatives effectively inhibit the aggregation of blood platelets and can thus be used to treat diseases which can be attributed to thromboembolic events such as stroke, myocardial infarction or occlusive arterial diseases as well as inflammations, osteoporosis or tumour diseases.

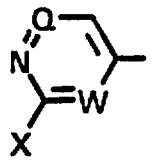
The present invention concerns compounds of the general formula I



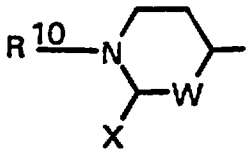
(I)

in which

E denotes a residue of formula (a) or (b)



(a)



(b)

M denotes oxygen, sulphur or NR^{00},

X denotes hydrogen or NR^1R^2,

W denotes nitrogen or NH or CH or CH_2,

Q denotes nitrogen or CH,

Y denotes nitrogen or CH,

Z denotes nitrogen, CH or C-OH,

A denotes an alkylene chain $-(CH_2)p-$ which is optionally substituted,

D denotes a side chain of the form $-(CHR^3)_m-COO-R^8$ or $=CR^3-COO-R^8$,

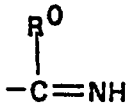
n denotes 1-3,

m denotes 0 or 1

p denotes 0-3

R^1, R^2 denote independently of one another hydrogen, lower alkyl, aryl, arylalkyl, hetaryl, acyl or an optionally substituted carbocyclic or heterocyclic ring or, together with the nitrogen to which they are bound, form an optionally substituted five-membered or six-

membered ring which can contain a further 1 to 3 heteroatoms, or denote a group (c)



(c)

R^3 denotes hydrogen or a group $-OR^5$ or $-NR^6R^7$

R^4 denotes hydrogen, lower alkyl, aryl, arylalkyl, hetaryl or a group $-OR^5$,

R^5 denotes hydrogen, lower alkyl, aryl or arylalkyl,

R^6 denotes hydrogen, lower alkyl or arylalkyl,

R^7 denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl or arylsulfonyl,

R^8 denotes hydrogen, methyl, ethyl, isopropyl, tert.-butyl, phenyl or benzyl, in particular hydrogen, ethyl, phenyl or isopropyl,

R^{10} denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl, arylsulfonyl or a group (c),

R^0 denotes hydrogen, lower alkyl, arylalkyl or a group $-NHR^{00}$,

R^{00} denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl or arylsulfonyl,

as well as their pharmacologically acceptable salts.

Lower alkyl should in all cases represent a straight-chained or branched C_1-C_6 alkyl group such as e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl in particular methyl, ethyl, propyl, isobutyl and pentyl.

Aryl usually denotes a phenyl residue optionally substituted once or several-fold.

Hetaryl usually denotes an unsubstituted or once or several-fold substituted pyridyl, pyrimidyl, piperazyl, imidazolyl, pyrrolyl, furyl or thiophenyl residue preferably a pyridyl, pyrimidyl, indolyl or imidazolyl residue.

Arylalkyl usually denotes an unsubstituted or a once or several-fold substituted benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue preferably a benzyl, phenethyl or phenylpentyl residue. C_1-C_6 alkyl residues, preferably methyl, ethyl or isopropyl as well as chlorine, bromine, fluorine or hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups come into consideration as substituents.

Acyl usually denotes a formyl, acetyl, propionyl, butyryl or benzoyl residue in particular an acetyl or benzoyl residue.

Alkylsulfonyl usually denotes a methanesulfonyl, ethanesulfonyl, propanesulfonyl or butanesulfonyl residue, in particular a butanesulfonyl residue.

Arylsulfonyl usually denotes a benzenesulfonic acid or toluenesulfonic acid residue.

A carbocyclic ring usually denotes a saturated or unsaturated 5-6-membered ring optionally substituted once or twice by lower alkyl such as a cyclopentyl, cyclohexyl, cyclopentenyl or cyclohexenyl ring.

A heterocyclic ring usually denotes a saturated or unsaturated 5-6-membered ring optionally substituted once or twice by lower alkyl such as a pyrolidine, piperidine, piperazine, morpholine, tetrahydropyrimidine, dihydropyridine or dihydroimidazole ring preferably a piperidine or tetrahydropyrimidine ring.

In the case that the residues R^1 and R^2 together with the nitrogen to which they are bound form a five-membered or six-membered ring this is a saturated or unsaturated 5-6-membered ring optionally substituted once or twice by lower alkyl such as a pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyrimidine, dihydropyridine or dihydroimidazole ring preferably a piperidine, pyrrolidine or tetrahydropyrimidine ring.

The heterocyclic ring of formula (a) usually represents a pyridine, pyridazine or pyrimidine ring in particular a pyridine or pyrimidine ring.

A heterocyclic ring of formula (b) usually represents a piperidine or hexahydropyrimidine ring in particular a piperidine ring.

Compounds of the general formula I contain at least one asymmetric carbon atom and therefore optically active compounds of the general formula I are also a subject matter of the present application. Conformation isomers

of compounds of the general formula I which may occur are an additional subject matter of the present application.

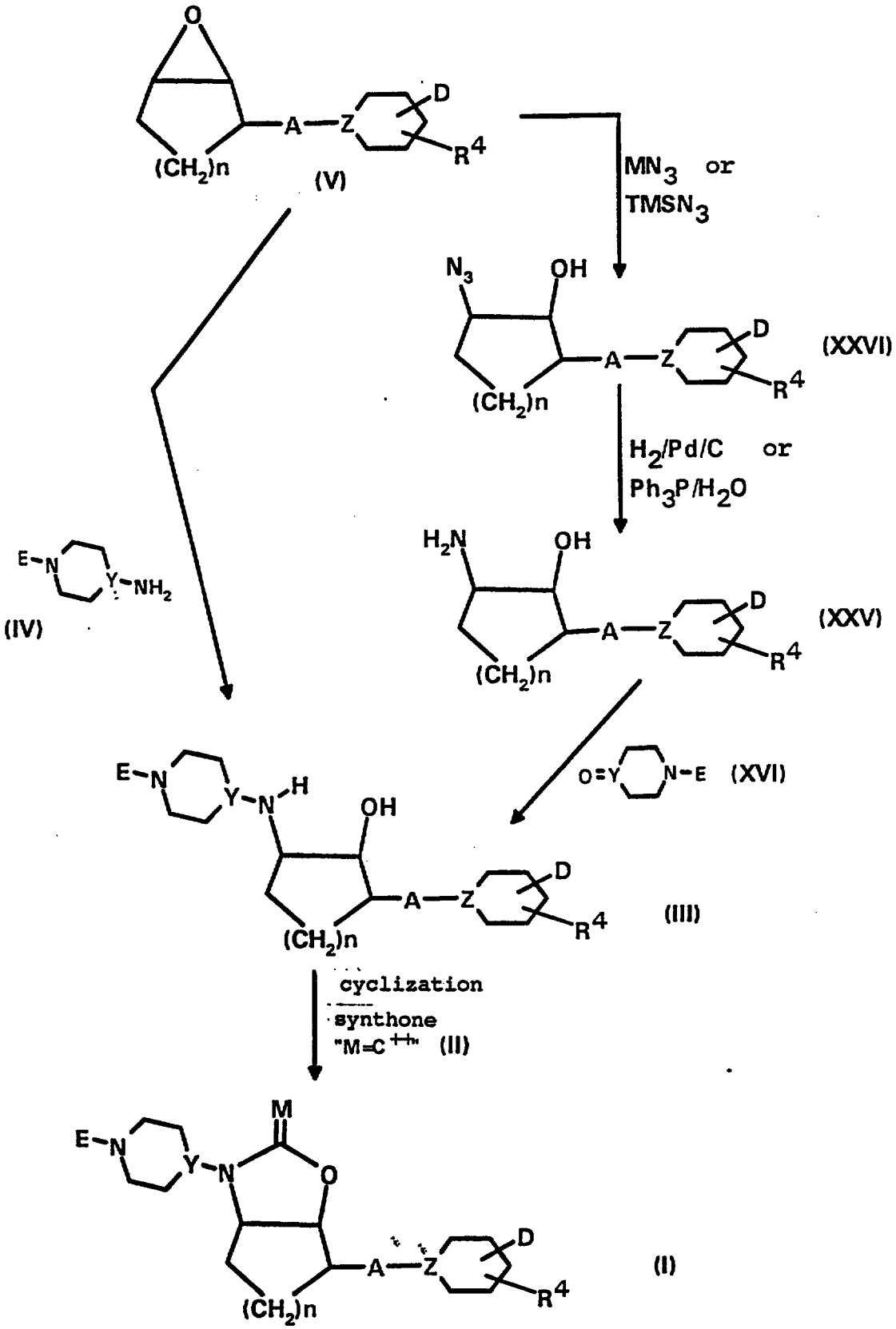
Preferred compounds are compounds of formula I in which n=1-2, p=0-1 and E, D, Y, Z and R^4 have the given meanings.

Compounds of formula I are particularly preferred in which D denotes a group $-COOR^5$, n=2, p=0, and Y=CH, Z denotes nitrogen, M denotes oxygen and E denotes a substituted or unsubstituted pyridine, pyrimidine or piperidine ring.

Compounds of the general formula I in which R^8 denotes hydrogen are produced by known processes by hydrolysing an ester of the general formula I in which $R^8 \neq H$.

Compounds of the general formula I in which $R^8 \neq H$ can be produced according to the reaction path outlined in scheme 1.

Scheme 1

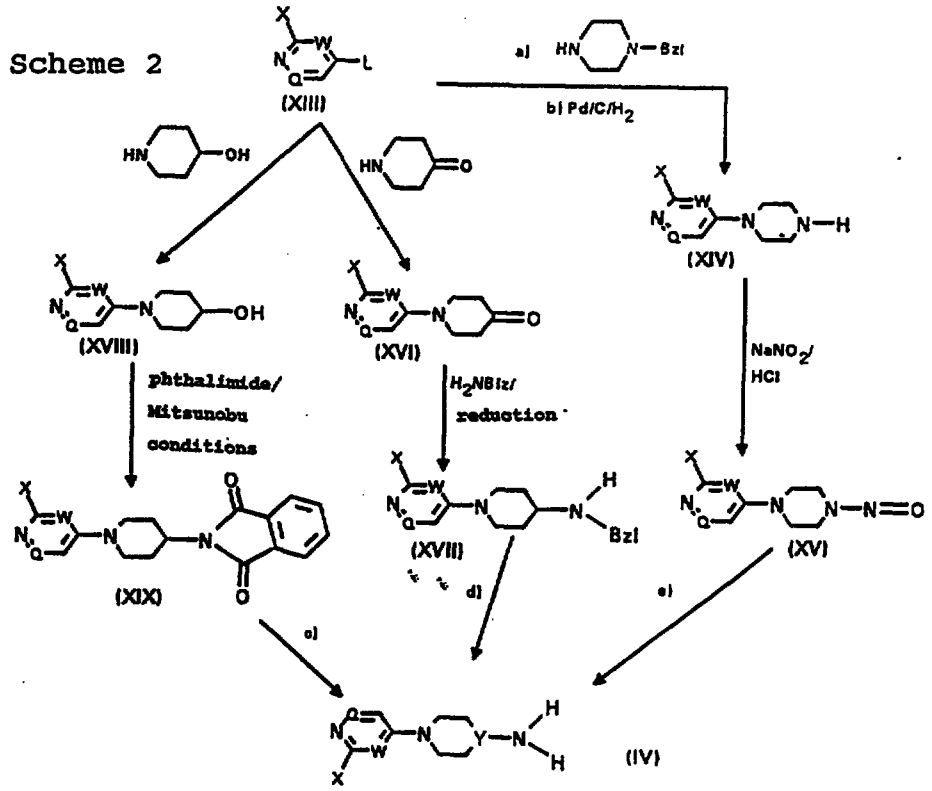

O
A
Z
D
R4
(CH2)n
(V)
MN3 or
TMSN3
N3
OH
(XXVI)
H2/Pd/C or
Ph3P/H2O
H2N
(XXV)
E-N
Y-NH2
(IV)
O=Y
N-E
(XVI)
H
(III)
cyclization
synthone
"M=C"
(II)
M
(I)

Scheme 1

In scheme 1 R^4, A, D, E, M, Y, Z and n have the above-mentioned meanings. As a rule cyclization synthone "M=C^{++}" denotes phosgene, diphosgene, triphosgene, carbonyl-diimidazole, carbonic acid dimethyldiethyl or diphenyl ester, chloroformic acid methyl or ethyl ester, thiophosgene, thiocarbonyldiimidazole, carbon disulphide, alkylisonitrile, N,N-dimethylformamide, bromocyanogen or chlorocyanogen, (N-acyl or N-sulfonyl)-dithiocarbamic acid dimethyl ester, dialkylcarbonyl diimide, 1-amidino-3,5-pyrazole-nitrate in particular carbonyldiimidazole, carbonic acid diethyl ester, chloroformic acid ethyl ester, thiocarbonyl diimidazole or bromocyanogen. MN_3 denotes a metal azide such as lithium, sodium, potassium, tributyltin or magnesium azide in particular lithium or sodium azide. $TMSN_3$ is an abbreviation for trimethylsilylazide.

