Aryl-substituted polycyclic amines, method for the production thereof, and use thereof as a medicament

The invention relates to aryl-substituted polycyclic amines, especially bicyclic amines, and to the physiologically tolerated salts and physiologically functional derivatives thereof.

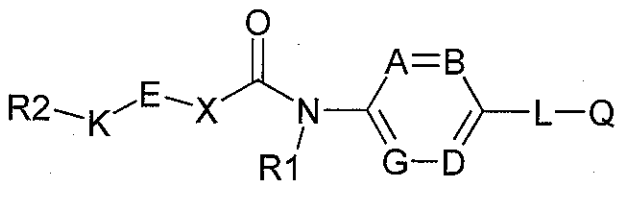
Compounds which have a similar overall structure to the aryl-substituted polycyclic amines described herein and have a pharmacological effect have been described in the prior art. WO95/03302 discloses aryl ethers of bicyclic amino alcohols having a calcium-antagonistic effect. WO2002010146 describes an amidoaryl ether of hydroxyquinuclidine as antagonist of the 11CBY receptor for the treatment of obesity.

Compounds having an MCH-antagonistic effect for the treatment of obesity are described in the prior art (examples: WO2001021577, WO2003035624, WO2002089729, WO2002006245, WO2002002744, WO2002057233, WO2003045313, WO2003097047, WO2002010146, WO 2003087044).

The invention was based on the object of providing compounds which bring about a weight reduction in mammals and are suitable for the prevention and treatment of obesity and diabetes and the diverse sequelae thereof.

Surprisingly, a series of compounds which modulate the activity of MCH receptors has been found. The compounds are distinguished In particular by antagonism of the MCH1R.

The invention therefore relates to compounds of the formula I



I

in which the meanings are

A, B, D, G

independently of one another N, C(R3);

or

groups A and B or groups D and G are in each case C(R3) and form together a 5- or 6-membered carbocyclic or heterocyclic radical to result overall in a bicyclic system;

R3 H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_3-C_8)-cycloalkyl, O-(C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkenyl, (C_2-C_6)-alkynyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R4)(R5), SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, CON(R6)(R7), N(R8)CO(R9), N(R10)SO_2(R11), CO(R12), $(CR13R14)_x$-O(R15);

R4, R5, R6, R7, R8, R10

independently of one another H, (C_1-C_8)-alkyl;

or

R4 and R5, R6 and R7

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R9, R11, R12

independently of one another H, $(C_1$-$C_8)$-alkyl, aryl;

R13, R14

independently of one another H, $(C_1$-$C_8)$-alkyl;

R15 H, $(C_1$-$C_6)$-alkyl, aryl;

x 0, 1, 2, 3, 4, 5, 6;

R1 H, $(C_1$-$C_8)$-alkyl, $(C_3$-$C_6)$-alkenyl, $(C_3$-$C_6)$-alkynyl;

X N(R16), O, a bond, (R17)C=C(R18), C≡C, a group of the formula $(CR19R20)_y$, in which one or two (CR19R20) groups may be replaced by Y to result in a chemically reasonable radical;

Y O, S, N(R21), C=O;

R16, R17, R18

independently of one another H, $(C_1$-$C_8)$-alkyl;

R19, R20

independently of one another H, $(C_1$-$C_4)$-alkyl, where R19 and R20 in the y groups may in each case have identical or different meanings;

y 1, 2, 3, 4, 5, 6;

R21 H, $(C_1$-$C_8)$-alkyl;

E 3-14 membered bivalent carbo- or heterocyclic ring structure having 0-4 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, I, OH, CF_3, CN, OCF_3, oxo, O-$(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, S-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_3$-$C_8)$-cycloalkyl, O-$(C_3$-$C_8)$-cycloalkyl, $(C_3$-$C_8)$-cycloalkenyl, O-$(C_3$-$C_8)$-cycloalkenyl, $(C_2$-$C_6)$-alkynyl, $(C_0$-$C_8)$-alkylene-aryl, O-$(C_0$-$C_8)$-alkylene-aryl, S-aryl, N(R22)(R23), SO_2-CH_3, CON(R24)(R25), N(R26)CO(R27), N(R28)SO_2(R29), CO(R30) and be mono- or bicyclic, where E is not a tetrazol-5-yl group;

R22, R23, R24, R25, R26, R28

independently of one another H, $(C_1$-$C_8)$-alkyl, aryl;

or

R22 and R23, R24 and R25

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

R27, R29, R30

independently of one another H, $(C_1$-$C_8)$-alkyl, aryl;

K a bond, C≡C, (R31)C=C(R32), a group of the formula $(CR33R34)_z$ in which one or more (CR33R34) groups may be replaced by Z to result in a chemically reasonable radical, preferably a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2;

v 1, 2, 3, 4;

R31, R32, R35, R36, R37, R38, R39

independently of one another H, $(C_1$-$C_8)$-alkyl;

Z O, S, N(R40), CO, SO, SO_2;

R33, R34

independently of one another H, $(C_1$-$C_8)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, hydroxy, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, where R38 and R39 in the z groups may in each case have identical or different meanings;

z 1, 2, 3, 4, 5, 6;

R40 H, $(C_1$-$C_8)$-alkyl;

R2 H, $(C_1$-$C_8)$-alkyl, $(C_1$-$C_8)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_8)$-alkenyl, $(C_3$-$C_8)$-alkynyl, a 3 to 10-membered mono-, bi-, tri- or spirocyclic ring which may include 0 to 4 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where

the ring system may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, NO_2, CN, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_0$-$C_8)$-alkylene-aryl, oxo, CO(R41), CON(R42)(R43), hydroxy, COO(R44), N(R45)CO$(C_1$-$C_6)$-alkyl, N(R46)(R47), SO_2CH_3, SCF_3 or S-$(C_1$-$C_6)$-alkyl, where R2 is not a tetrazol-5-yl group;

R41, R42, R43, R44, R45, R46, R47

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

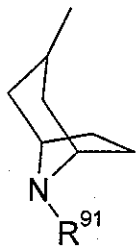
R42 and R43, R46 and R47

independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

E, K and R2

together form a tricyclic system where the rings may independently of one another saturated, partially saturated or unsaturated and in each case comprise 3 – 8 ring atoms;

L a group of the formula $(CR48R49)_m$ in which one or more (CR48R49) groups may be replaced by M to result in a chemically reasonable radical, where L is O if Q is



where R91 is as defined below;