Compounds of the general formula IV in which E denotes the formula (a) can be produced according to the reaction paths outlined in scheme 2.

Scheme 2



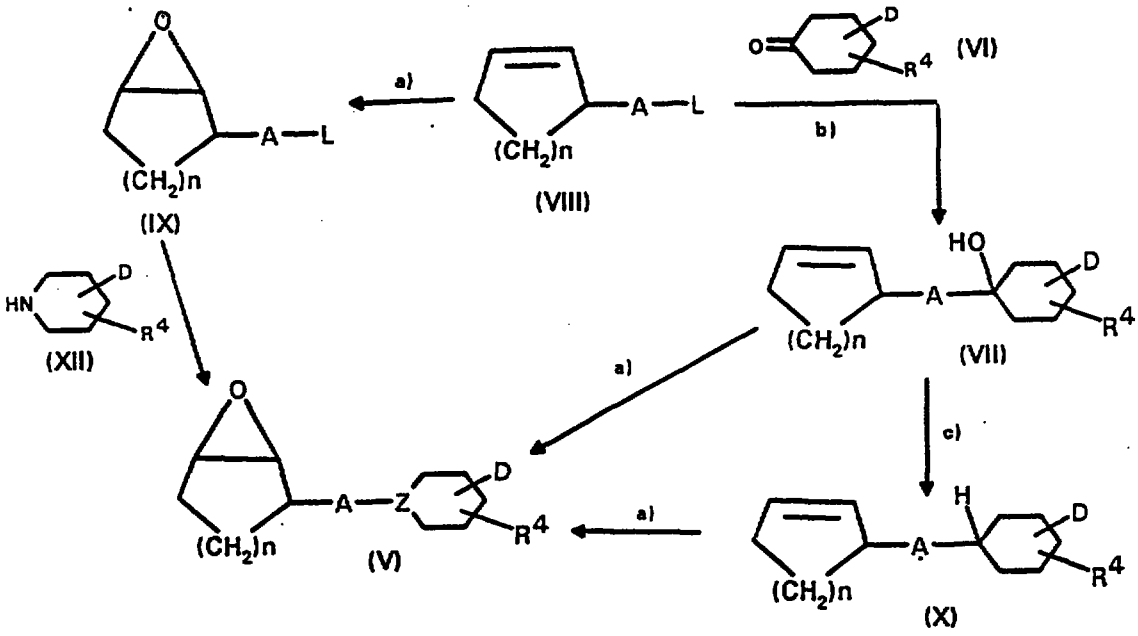
c) hydrolysis of the phthalimide; d) hydrogenation of the benzyl groups; e) reduction of the nitroso group

Scheme 2

In scheme 2 X, Q, W and Y have the above-mentioned meanings; as a rule L denotes a leaving group such as chlorine, bromine, iodine, mesylate, triflate or tosylate, in particular chlorine or tosylate.

Compounds of the general formula IV in which E denotes the formula (b) can be produced by ring hydrogenation of compounds of formula XVI or XVIII.

Compounds of the general formula V can be prepared by the reaction paths outlined in scheme 3.

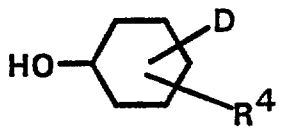


a) epoxidation; b) metallo-organic reaction; c) dehydroxylation

Scheme 3

In scheme 3 R^4, A, D, L and n have the above-mentioned meanings.

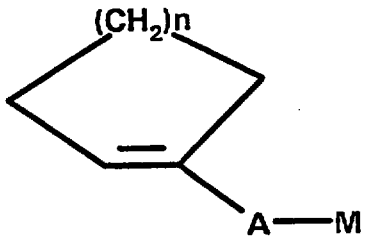
Some of the compounds of the general formula VI are commercially available and can be obtained in special cases by oxidizing an alcohol of the general formula XI



(XI)

in which D and R^4 have the above-mentioned meanings.

Compounds of the general formula VII can be produced by reacting a compound of the general formula VI with a metallo-organic compound of the general formula XX prepared from a compound of the general formula VIII

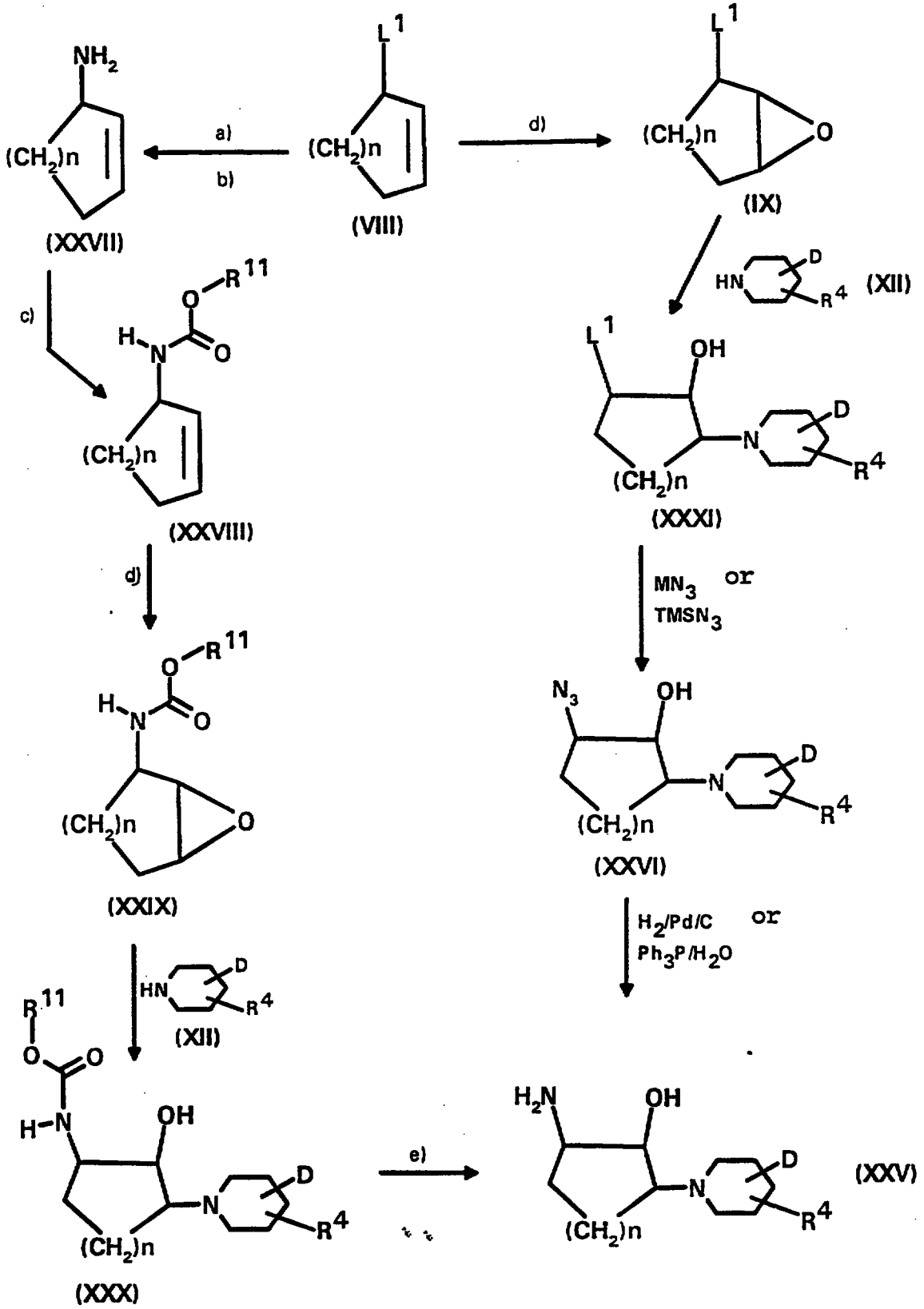


(XX)

in which A and n have the above-mentioned meanings and M denotes a metal such as lithium, magnesium or titanium.

Compounds of the general formula XXV (scheme 1) in which $R^8 \neq H$, p=0 and Z=N can also be produced by the reaction paths outlined in scheme 4.

Scheme 4



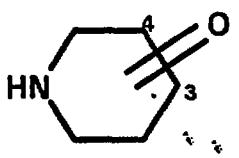
a) potassium phthalimide; b) hydrolysis; c) acylation;
d) peroxy acid; e) deacylation

Scheme 4

In scheme 4 R^4, D, MN_3, $TMSN_3$ and n have the above-mentioned meanings. As a rule L^1 denotes a hydroxyl or acetyloxy group or has one of the meanings of L. As a rule R^{11} denotes a methyl, ethyl, tert.-butyl, phenyl or benzyl residue in particular a tert.-butyl or benzyl residue.

In the case of the compounds of the general formula VIII these are commercially available cycloalkenyl halogenides or alcohols if p=0. If p>0 compounds of the formula VIII are known in the literature or can be produced according to processes described there (Brinker U.H., Tetrahedron Lett., **1991**, 4461-4464; Atkinson P.H., J. Chem. Soc. Perkin Trans 1, **1977**, 230-238; Müller E., Chem. Ber. **108**, 1401-1412 (1975); Walton J.C., J. Chem. Soc. Perkin Trans 2, **1986**, 1641-1646; Balme G., Tetrahedron **48**, 3891-3902 (1992); Fieser et al., J. Amer. Chem. Soc., **70**, 3174-3196 (1948); Lee G.M., J. Oerg. Chem., **55**, 1281-1285 (1990)).

Compounds of the general formula XII are as a rule commercially available pipecolic carboxylic acid derivatives; in special cases compounds of the general formula XII can be produced by reacting a commercially available 3-piperidone or 4-piperidone of formula XXI



(XXI)

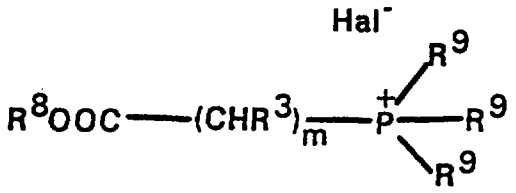
with a commercially available acetic acid ester of the

general formula XXII,



(XXII)

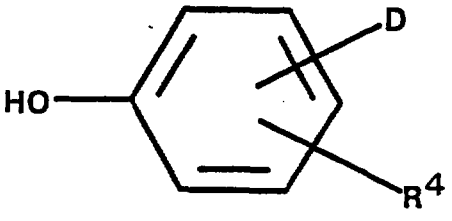
in which R^3 and R^8 have the above-mentioned meanings or with a Wittig reagent of the general formula XXIII



(XXIII)

in which R^3, R^8 and m have the above-mentioned meanings, R^9 denotes butyl, phenyl or p-tolyl and Hal^- denotes chloride, bromide or iodide.

Some of the compounds of the general formula XI are commercially available and can in special cases be obtained according to known methods by ring hydrogenation of an arylcarboxylic acid of the general formula XXIV



(XXIV)

in which R^4 and D have the meanings stated above.

Compounds of the general formula XX can be synthesized in situ according to general methods for the production of metallo-organic compounds.

Some Wittig reagents of the formula XXIII are commercially available and can be prepared from the corresponding commercial halogen compounds and triphosphines.

Hydrolysis of an ester of the general formula I to form the corresponding carboxylic acid of the general formula I is usually carried out according to standard methods in which a carboxylic acid ester of the general formula I in water or in a mixture of water, tetrahydrofuran, dioxane, methanol or ethanol preferably in a water/tetrahydrofuran mixture is treated at temperatures between room temperature and 80°C, preferably at room temperature with a hydroxide such as sodium, potassium or lithium hydroxide preferably sodium or lithium hydroxide or with an acid such as hydrochloric acid, sulphuric acid or trifluoroacetic acid preferably trifluoroacetic acid.

As a rule the reaction of a compound of the general formula XIII with 1-benzylpiperazine or 4-hydroxy-piperidine or 4-oxopiperidine (scheme 2) or the reaction of a compound of formula IX with a compound of formula XII (scheme 3) is carried out in an aprotic solvent such as toluene, tetrahydrofuran, diethyl ether, dimethylformamide or methylene chloride preferably dimethyl formamide or tetrahydrofuran using a base such as potassium hydride, sodium hydride, potassium carbonate or sodium hydrogen carbonate preferably sodium hydride or potassium carbonate and at temperature

between room temperatures and 180°C preferably at 120°C or room temperature.

The reaction between the 3-piperidone or 4-piperidone of formula XXI and an ester of formula XXII usually takes place under the conditions of an aldol reaction in a solvent such methanol, ethanol, toluene, tetrahydrofuran, diethyl ether or dimethylformamide, preferably tetrahydrofuran or dimethylformamide using a base such as sodium methylate or potassium methylate or potassium ethylate, sodium hydride, potassium hydride, lithium diisopropylamide, potassium hexamethyldisilazide preferably sodium hydride or lithium diisopropylamide and at temperatures between -78°C and 90°C preferably, however, at -78°C and room temperature.

The benzyl protecting groups are removed if necessary by catalytic hydrogenation such as e.g. by palladium/carbon/hydrogen.

The Mitsunobu reaction between a compound of formula XVIII and phthalimide is carried out according to methods known in the literature (Mitsunobu O., Synthesis, page 1 (1981)).

The reductive amination of a ketone of formula XVI with dibenzylamine or an amine of formula XXV is carried out according to methods known in the literature by reacting the ketone and amine component in a solvent such as methanol or ethanol in the presence of a reducing agent such as sodium cyanoborohydride or sodium triacetate borohydride with addition of a Brönsted or Lewis acid such as hydrochloric acid, acetic acid, titanium tetrachloride or titanium tetraisopropylate and at a

temperature between 0°C and 100°C preferably at room temperature or in the presence of a hydrogenation catalyst such as platinum dioxide and a hydrogen atmosphere (Borch R.F., Org. Synth. Coll. Vol. 6, 499 (1988); Heinzelman R.V.Z. Chem. 8, 270 (1968); Mattson R.J., J. Org. Chem. 55, 2552 (1990); Barney C.L. Tetr. Letters 31, 5547 (1990); Hutchins R.O., J. Org. Chem. 46, 3571 (1981)).

The nitrosation of a compound of the general formula XIV to form a compound of formula XV is usually carried out with sodium nitrite or isoamyl nitrite in water or ethanol with addition of an acid such as hydrochloric acid or acetic acid and at a temperature between -20°C and 80°C preferably at room temperature.

A nitroso compound of the general formula XV is reduced according to known methods by reacting a compound of formula XV in a solvent such as water, acetic acid, ethanol, tetrahydrofuran or diethyl ether preferably acetic acid or tetrahydrofuran with a reducing agent such as elemental zinc, lithium aluminium hydride or sodium aluminium hydride preferably elemental zinc or lithium aluminium hydride and at a temperature between room temperature and 120°C preferably, however, at 70°C. A compound of the general formula XV can also be converted into a compound of formula IV by a hydrogenolytic process using a catalyst such as palladium/carbon (Hatt, H.H., Org. Synth. Coll. Vol. 2, 211 (1943); Schüler F.W., J. Amer. Chem. Soc. 73, 4996 (1951).

The oxidation of an alcohol of the general formula XI to form a ketone of the general formula VI is carried out

according to known methods such as the Jones oxidation (Jones E.R.H., J. Chem. Soc. 36 (1946)), the Swern oxidation (Swern D. Tetrahedron 34, 1651 (1978), the Dess-Martin oxidation (Dess D.B., Martin J. C., J. Org. Chem. 48, 4155 (1983) or using a bromo-urotropin complex as the oxidation agent (Yavari I., J. Chem. Res. (S) 274 (1994).

The Wittig reagents used are optionally produced analogously to methods known in the literature (Buddras J., "Angew. Chem." 80, 535 (1968); Bestmann H.J. "Angew. Chem. 77, 620, 651 (1965); Wittig G. Ber. Deutsch.Chem. Ges. 88, 1654 (1955)).

The Wittig reaction is carried out according to known methods by reflux heating the reactants in an aprotic solvent such as benzene, toluene or xylene preferably toluene.

As a rule the phthalimide hydrolysis is carried out according to known methods by treating the phthalimide with hydrazine hydrate or a semi-concentrated mineral acid such as hydrochloric acid or sulphuric acid preferably with hydrazine hydrate or hydrochloric acid at room temperature.

The acylation of amines with an acylating agent is carried out as a rule in a solvent such as methylene chloride, dimethylformamide or pyridine preferably methylene chloride or pyridine with addition of an auxiliary base such as triethylamine or 4-dimethylamino-pyridine and at a temperature between -10°C and 50°C preferably, however, at room temperature. Carboxylic acid halogenides such as acetyl chloride, propionide

bromide or benzyloxycarbonyl chloride or carboxylic acid anhydrides such as acetic anhydride or di-tert.-butyl dicarbonate come into consideration as an acylating agent but acetic anhydride, benzyloxycarbonyl chloride or di-tert.-butyl dicarbonate are preferably used.

The epoxidation of an olefin of formula VII or of formula X or of formula VIII or of formula XXVIII is carried out according to methods known in the literature by reacting them with a peracid such as m-chloroperbenzoic acid, peracetic acid or trifluoroperacetic acid preferably m-chloroperbenzoic acid in an aprotic solvent such as methylene chloride and at a temperature between -30°C and 50°C preferably at room temperature; in addition the olefins listed above can be converted into the corresponding epoxides by means of the Sharpless epoxidation (Sharpless K.B., Org. Syntheses, Vol. 63, 66 (1985)).

As a rule the metallo-organic reaction in scheme 3 is a Grignard reaction which is carried out according to methods known in the literature. However, the magnesium reagent of formula XX can optionally be converted into a lithium or titanium reagent before it is reacted with a carbonyl compound of formula VI (Reetz M.T., Chem. Ber. 118, 1421 (1985)).

The conversion of an aminoalcohol of formula III into a compound of formula I (scheme 1) is carried out according to methods known in the literature by reacting an aminoalcohol of formula III with diethylcarbonate (Evans D.A., Org. Syntheses, Vol. 68, 77 (1989)) or carbonyldiimidazole (Chadwick D.I., J. Chem. Soc. Perkin Trans 481 (1984); Geffken D. Arch. Pharm. 313, 817

(1980)) or phosgene (Newman W.S., J. Am. Chem. Soc. 73, 4199 (1951)) or diphosgene or triphosgene (Hassner A., Synth. Commun. 23, 2839 (1993)) or chloroformic acid methyl, ethyl or benzyl ester (Kanoshinzo, J. Org. Chem. 53, 3865 (1988)) or thiophosgene (Dubey S.K., Can. J. Chem., 61 565, (1983)) or thiocarbonyldiimidazole (Goering B.K., Tetrahedron Lett. 35 (38), 6997, (1994)) or carbon disulphide (Zinner H., J. Prakt. Chem., 15, 72 (1962)) or bromocyanogen (Mousseron, Bull. Soc. Chim. Fr., 737 (1953)) or alkylisonitrile (Ito Y., J. Organomet. Chem. 131 121 (1977)) or (N-acyl or N-sulfonyl)-dithiocarbamic acid dimethyl ester (Bretschneider H., Monatsh. Chem. 103, 1377 (1972); Evers R., J. Prakt. Chem., 333, 699 (1991)) or 1-amidino-3,5-pyrazole-nitrate (Fotsch C.H., Tetrahedron Lett., 35, 2481 (1994) in a solvent such as methylene chloride, dimethylformamide, toluene, xylene, ethanol, dioxane, tetrahydrofuran, water or diethyl-ether, preferably dimethylformamide, methylene chloride, ethanol or tetrahydrofuran optionally with the addition of an auxiliary base such as triethylamine or pyridine and at a temperature between -50°C and 80°C preferably at room temperature.

The catalytic hydrogenation of a compound of formula XXIV is carried out in a solvent such as methanol or ethanol with addition of a catalyst such as ruthenium oxide, rhodium oxide or palladium/strontium carbonate preferably rhodium oxide in a hydrogen atmosphere at a pressure of 1-200 bar preferably at 200 bar and a temperature between room temperature and 200°C (Rastin R.H., I. Chem. Soc. 1855 (1949)).

The epoxide opening of an epoxide of formula V with an amine of formula IV (scheme 1) or of an epoxide of

formula IX with an amine of formula XII (scheme 4) is usually carried out in a solvent such as methanol, ethanol, dimethylformamide or toluene preferably ethanol or toluene and at a temperature between 0°C and 120°C preferably 80°C.

The epoxide opening of an epoxide of formula V (scheme 1) with a metal azide is carried out according to methods known in the literature by reacting an epoxide of formula V with a metal azide such as lithium, sodium, potassium, tributyltin or magnesium azide, preferably sodium azide, in a solvent such as methanol, ethanol, 1,4-dioxane, water, dimethylformamide, tetrahydrofuran, acetonitrile or hexamethylphosphorotriamide or in mixtures of the said solvents but preferably in methanol, dimethylformamide or 1,4-dioxane-water mixtures and at a reaction temperature between -10°C and 120°C preferably 80°C (Vanderverf C.A., J. Am. Chem.Soc. 76, 1231 (1954); Saito S., Tetrahedron Lett. 30, 4153 (1989); Hudlicky T., J.Chem.Soc. Perkin Trans. I, 2907 (1991)). As a rule an epoxide of formula V is reacted with trimethylsilyl-azide in a solvent such as methanol, tetrahydrofuran, methylene chloride, chloroform, dichloroethane or benzene, preferably tetrahydrofuran or methylene chloride, without further additives or using additives such as titanium tetraisopropylate, aluminium triisopropylate, dichlorotitanium diisopropylate or diethylaluminium fluoride, preferably titanium tetraisopropylate or aluminium triisopropylate, and at a temperature between 0°C and 100°C but preferably at room temperature (Emziane M., Synthesis, p. 541 (1988); Saito S., Tetrahedron Lett. 26, 5309 (1985); Blandy C., Tetrahedron Lett. 24, 4189 (1983); Jung M.E., J. Org. Chem., 56, 2614 (1991)).

The reaction of a compound of formula XXXI with a metal azide to form a compound of formula XXVI (scheme 4) is a nucleophilic substitution in the case that L^1 has the meaning of L which is carried out according to standard methods of organic synthesis.

The deacylation of a compound of formula XXX to form a compound of formula XXV is carried out according to standard methods in which a compound of formula XXX in water or in a mixture of water, tetrahydrofuran, dioxane, methanol or ethanol, preferably in a water/tetrahydrofuran mixture, is treated with a hydroxide such as sodium, potassium or lithium hydroxide, preferably sodium or lithium hydroxide, or with an acid such as hydrochloric acid, sulphuric acid or trifluoroacetic acid, preferably trifluoroacetic acid, or with palladium/carbon/hydrogen and at temperatures between room temperature and 80°C preferably at room temperature.

The conversion of an azide of formula XXVI into an amine of formula XXV is carried out according to known methods: Suami T., Bull.Chem.Soc. Jpn., 51, 855 (1978); (Boullanger P., Bull.Soc.Chim.Fr., p. 2149 (1973; Ackerman K., Can.J.Chem., 50, 3886 (1972); Hanessian S., Chem.Ind., p. 1296 (1965); Horner L., Liebigs Ann.Chem., 591, 117 (1955); Koziara A. Synthesis, p. 487 (1987); Vogel E., Ang.Chem. Int.Ed.Engl., 18, 962 (1979); Purwono B., Synlett, 3, 231 (1992).

Compounds of formula I contain one or several chiral centres and can therefore be present in a racemic or in an optically-active form. Racemates can be resolved mechanically or chemically by known methods into the

enantiomers. Preferably diastereomers are formed from the racemic mixture by reaction with an optically-active acid such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically-active camphorsulfonic acids such as ß-camphorsulfonic acid.

It is of course also possible to obtain optically-active compounds of formula I using the methods described above by using starting materials (e.g. those of formula V or VIII) which are already optically-active.

Within the sense of the present invention all prodrug forms of compounds of the general formula I are also claimed but especially carboxylic acid esters of the general formula I in which R^8 denotes a methyl, ethyl, n-propyl, isopropyl, butyl, phenyl or benzyl residue in particular a methyl, ethyl or benzyl residue.

Alkali salts, ammonium salts, trifluoroacetates or hydrochlorides are used above all as pharmacologically acceptable salts which are produced in the usual manner e.g. by titrating the compounds with inorganic or organic bases or acids such as e.g. sodium hydrogen carbonate or potassium hydrogen carbonate, sodium hydroxide solution, potassium hydroxide solution, aqueous ammonia or amines such as e.g. trimethylamine or triethylamine, trifluoroacetic acid or hydrochloric acid. As a rule the salts are purified by precipitation from water/acetone.

The new substances of formula I according to the invention and the salts thereof can be administered

enterally or parenterally in a liquid or solid form. All the usual forms of application come into consideration such as tablets, capsules, drageés, syrups, solutions, suspensions etc.. Water is preferably used as the injection medium which contains the usual additives such as stabilizing agents, solubilizers and buffers for injection solutions.

Such additives are e.g. tartrate and citrate buffer, ethanol, complexing agents (such as ethylenediamine tetraacetic acid and non-toxic salts thereof), high-molecular polymers (such as liquid polyethylene oxide) to regulate viscosity. Liquid carrier substances for injection solutions have to be sterile and are preferably filled into ampoules. Solid carrier substances are e.g. starch, lactose, mannitol, methyl cellulose, talcum, highly-dispersed silicic acids, higher molecular fatty acids (such as stearic acid), gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycols); preparations suitable for oral application can optionally contain flavourings and sweeteners.

The dose can depend on various factors such as manner of application, species, age and/or individual state. The daily doses to be administered are about 1-1000 mg/human preferably at 100-500 mg/human and can be taken singly or divided into several administrations.

Within the sense of the present invention the following oxazolidininone derivatives are preferred in addition to the compounds mentioned in the examples and compounds which can be derived by combining all meanings for substituents mentioned in the claims.

1) 1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid
2) 1-{2-Oxo-3-[1-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid
3) {1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-acetic acid
4) (1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidin-4-yl)-acetic acid
5) (1-{3-[1-(2-Methylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidin-4-yl)-acetic acid
6) (1-{2-Oxo-3-[1-(2-phenylamino-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-piperidin-4-yl)-acetic acid
7) 2-Methanesulfonyl amino-3-{1-[2-oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-propionic acid
8) 1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-ylmethyl]-piperidine-4-carboxylic acid
9) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-ylmethyl]-piperidine-4-carboxylic acid
10) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-ylmethyl}-piperidine-4-carboxylic acid
11) 1-{2-Oxo-3-[1-(2-piperidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-ylmethyl}-piperidine-4-carboxylic acid
12) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

13) 1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-ylmethyl}-piperidine-4-carboxylic acid

14) 4-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-ylmethyl}-cyclohexanecarboxylic acid

15) 4-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-ylmethyl}-4-hydroxy-cyclohexanecarboxylic acid

16) 4-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-cyclohexane-carboxylic acid

17) 4-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-cyclohexanecarboxylic acid

18) 4-Hydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-cyclohexanecarboxylic acid

19) 4-Hydroxy-4-{2-oxo-3-[1-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-cyclohexanecarboxylic acid

20) {1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-acetic acid

21) 2-(Butane-1-sulfonylamino)-3-{1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-propionic acid

22) 1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-ethyl}-piperidine-4-carboxylic acid

23) 1-{3-[1-(2-Methylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

24) 1-{3-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-propyl}-piperidine-4-carboxylic acid

25) 1-{3-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-propyl}-piperidine-4-carboxylic acid

26) 1-(3-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-propyl)-piperidine-4-carboxylic acid

27) 1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

28) {1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-acetic acid

29) 1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-ylmethyl]-piperidine-4-carboxylic acid

30) 4-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-cyclohexanecarboxylic acid

31) 1-{3-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-octahydro-benzooxazol-7-yl]-propyl}-piperidine-4-carboxylic acid

32) 1-[2-Oxo-3-(4-pyrimidin-4-yl-piperazin-1-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

33) 4-[2-Oxo-3-(4-pyrimidin-4-yl-piperazin-1-yl)-octahydro-benzooxazol-7-yl]-cyclohexanecarboxylic acid

34) (±)-(3'α,7'ß,7α)-1-{3-[1-(2-benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

35) 1-{2-[2-Oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-octahydro-benzooxazol-7-yl]-ethyl}-piperidine-4-carboxylic acid

36) 1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-hexahydro-cyclopentaoxazol-6-yl]-piperidine-4-carboxylic acid

37) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-hexahydro-cyclopentaoxazol-6-yl]-piperidine-4-carboxylic acid

38) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-hexahydro-cyclopentaoxazol-6-yl}-piperidine-4-carboxylic acid

39) (1-{2-Oxo-3-[1-(2-phenylamino-pyrimidin-4-yl)-piperidin-4-yl]-hexahydro-cyclopentaoxazol-6-yl}-piperidin-4-yl)-acetic acid

40) 1-{2-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-hexahydro-cyclopentaoxazol-6-yl]-ethyl}-piperidine-4-carboxylic acid

41) 1-[2-Oxo-3-(1-pyridazin-4-yl-piperidin-4-yl)-hexahydro-cyclopentaoxazol-6-yl]-piperidine-4-carboxylic acid

42) 1-[2-Oxo-3-(4-pyridin-4-yl-piperazin-1-yl)-hexahydro-cyclopentaoxazol-6-yl]-piperidine-4-carboxylic acid

43) 4-Hydroxy-4-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-hexahydro-cyclopentaoxazol-6-yl]-cyclohexanecarboxylic acid

44) 1-[2-Oxo-3-(1-pyrimidin-4-yl-piperidin-4-yl)-octahydro-cycloheptaoxazol-8-yl]-piperidine-4-carboxylic acid

45) 1-{2-Oxo-3-[1-(2-phenylamino-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

46) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-cycloheptaoxazol-8-yl]-piperidine-4-carboxylic acid

47) 1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-cycloheptaoxazol-8-yl}-piperidine-4-carboxylic acid

48) (1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-cycloheptaoxazol-8-yl}-piperidin-4-yl)-acetic acid

49) 1-{2-Oxo-3-[1-(2-piperidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-cycloheptaoxazol-8-ylmethyl}-piperidine-4-carboxylic acid

50) 1-(2-Oxo-3-{1-[2-(pyridin-4-ylamino)-pyrimidin-4-yl]-piperidin-4-yl}-octahydro-benzooxazol-7-yl)-piperidine-4-carboxylic acid

51) 1-(2-Oxo-3-{1-[2-(pyrimidin-2-ylamino)-pyrimidin-4-yl]-piperidin-4-yl}-octahydro-benzooxazol-7-yl)-piperidine-4-carboxylic acid

52) 1-(2-Oxo-3-{1-[2-(1,4,5,6-tetrahydro-pyrimidin-2-ylamino)-pyrimidin-4-yl]-piperidin-4-yl}-octahydro-benzooxazol-7-yl)-piperidine-4-carboxylic acid

53) 1-{3-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

54) 1-{3-[1-(2-Pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-2-thioxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

55) 1-{2-Oxo-3-[1-(2-pyrrolidin-1-yl-hexahydro-pyrimidine-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

56) 1-{2-Oxo-3-[1-(2-pyrrolidin-1-yl-1,4,5,6-tetrahydro-pyrimidin-4-yl)-piperidin-4-yl]-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid

57) 1-[3-(1'-Benzyl-[1,4']bipiperidinyl-4-yl)-2-thioxo-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

58) 1-[2-Acetylimino-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

59) 1-[2-Imino-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

60) 4-(1*H*-Indol-3-ylmethyl)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

61) 4-Butyl-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

62) 1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-4-phenethyl-piperidine-4-carboxylic acid

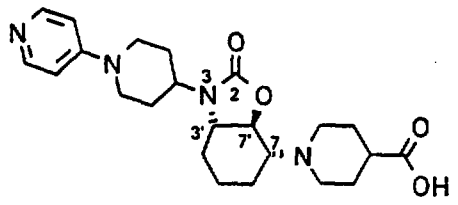
63) (-)-(3'S,7'S,7R)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid $[\alpha]^{20}_D$=-17.4°(c=1.18; $CHCl_3$)

64) (+)-(3'R,7'R,7S)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid $[\alpha]^{20}_D$=+18.7°(c=1.2; $CHCl_3$)

The following examples show some of the variants of the process that can be used to synthesize the compounds according to the invention. However, they are not intended to represent a limitation of the subject matter of the invention. The structure of the compounds was confirmed by ^1H and optionally by ^{13}C-NMR spectroscopy as well as by mass spectrometry. The purity of the substances was determined by means of C, H, N as well as thin layer chromatography.

Example 1

(±)-(3'α,7'β,7α)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid



a) A solution of 46 g (0.4 mol) 4-chloropyridine and 123.5 g (0.86 mol) 4-piperidone-ethylene ketal is heated in 400 ml p-xylene for 48 h under reflux. Subsequently the reaction mixture is cooled, the precipitated precipitate is removed by filtration, the mother liquor is concentrated to dryness and the residue is purified by column chromatography on silica gel (ethyl acetate/saturated ammonia-alkaline methanol 9/1). In this way 79.7 g (90 %) 8-pyridin-4-yl-1,4-dioxa-8-aza-spiro-[4.5]decane is obtained as a white powder. m/e=220; F_p=65°C.

b) A solution of 79.7 g of the ketal produced in a) in 2 l tetrahydrofuran is admixed with 1 l 6 N hydrochloric acid and the reaction mixture is stirred for 2 h at room temperature. Subsequently the tetrahydrofuran is removed in a vacuum on a rotary evaporator, the hydrochloric acid solution is alkalysed with semi-concentrated ammonium hydroxide solution and extracted four times with 100 ml methylene chloride each time. After drying

the combined organic extracts over sodium sulfate and removing the solvent, the residue is purified by column chromatography on silica gel. In this way 64.2 g (100 % yield) 2,3,5,6-tetrahydro-[1,4']bipyridinyl-4-one is obtained as a grey powder. m/e=176; Fp=102°C.

c) A solution of 41.6 g cis-2,3-epoxycyclohexanol (Svante T., J. Org. Chem., 38, 1380 (1973)) and 54 g imidazole in 650 ml dimethylformamide (DMF) is admixed at 0°C with 67.7 g tert.-butyl dimethyl-chlorosilane. Afterwards the reaction mixture is stirred for a further 4 hours at 0°C, it is then admixed with 600 ml water and the aqueous solution is extracted four times with 100 ml ethyl acetate. After drying the combined organic phases over sodium sulfate and removing the solvent under reduced pressure, the residue is distilled in a vacuum. 50 g cis-1-tert.-butyl-dimethyl-silyloxy-2,3-epoxycyclohexane is obtained. $bp_{0.05}$=74°C. ^{1}H-NMR ($CDCl_3$):δ = 3.90 ppm (m, 1H); 3.10 (broad s, 1H); 3.0 (broad s, 1H); 1.65 (m, 2H); 1.40 (m, 3H); 1.15 (m, 1H); 1.82 (s, 9H); 0.01 (s, 6H).

d) A mixture of 20 g epoxide 1c) and 34 ml 4-piperidine carboxylic acid ethyl ester in 160 ml ethanol is heated for 48 hours under reflux. Subsequently the reaction mixture is evaporated to dryness and the residue is purified by column chromatography on silica gel (ethyl acetate/ isohexane=1/2). 22.2 g (±)-(1α,2β,3β)-1-[3-(tert-butyl-dimethylsilanyloxy)-2-hydroxy-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained as a white powder. m/e=385.

e) A solution of 18.7 g of the alcohol 1d) and 12 ml triethylamine in 200 ml methylene chloride is admixed at 5-10°C internal temperature with 5.4 ml methanesulfonic acid chloride. The reaction mixture is allowed to stir for one hour at room temperature, subsequently 50 ml saturated sodium hydrogen carbonate solution is added, the phases are separated, the organic phase is washed with 100 ml water and dried over sodium sulfate. After removing the solvent on a rotary evaporator, the residue is purified by column chromatography on silica gel (ethyl acetate/isohexane=1/3). 21 g (±)-(1α,2β,3β)-1-[3-(*tert.*-butyl-dimethylsilanyloxy)-2-methanesulfonyloxy-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained as a light-yellow oil. ^{1}H-NMR (d^6-DMSO):δ=4.45 ppm (d, 1H); 4.20 (broad s, 1H); 3.95 (q, 2H); 3.10 (s, 3H); 2.88-263 (m, 2H); 2.50 (m, 1H); 2.20-2.00 (m, 2H); 1.75-1.62 (m, 1H); 1.58-1.18 (m, 7H); 1.10 (t, 3H); 0.80 (s, 9H); 0.01 (s, 6H).

f) A solution of 21 g of the silyl derivative 1e) in 200 ml tetrahydrofuran is admixed with 63 ml of a 1.1 molar tetrabutylammonium fluoride solution in tetrahydrofuran. The reaction mixture is allowed to stir for 30 hours at room temperature, then concentrated to dryness and the residue is chromatographed on silica gel (ethyl acetate/isohexane=95/5). 6.3 g (±)-(1α,2β,3β)-1-(3-hydroxy-2-methanesulfonyloxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained as a white powder. m/e=349.

g) A mixture of 5.48 g of the hydroxymesylate 1f) and 550 mg sodium hydride is stirred for one hour at

5°C in 200 ml tetrahydrofuran (THF) and after subsequent addition of 50 ml water it is stirred for 15 hours at 50°C. Afterwards the THF is removed on a rotary evaporator and the aqueous mixture is extracted three times with 30 ml methylene chloride each time. After drying the combined organic phases over sodium sulfate and removing the solvent in a vacuum 3.9 g (±)-trans-1-(2,3-epoxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained as a yellow oil which is reacted further without additional purification.

h) A solution of 3.4 g of the epoxide produced under 1g), 5.3 g sodium azide and 4.3 g ammonium chloride is heated for 24 hours at 70°C in 50 ml of an ethanol/water mixture (80/20). Subsequently the ethanol is removed in a vacuum, the residue is diluted with 10 ml water and the aqueous solution is extracted three times with 15 ml methylene chloride each time. After drying the combined organic phases over sodium sulfate and removing the solvent on a rotary evaporator the crude product is chromatographed on silica gel (ethyl acetate/ isohexane: 4/1). In this way 2.74 g (±)-(1α,2β,3α)-1-(3-azido-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained as an orange-coloured oil, which slowly solidifies. ^{1}H-NMR (d^6-DMSO): δ=4.53 ppm (broad s, 1H, OH); 4.05 (q, 2H); 3.30 (broad d, 2H); 2.80 (quasi d, 1H); 2.65 (quasi d, 1H); 2.50 (m, 1H); 2.25 (m, 3H); 1.90-1.40 (m, 7H); 1.30-1.02 (m+t, 6H).

i) A solution of the azide produced in 1h) in 20 ml ethanol is admixed with 0.8 g 10 % palladium/carbon and the mixture is hydrogenated for 6 h/40 mbar at

room temperature. Subsequently the catalyst is removed by filtration and the solution is concentrated on a rotary evaporator. In this way 2.4 g (±)-(1α,2β,3α)-1-(3-amino-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ester is obtained. FAB 271.

j) A solution of 2.4 g amine 1i), 1.6 g ketone 1b) and 3.75 g sodium triacetate borohydride in 40 ml methylene chloride is stirred for 48 h at room temperature. Subsequently the reaction mixture is admixed with 10 ml water and acidified with 1 N hydrochloric acid. After separating the phases the aqueous acidic phase is again extracted with 10 ml methylene chloride and then alkalized with 1 N sodium hydroxide solution. After extracting the alkaline mixture three times with 15 ml methylene chloride each time and drying the combined organic phases over sodium sulfate, the solvent is removed on a rotary evaporator. The crude product is then purified by means of preparative HPLC (RP 18, methanol/buffer (pH=7.5) 70/30). In this way 2.5 g (±)-(1α,2β,3α)-1-[2-hydroxy-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylamino)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained. ^{1}H-NMR (d^6-DMSO): δ=8.20 ppm (d, 2H); 6.85 (d, 2H); 4.15 (m, 1H); 4.12 (q, 2H); 3.85 (broad d, 2H); 3.10 (t, 1H); 3.0-2.8 (m, 4H); 2.70 (d, 1H); 2.55 (m, 2H); 2.30 (broad t, 3H); 2.0 (d, 1H); 1.88 (m, 4H); 1.80-1.50 (m, 5H); 1.38-0.88 (m, 5H); 1.25 (t, 3H).

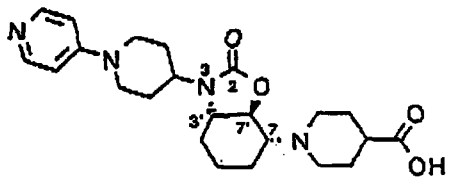
k) A solution of 2.5 g of the aminoalcohol from 1j) and 1.9 g carbonyldiimidazole in 20 ml dimethyl-formamide is stirred for 15 h at room temperature.

Subsequently the reaction solution is evaporated to dryness and the residue is purified by means of preparative HPLC (Merck, Select B, methanol/buffer (pH=7.5) 65/35). In this way one obtains 2.78 g (±)-(3'α,7'ß,7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid ethyl ester as a yellow oil. m/e=456.

l) A solution of 1.85 g of the ethyl ester 1k) and 4.60 ml 1 N sodium hydroxide solution in 30 ml methanol is stirred for 1 h at room temperature. Subsequently the methanol is removed in a vacuum and the product is purified by means of an ion exchanger (Dowex 50, H form). In this way 0.95 g of the title compound is obtained as a white powder Fp.> 200°C. m/e (EI spectrum)=500 (measured as a trimethylsilyl derivative).

Example 1a

(-)-(3'S,7'S,7R)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid



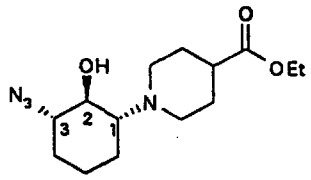
After carrying out reaction steps 2a)-2c) substitution of the racemic cis-2,3-epoxycyclohexanol in example 2a)

by (1R,2R,3S)-1-hydroxy-2,3-epoxycyclohexane yields the optically active compound (1S,2S,3R)-1-azido-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester ($[a]_D^{20}$=-41.4°C (C1.2; $CHCl_3$)) from which the title compound is obtained analogously to example 1i)-1l). $[a]_D$= -17.4° (C1.18; $CHCl_3$).

(1R,2R,3S)-1-hydroxy-2,3-epoxycyclohexane is obtainable according to Svante T. (J. Org. Chem. 38, 1380 (1973)) by epoxidizing (R)-cyclohex-2-enol known in the literature (Fukazawa et al., Tetrahydron Asymmetry 4, 2323 (1993)) by means of meta-chloroperbenzoic acid.

Example 2

Additional process for the production of (±)-(1α,2β,3α)-1-(3-azido-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester 1h)



a) A solution of 119.65 g cis-2,3-epoxycyclohexanol (see example 1c) and 188 ml triethylamine in 400 ml methylene chloride is admixed at 0°C with a solution of 240 g p-toluenesulfonic acid chloride in 500 ml methylene chloride. Subsequently the reaction mixture is stirred for 15 hours at room temperature, the precipitated salt is then removed by filtration and the filtrate is washed with 100 ml saturated sodium hydrogen carbonate solution. After drying the methylene chloride phase

over sodium sulfate and removing the solvent, the crude product is purified by column chromatography on silica gel (ethyl acetate/isohexane = 1/1). In this way 211 g (75 %) cis-2,3-epoxycyclohexyl-tosylate is obtained as a yellow oil, which slowly solidifies. ^{1}H-NMR ($CDCl_3$): δ = 7.85 ppm (d, 2H); 7.35 (d, 2H); 4.90 (m, 1H); 3.27 (broad s, 1H); 3.17 (broad s, 1H); 2.45 (s, 3H); 1.80 (m, 2H); 1.65 (m, 3H); 1.22 (m, 1H).

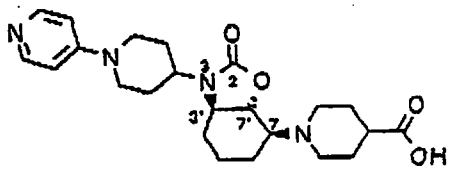
b) A mixture of 112 g epoxide 2a) and 110 ml 4-piperidine-carboxylic acid ethyl ester in 250 ml ethanol is irradiated for 2.75 hours in a microwave oven with an energy of 500 W so that the reaction temperature is 65°C. Subsequently the reaction solution is cooled to 0°C, the product is suction filtered, washed twice with 50 ml cold ethanol each time and washed three times with 50 ml diethyl ether each time and dried in a vacuum at 30°C. In this way 96 g (54 %) (1α,2ß,3ß)-1-(3-p-toluene-sulfonyloxy-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained. Fp = 135 - 137°C. m/e=425. ^{1}H-NMR ($CDCl_3$): δ = 7.75 ppm (d, 2H); 7.22 (d, 2H); 4.85 (broad s, 1H); 4.05 (q, 2H); 3.28 (d with fine resolution, 1H); 2.62 (m, 2H); 2.50 (t, 1H); 2.35 (s, 3H); 2.18 (m, 1H); 2.05 (t, 2H); 1.75 (m, 3H); 1.55 (m, 4H); 1.32 (m, 1H); 1.15 (t, 3H); 1.10 (m, 1H).

c) A mixture of 37 g tosylate 2b) and 34.3 g sodium azide in 250 ml dimethylformamide is irradiated in a microwave oven for 20 min with an energy of 500 W in such a way that the reaction temperature is 90°C. Subsequently the reaction solution is cooled to room temperature, the salt is suction filtered,

the filtrate is evaporated to dryness in a vacuum at 50°C, the residue is taken up in 50 ml water and the aqueous mixture is extracted three times with 50 ml diethyl ether each time. After drying the combined organic phases over sodium sulfate and removing the solvent, the crude product is purified by column chromatography on silica gel (ethyl acetate/ isohexane=6/4). In this way 21.8 g (84 %) of the title compound is obtained as a light grey powder. Fp.: 61-63°C. The title compound is obtainable according to this process in a better yield and higher purity than by the process of 1h).

Example 2a

(+)-(3'R,7'R,7S)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

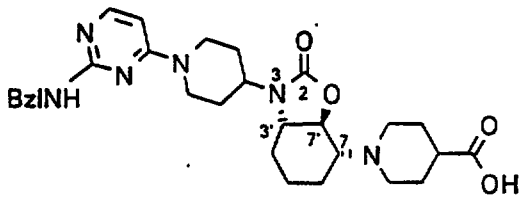


After carrying out reaction steps 2a)-2c) substitution of the racemic cis-2,3-epoxycyclohexanol in example 2a) by (1S,2S,3R)-1-hydroxy-2,3-epoxycyclohexane yields the optically active compound (1R,2R,3S)-1-azido-2-hydroxycyclohexyl)-piperidine-4-carboxylic acid ethyl ester ($[a]_D^{20}$ = +42° (C1.23; $CHCl_3$)), from which the title compound is obtained analogously to example 1i)-1l). $[a]_D$ = +18.7°(C1.2; $CHCl_3$).

(1S,2S,3R)-1-hydroxy-2,3-epoxycyclohexane is obtainable according to Svante T. (J. Org. Chem. 38, 1380 (1973)) by epoxidizing (S)-cyclohex-2-enol known in the literature (Singh V.K., et al., Synth. Commun. 24, 375 (1994)) by means of metachloroperbenzoic acid.

Example 3

(±)-(3'α,7'β,7α)-1-{3-[1-(2-Benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid



a) A solution of 16 ml (0.12 mol) 4-piperidone-ethylene ketal in 100 ml ethanol is added dropwise to a solution of 18.5 g (0.12 mol) 2,4-dichloro-pyrimidine and 17.5 ml triethylamine in 150 ml ethanol while cooling on ice. Subsequently the reaction mixture is stirred for 2.5 hours at room temperature and then it is evaporated to dryness. The residue is taken up in 50 ml water and the aqueous solution is extracted three times with 20 ml methylene chloride each time. After drying the combined organic phases over sodium sulfate and removing the solvent, the residue is recrystallized from ethyl acetate/isohexane. In this way 21.8 g 8-(2-chloro-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro-[4.5]decane is obtained as a white powder. m/e=256.

^{1}H-NMR ($CDCl_3$): δ = 7.92 ppm (d, 1H; Ar-H); 6.35 (d, 1H; Ar-H); 3.91 (s, 4H; ketal-CH_2); 3.65 (broad s, 4H); 1.68 (t, 4H).

b) A mixture of 8 g 2-chloropyrimidine 3a) and 7.2 ml benzylamine is heated for 2 hours at 150°C. Subsequently the reaction mixture is cooled to room temperature, admixed with 30 ml water, the aqueous solution is extracted three times with 20 ml methylene chloride each time, the combined extracts are dried over sodium sulfate, the solvent is removed on a rotary evaporator and the residue is crystallized from ethyl acetate. In this way 7 g 8-(2-benzylamino-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro-[4.5]decane. m/e=326. ^{1}H-NMR (d^6-DMSO): δ = 7.88 ppm (d, 1H; Ar-H); 7.32 (m, 5H; Ar-H); 7.25 (broad s, 1H; NH); 6.12 (d, 1H; Ar-H); 4.45 (d, 2H; pH-$\underline{CH_2}$-) 3.98 (s, 4H; ketal-CH_2); 3.65 (broad s, 4H); 1.72 (broad s, 4H).

c) Analogously to example 1b) 6.3 g 1-(2-benzylamino-pyrimidin-4-yl)-piperidin-4-one is obtained as a brown oil from 7 g ketal 3b) and 80 ml 6 N hydrochloric acid which is reacted further as a crude product.

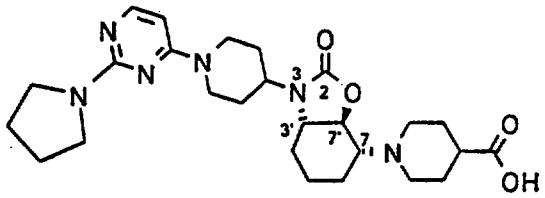
d) 0.77 g (±)-(1α,2ß,3α)-1-{2-hydroxy-3-[1-(2-benzylamino-pyrimidin-4-yl)-piperidin-4-ylamino]-cyclohexyl}-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1j) from 0.42 g amine 1i), 0.44 g ketone 3c), 0.66 g sodium triacetateborohydride and 0.3 ml 100 % acetic acid. m/e=537.

e) 0.54 g (±)-(3'α,7'β,7α)-1-{3-[1-(2-benzylamino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1k) from 0.77 g amino alcohol 3d) and 0.28 g carbonyl diimidazole. pos. FAB = 562. ^{1}H-NMR (d^6-DMSO): δ = 7.75 ppm (d, 1H); 7.20 (m, 5H); 7.12 (broad s, 1H; NH); 6.03 (d, 1H); 4.43 (d, 2H); 4.39 (broad s, 1H); 4.05 (q, 2H); 3.80 (t, 1H); 3.69 (m, 1H); 3.25 (broad t, 1H); 2.76 (m, 5H); 2.48 (m, 2H); 2.25 (m, 2H); 1.95-1.20 (m, 14H); 1.18 (t, 3H).

f) 0.065 g of the title compound is obtained analogously to example 1l) from 0.1 g ethyl ester 3e) and 0.4 ml 1 N sodium hydroxide solution. m/e=534. Fp=180°C.

Example 4

(±)-(3'α,7'β,7α)-1-{3-[1-(2-Pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid



a) A mixture of 7.7 g chloropyrimidine derivative 3a) and 25 ml pyrrolidine is irradiated in a microwave oven for 15 min with an energy of 500 W in such a way that the reaction temperature is 50°C.

Subsequently the reaction solution is evaporated to dryness, the residue is taken up in 20 ml water and the aqueous solution is extracted four times with 20 ml methylene chloride each time. After drying the combined extracts over sodium sulfate and removing the solvent, the residue is purified by means of preparative HPLC (Merck, Select B, methanol/buffer (pH=7.5) 75/25). In this way 7.8 g 8-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro-[4.5]decane is obtained. m/e=290.

b) 5.9 g 1-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-one is obtained analogously to example 1b) from 7.8 g ketal 4a) and 72 ml 6 N hydrochloric acid which is reacted further as a crude product.

c) 3.4 g (±)-(1α,2β,3α)-1-{2-hydroxy-3-[1-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-ylamino]-cyclohexyl}-piperidine-4-carboxylic acid ethyl ester is obtained as a yellow oil analogously to example 1j) from 2.46 g ketone 4b), 2.7 g amine 1i), 3.2 g sodium triacetate borohydride and 6 ml 100 % acetic acid. ^{1}H-NMR (d^6-DMSO + AcOH): δ = 7.92 ppm (d, 1H); 6.29 (d, 1H); 4.52 (broad d, 2H); 4.15 (q, 2H); 3.79 (t, 1H); 3.53 (m, 4H); 3.20 (m, 3H); 3.00 (m, 3H); 2.55 (m, 2H); 2.20-1.70 (m, 13H); 1.62-1.35 (m, 5H); 1.25 (t, 3H).

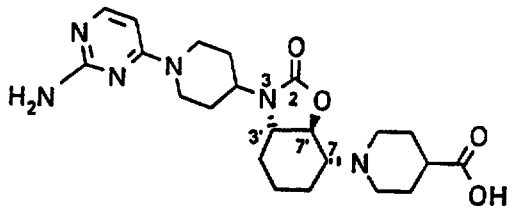
d) 2.5 g (±)-(3'α,7'β,7α)-1-{3-[1-(2-pyrrolidin-1-yl-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid ethyl ester is obtained as a light-grey powder analogously to example 1k) from 3.3 g amino-alcohol 4c) and 1.6 g carbonyldiimidazole. Fp = 140°C.

m/e=526. ^{1}H-NMR (d^6-DMSO):δ = 8.01 ppm (d, 1H); 6.21 (d, 1H); 4.62 (broad t, 2H); 4.20 (q, 2H); 3.99 (t, 1H); 3.88 (m, 1H); 3.55 (m, 5H); 2.98 (m, 5H); 2.65 (m, 1H); 2.45 (m, 2H); 2.13 (m, 1H); 2.08-1.40 (m, 18H); 1.33 (t, 3H).

e) 0.16 g of the title compound is obtained analogously to example 1l) from 0.4 g ethyl ester 4d) and 0.9 ml 1N sodium hydroxide solution. m/e=498. ^{1}H-NMR (d^6-DMSO+AcOH): δ = 7.60 ppm (d, 1H); 6.25 (d, 1H); 4.35 (broad s, 2H); 3.78 (t, 1H); 3.59 (broad t, 1H); 3.25 (m, 5H); 3.05-2.70 (m, 5H); 2.60 (broad t, 1H); 2.42 (broad t, 1H); 2.15 (m, 1H); 1.80-1.38 (m, 14H); 1.20 (m, 4H).

Example 5

(±)-(3'α,7'ß,7α)-1-{3-[1-(2-Amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid



a) A solution of 26 g chloropyrimidine 3a) and 120 ml liquid ammonia in 500 ml ethanol is kept in a 1 l autoclave for 60 hours at 5 bar and 90°C. Subsequently the reaction mixture is evaporated to dryness, the residue is taken up in 20 ml water and the aqueous solution is extracted five times with

20 ml methylene chloride each time. After drying the combined organic phases over sodium sulfate and removing the solvent the solid residue is stirred out with 40 ml ethyl acetate. In this way 5.7 g 8-(2-amino-pyrimidin-4-yl)-1,4-dioxa-8-aza-spiro-[4.5]decane is obtained as a yellow powder. m/e=236.

b) 5.5 g (2-amino-pyrimidin-4-yl)-piperidin-4-one is obtained analogously to example 1b) as a yellow solid from 6 g ketal 5a) and 65 ml 6 N hydrochloric acid. m/e=192.

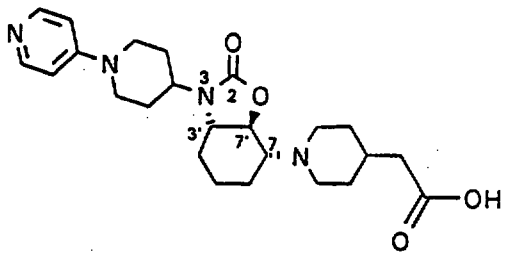
c) 1.5 g (±)-(1α,2ß,3α)-1-{2-hydroxy-3-[1-(2-amino-pyrimidin-4-yl)-piperidin-4-yl)-piperidin-4-ylamino]-cyclohexyl}-piperidine-4-carboxylic acid ethyl ester is obtained as a yellow oil analogously to example 1j) from 1 g amine 1i), 0.7 g ketone 5b), 1.6 g sodium triacetate borohydride and 0.8 ml 100 % acetic acid. m/e=446. ^{1}H-NMR (d^6-DMSO): δ = 7.80 ppm (d, 1H); 6.08 (d, 1H); 6.00 (s, 1H; NH); 4.24 (d, 2H); 4.15 (m, 4H); 3.12 (t, 1H); 2.90 (m, 4H); 2.72 (broad d, 1H); 2.60 (m, 3H); 2.30 (broad t, 3H); 1.88 (m, 5H); 1.70 (m, 5H); 1.25 (t, 3H); 1.15 (m, 3H).

d) 0.3 g ((±)-(3'α,7'ß,7α)-1-{3-[1-(2-amino-pyrimidin-4-yl)-piperidin-4-yl]-2-oxo-octahydro-benzooxazol-7-yl}-piperidine-4-carboxylic acid ethyl ester is obtained as a light-grey powder analogously to example 1k) from 1.1 g amino-alcohol 5c) and 0.5 g carbonyldiimidazole. m/e=472. Fp=120-122°C.

e) 0.07 g of the title compound is obtained analogously to example 11) from 0.11 g ethyl ester 5d) and 0.25 ml 1 N sodium hydroxide solution. m/e=444. Fp > 200°C.

Example 6

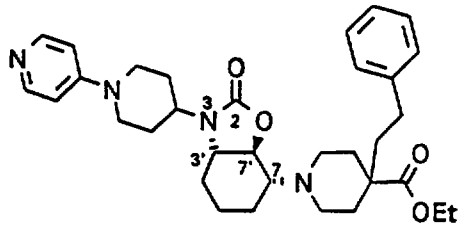
(±)-(3'α,7'β,7α)-{1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl-octahydro-benzooxazol-7-yl]-piperidin-4-yl}-acetic acid



The title compound is obtained analogously to examples 2b), 2c) and 1i)-1l) by substituting the 4-piperidine-carboxylic acid ethyl ester in example 2b) by 4-piperidineacetic acid ethyl ester. Fp=135°C (decomposition). m/e=(EI spectrum)=514 (measured as trimethylsilyl derivative).

Example 7

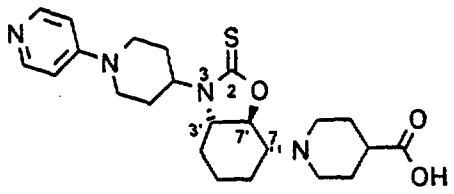
(±)-(3'α,7'β,7α)-{1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl-octahydro-benzooxazol-7-yl]-4-(2-phenylethyl}-piperidine-4-carboxylic acid ethyl ester



The title compound is obtained by substituting 4-piperidine-carboxylic acid ethyl ester in example 2b) by 4[4-(2-phenylethyl)]piperidine-carboxylic acid ethyl ester analogously to examples 2b), 2c) and 1i)-1k) (Gilligan et al., J. Med., Chem. 37, 364 (1994)). m/e=560. ^{1}H-NMR (d^6-DMSO): δ = 8.13 ppm (d, 2H); 7.25 (m, 2H); 7.15 (m, 3H); 6.80 (d, 2H); 4.12 (q, 2H); 4.01 (m, 2H); 3.80 (t, 1H); 3.70 (m, 1H); 3.60 (m, 4H); 3.28 (m, 1H); 2.80 (m, 5H); 2.45 (m, 2H); 2.32 (t, 3H); 2.05 (m, 2H); 1.95 (m, 2H); 1.70 (m, 9H); 1.35 (m, 5H); 1.20 (t, 3H).

Example 8

(±)-(3'α,7'β,7α)-{1-[2-Thiooxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

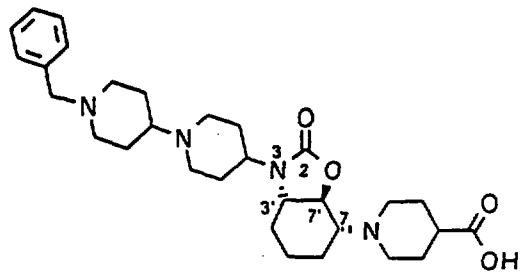


a) 0.2 g (±)-(3'α,7'β,7α)-1-[2-thiooxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1k) from 0.3 g amino-alcohol 1j) and 0.21 g thiocarbonyldiimidazole. Pos. FAB=472.

b) 0.1 g of the product was obtained analogously to example 1l) from 0.14 g ethyl ester 8a) and 0.35 ml 1 N sodium hydroxide solution from which 143 mg of the title compound was isolated as a HCl salt after addition of 0.6 ml 1 N hydrochloric acid. Pos. FAB = 472. Fp = 180°C.

Example 9

(±)-(3'α,7'β,7α)-1-[3-(1'Benzyl-[1,4']bipiperidinyl-4-yl)-2-oxo-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid



a) A mixture of 15 g pyridine derivative 1a) and 4 g ruthenium oxide is hydrogenated until hydrogen uptake is completed (30 hours). Subsequently the catalyst is removed by filtration, the filtrate is concentrated in a vacuum, the residue is taken up in 120 ml 1,4 dioxane and the solution obtained in this way is admixed with 18 ml benzyl chloride and 15 g potassium carbonate. The reaction mixture is then heated for 5 hours under reflux, afterwards it is cooled, the precipitate is removed by filtration and the filtrate is evaporated to dryness. The crude product is purified by column chromatography on silica gel (ethyl acetate + 10 % saturated ammoniacal methanol). In this way one obtains 3.4 g 8-(1-benzyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane. ^{1}H-NMR (d^6-DMSO): δ = 7.30 ppm (m, 5H); 3.85 (s, 4H); 3.45 (s, 2H); 2.84 (d, 2H); 2.52 (m, 4H); 2.25 (m, 1H); 1.88 (t, 2H); 1.63 (m, 6H); 1.42 (q with fine resolution, 2H).

b) 1.2 g 1'-benzyl-[1,4']bipiperidinyl-4-one is obtained analogously to example 1b) from 1.5 g ketal 9a) and 10 ml 6 N hydrochloric acid. m/e=272. ^{1}H-NMR (d^6-DMSO): δ = 7.35 ppm (m, 5H); 4.01 (s, 2H); 3.22 (d, 2H); 3.01 (m, 1H); 2.84 (d, 3H); 2.65 (q, 3H); 2.33 (t, 3H); 1.80 (m, 5H).

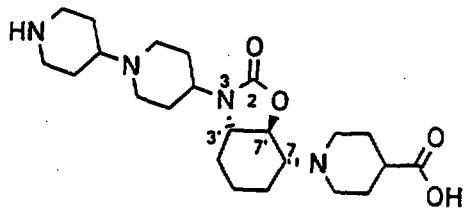
c) 1.4 g 1-[3-(1'-benzyl-[1,4']bipiperidinyl-4-ylamino)-2-hydroxy-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained as a light-grey solid analogously to example 1j) from 1.2 g amine 1i), 1.2 g ketone 9b) and 1.9 g sodium triacetate borohydride. Fp=92°C.

d) 0.51 g (±)-(3'α,7'ß,7α)-1-[3-(1'-benzyl-[1,4']bipiperidinyl-4-yl)-2-oxo-octahydro-benzooxazol-7-yl]-piperidin-4-carboxylic acid ethyl ester is obtained as a white powder analogously to example 1k) from 0.99 g amino-alcohol 9c) and 0.45 g carbonyldiimidazole. Fp=148-150°C.

e) 0.12 g of the title compound is obtained analogously to example 1l) from 0.25 g ethyl ester 9d) and 0.5 ml 1 N sodium hydroxide solution. m/e=524. ^{1}H-NMR (D_2O): δ = 7.25 ppm (m, 5H); 3.92 (t, 1H); 3.60 (s, 2H); 3.45 (m, 2H); 3.01 (d, 4H); 2.82 (m, 3H); 2.48 (t, 2H); 2.38-2.00 (m, 7H); 1.95-1.60 (m, 10H); 1.35 (m, 7H).

Example 10

(±)-(3'α,7'ß,7α)-1-(3-[1,4']Bipiperidinyl-4-yl-2-oxo-octahydro-benzooxazol-7-yl)-piperidine-4-carboxylic acid

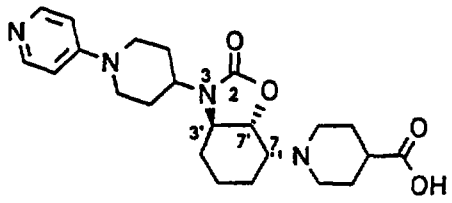


a) A mixture of 0.74 g N-benzyl derivative 9d) and 0.3 g 10 % palladium/carbon in 20 ml ethanol is hydrogenated at 50°C/4 bar until the hydrogen uptake is completed (2 hours). Afterwards the catalyst is removed by filtration and the filtrate is evaporated to dryness. In this way one obtains 0.355 g (±)-(3'α,7'ß,7α)-1-(3-[1,4']bipiperidinyl-4-yl-2-oxo-octahydro-benzooxazol-7-yl)-piperidine-4-carboxylic acid ethyl ester. Pos. FAB=524. Fp = > 200°C.

b) 0.13 g of the title compound is obtained analogously to example 11) from 0.2 g ethyl ester 10a) and 0.7 ml 1 N sodium hydroxide solution. Pos. FAB (MH^+) = 435. Fp > 200°C.

Example 11

(±)-(3'β,7'α,7α)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid



a) A mixture of 1.77 g trans-3-bromo-1,2-epoxycyclohexane (Lier E. et al., Helv. Chim. Acta, 62, 932 (1979)), 1.7 ml 4-piperidinecarboxylic acid ethyl ester and 1.8 g potassium carbonate in 30 ml dimethylformamide is stirred for 24 hours at room temperature. Subsequently the reaction mixture is admixed with 400 ml water and the aqueous solution is extracted three times with 40 ml diethyl ether each time. After drying the combined organic phases over sodium sulfate and removing the solvent, the crude product is purified by column chromatography on silica gel (ethyl acetate + 1 % saturated ammoniacal methanol). In this way 0.6 g (±)-cis-1-(2,3-epoxy-cyclohexyl)-piperidine-4-carboxylic acid ester is obtained. ^{1}H-NMR ($CDCl_3$): δ = 4.05 ppm (q, 2H); 3.20 (d, 1H); 3.05 (t, 1H); 2.98 (m, 1H); 2.82 (m, 2H); 2.40 (m, 12 lines, 2H); 2.18 (m, 1H); 1.85 (m, 2H); 1.70 (m, 6H); 1.50 (m, 1H); 1.36 (m, 1H); 1.19 (t, 3H).

b) 0.6 g (±)-(1α,2α,3β)-1-(3-azido-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained as a grey solid analogously to example 2c) from 0.6 g epoxide 11a) and 0.23 g sodium azide. m/e=296. Fp = 90°C.

c) 0.2 g (±)-(1α,2α,3β)-1-(3-amino-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1i) from 0.44 g azide 11b). Pos. FAB = 270. ^{1}H-NMR ($CDCl_3$): δ = 4.05 ppm (q, 2H); 3.60 (t, 1H); 3.15 (q, 1H); 3.00 (m, 2H); 2.50 (m, 1H); 2.28-2.00 (m, 5H); 1.90-1.40 (m, 11H); 1.25 (m, 1H); 1.18 (t, 3H).

d) 0.12 g (±)-(1α,2α,3β)-1-(2-hydroxy-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylamino)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1j) from 0.2 g amine 11c), 0.13 g ketone 1b) and 0.31 g sodium triacetate borohydride. Pos. FAB = 430.

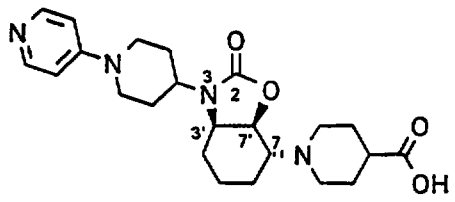
e) 0.35 g (±)-(3'β,7'α,7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1k) from 0.42 g amino-alcohol 11d) and 0.24 g carbonyl-diimidazole. m/e = 456. ^{1}H-NMR d^6-DMSO): δ = 8.20 ppm (d, 2H); 6.85 (d, 2H); 4.05 (q+m, 5H); 3.75 (m, 1H); 3.20 (broad d, 1H); 2.90 (m, 3H); 2.30 (m, 1H); 2.04 (m, 4H); 1.80 (m, 5H); 1.65 -1.35 (m, 9H); 1.20 (t, 3H).

f) 0.26 g of the title compound is obtained analogously to example 1l) from 0.3 g ethyl ester

11e) and 1 ml 1N sodium hydroxide solution. Pos. FAB = 428.

Example 12

(±)-(3'ß,7'ß,7α)-1-[2-Oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid



a) 0.9 g (±)-(1α,2ß,3ß)-1-(3-benzyloxycarbonyl-amino-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester is obtained as a viscous oil analogously to example 1d) from 0.65 g cis-3-benzyloxycarbonyl amino-1,2-epoxycyclohexane (Brouillette W.J. et al., J. Org. Chem., 59, 4297 (1994)) and 0.6 ml 4-piperidine-carboxylic acid ethyl ester, which is processed further as a crude product.

b) A solution of 0.9 g of the N-benzyloxycarbonylamine produced in 12a) in 15 ml ethanol is admixed with 0.8 g 10 % palladium/carbon and the mixture is hydrogenated at normal pressure and room temperature until the hydrogen uptake is completed (12 hours). Subsequently the catalyst is removed by filtration and the solution is concentrated on a rotary evaporator. In this way one obtains 0.5 g (±

)-(1α,2β,3β)-1-(3-amino-2-hydroxy-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester. m/e=270. ^{1}H-NMR (d^6-DMSO): δ = 4.05 ppm (q, 2H); 3.48 (dd, 1H); 3.20 (q, 1H); 2.80 (dt, 1H); 2.68 (dt, 1H); 2.58 (t with fine resolution, 1H); 2.42 (t with fine resolution, 1H); 2.25 (m, 1H); 2.13 (t with fine resolution, 1H); 1.78 (m, 2H); 1.63 (m, 2H); 1.55 (m, 4H); 1.38 (m, 2H); 1.19 (t, 3H); 1.15 (m, 2H).

c) 0.33 g (±)-(1α,2β,3β)-1-[2-hydroxy-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-ylamino)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester is obtained analogously to example 1j) from 0.4 g amine 12b), 0.26 g ketone 1b) and 0.42 g sodium triacetate borohydride. The subsequent reaction of the amino-alcohol produced in this way with 0.17 g carbonyldiimidazole analogously to example 1k) yields 0.22 g ethyl ester (±)-(3'β,7'β-7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid ethyl ester the saponification of which with 0.6 ml 1 N sodium hydroxide solution analogously to example 1l) yielded 0.11 g of the title compound. Fp = 150°C (decomposition). m/e=428. ^{1}H-NMR (d^6-DMSO+AcOH): δ = 4.05 ppm 8.15 (d, 2H); 7.10 (d, 2H); 4.65 (t, 1H); 4.25 (broad d, 2H); 3.98 (broad d, 1H); 3.61 (m, 1H); 3.05 (m, 4H); 2.70 (m, 2H); 2.35 (m, 1H); 2.10 (m, 1H); 2.0-1.10 (m, 16).

Example 13

Assay

Microtitre plates were coated overnight with 2 µg/ml isolated activated GpIIb/IIIa receptor. After unbound receptor had been removed by several washing steps, the surface of the plate was blocked with 1 % casein and it was washed again. The test substance was added at the required concentrations, subsequently the plates were incubated for 10 minutes while shaking in a linear shaker. The natural ligand of the gpIIb/IIIa receptor, fibrinogen, was added. After incubating for 1 hour unbound fibrinogen was removed by several washing steps and bound fibrinogen was determined by measuring the change in optical density at 405 nm caused by a peroxidase-conjugated monoclonal antibody in an ELISA reader. Inhibition of the fibrinogen GpIIb/IIIa interaction leads to lower optical densities. The IC_{50} value was determined on the basis of a concentration-effect curve.

Literature:

The GpIIb/IIIa fibrinogen ELISA is a modification of the assay which is described in the following references:

Nachman, R.L. & Leung, L.L.K. (1982): Complex formation of platelet membrane glycoproteins IIb and IIIa with fibrinogen. J. Clin. Invest. **69**: 263-269.
Wright, P.S. et al. (1993): An echistatin C-terminal peptide activated GpIIbIIIa binding to fibrinogen, fibronectin, vitronectin and collagen type I and type IV, Biochem. J. **293**: 263-267.

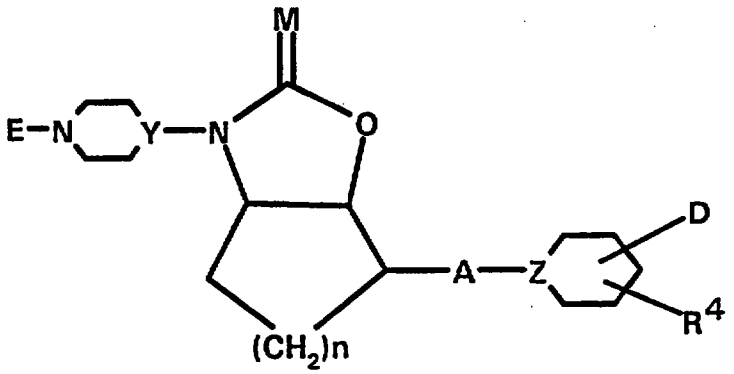
Pharmacological data:

Example	IC_{50} (nMol/l)	Name
1	25	(±)-(3'α,7'ß,7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

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Claims

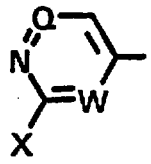
1. Compounds of the general formula I



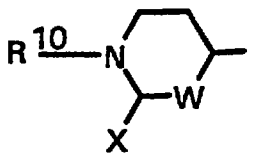
(I)

in which

E denotes a residue of formula (a) or (b)



(a)



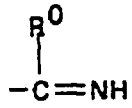
(b)

M denotes oxygen, sulphur or NR^{00},
X denotes hydrogen or NR^1R^2,
W denotes nitrogen or NH or CH or CH_2,
Q denotes nitrogen or CH,
Y denotes nitrogen or CH,
Z denotes nitrogen, CH or C-OH,
A denotes an alkylene chain $-(CH_2)p-$ which is optionally substituted,
D denotes a side chain of the form $-(CHR^3)_m-COO-R^8$ or $=CR^3-COO-R^8$,

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n denotes 1-3,
m denotes 0 or 1
p denotes 0-3

R^1, R^2 denote independently of one another hydrogen, lower alkyl, aryl, arylalkyl, hetaryl, acyl or an optionally substituted carbocyclic or heterocyclic ring or, together with the nitrogen to which they are bound, form an optionally substituted five-membered or six-membered ring which can contain a further 1 to 3 heteroatoms, or denote a group (c)



(c)

R^3 denotes hydrogen or a group $-OR^5$ or $-NR^6R^7$
R^4 denotes hydrogen, lower alkyl, aryl, arylalkyl, hetaryl or a group $-OR^5$,
R^5 denotes hydrogen, lower alkyl, aryl or arylalkyl,
R^6 denotes hydrogen, lower alkyl or arylalkyl,
R^7 denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl or arylsulfonyl,
R^8 denotes hydrogen, methyl, ethyl, isopropyl, tert.-butyl, phenyl or benzyl, in particular hydrogen, ethyl, phenyl or isopropyl,
R^{10} denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl, arylsulfonyl or a group (c),

R^0 denotes hydrogen, lower alkyl, arylalkyl or a group $-NHR^{00}$,
R^{00} denotes hydrogen, lower alkyl, arylalkyl, acyl, alkylsulfonyl or arylsulfonyl,

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as well as conformation and configuration isomers and pharmacologically acceptable salts thereof.

2. Compounds of the general formula I as claimed in claim 1, wherein n adopts a value of 1, 2 or 3 and p adopts a value of 0, 1 or 3.

3. The compounds

(±)-(3'α,7'ß,7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid

(±)-(3'α,7'ß,7α)-1-[2-oxo-3-(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)-octahydro-benzooxazol-7-yl]-piperidine-4-carboxylic acid ethyl ester

as well as conformation and configuration isomers and pharmacologically acceptable salts thereof.

4. Pharmaceutical composition containing at least one compound according to formula 1 as claimed in one of the claims 1-3 in addition to common carrier and auxiliary substances.

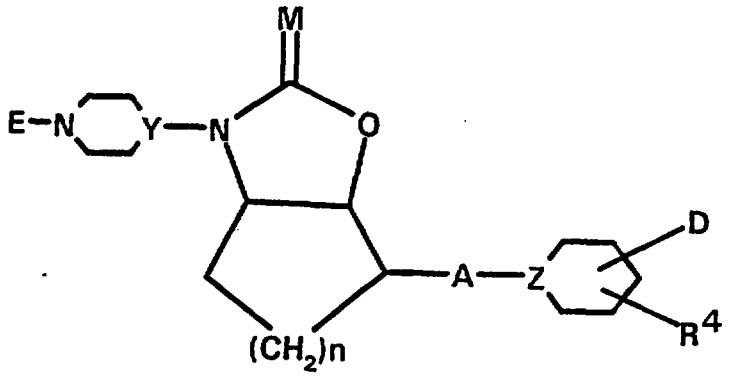
5. Use of substances as claimed in one of the claims 1-3 for the production of pharmaceutical agents for treating diseases which are due to blood platelet aggregation.

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Abstract:

The present invention concerns new oxazolidine derivatives, processes for their production as well as pharmaceutical agents which contain these substances.

The present invention concerns compounds of the general formula I



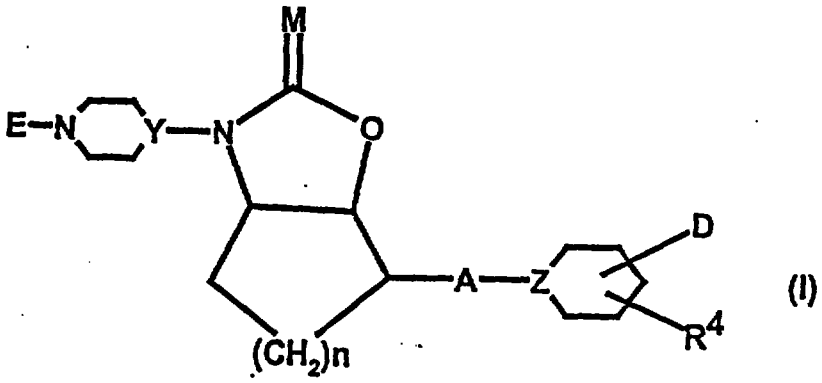
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in which the symbols have the meaning as listed in the claims.

* C L M S *

Claims

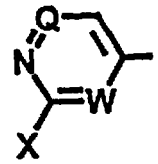
1. Compounds of the general formula I



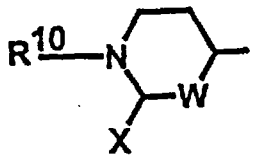
(I)

in which

E denotes a residue of formula (a) or (b)



(a)



(b)

M denotes oxygen, sulphur or NR^{00},
X denotes hydrogen or NR^1R^2,
W denotes nitrogen or NH or CH or CH_2,
Q denotes nitrogen or CH,
Y denotes nitrogen or CH,
Z denotes nitrogen, CH or C-OH,
A denotes an alkylene chain $-(CH_2)p-$ which is optionally substituted,

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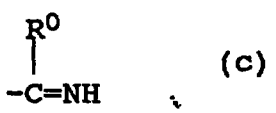
D denotes a side chain of the form $-(CHR^3)_m-COO-R^8$ or $=CR^3-COO-R^8$,

n denotes 1-3,

m denotes 0 or 1

p denotes 0-3

R^1, R^2 denote independently of one another hydrogen, C_1-C_6 alkyl, a phenyl residue which is optionally unsubstituted or substituted several times, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, a pyridyl, pyrimidyl, piperazyl, imidazolyl, pyrrolyl, furyl or thiophenyl residue which is unsubstituted or substituted once or several times, a formyl, acetyl, propionyl, butyryl or benzoyl residue or a saturated or unsaturated 5 to 6-membered carbocyclic ring which is optionally substituted once or twice by C_1-C_6 alkyl or a saturated or unsaturated 5 to 6-membered heterocyclic ring which is optionally substituted once or twice by C_1-C_6 alkyl, or together with the nitrogen to which they are bound, form an optionally substituted five-membered or six-membered ring which can contain a further 1 to 3 heteroatoms, or denote a group (c)



(c)

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* C L M S *

R^3 denotes hydrogen or a group $-OR^5$ or $-NR^6R^7$

R^4 denotes hydrogen, C_1-C_6 alkyl, a phenyl residue which is optionally unsubstituted or substituted several times, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, a pyridiyl, pyrimidyl, piperazyl, imidazolyl, pyrrolyl, furyl or thiophenyl residue which is unsubstituted or substituted once or several times, or a group $-OR^5$,

R^5 denotes hydrogen, C_1-C_6 alkyl, a phenyl residue which is optionally unsubstituted or substituted several times, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups,

R^6 denotes hydrogen, C_1-C_6 alkyl or a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl,

aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups,

R^7 denotes hydrogen, C_1-C_6 alkyl, or a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, a formyl, acetyl, propionyl, butyryl or benzoyl residue, a methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl residue or a benzenesulfonic acid or toluenesulfonic acid residue,

R^8 denotes hydrogen, methyl, ethyl, isopropyl, tert.-butyl, phenyl or benzyl, in particular hydrogen, ethyl, phenyl or isopropyl,

R^{10} denotes hydrogen, C_1-C_6 alkyl, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, a formyl, acetyl, propionyl, butyryl or benzoyl residue, a methanesulfonyl, ethanesulfonyl, propanesulfonyl,

butanesulfonyl residue or a benzenesulfonic acid or toluenesulfonic acid residue or a group (c),

R^0 denotes hydrogen, C_1-C_6 alkyl, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, or a group $-NHR^{00}$,

R^{00} denotes hydrogen, C_1-C_6 alkyl, a benzyl, phenethyl, phenylpropyl, phenylbutyl or phenylpentyl residue which is unsubstituted or substituted once or several times by C_1-C_6-alkyl, chlorine, bromine, fluorine, hydroxy, methoxy, benzyloxy, acetyloxy, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, cyano, amino, methylamino, dimethylamino, benzylamino, acetylamino, benzoylamino and amidino groups, a formyl, acetyl, propionyl, butyryl or benzoyl residue, a methanesulfonyl, ethanesulfonyl, propanesulfonyl, a butanesulfonyl residue or a benzenesulfonic acid or toluenesulfonic acid residue,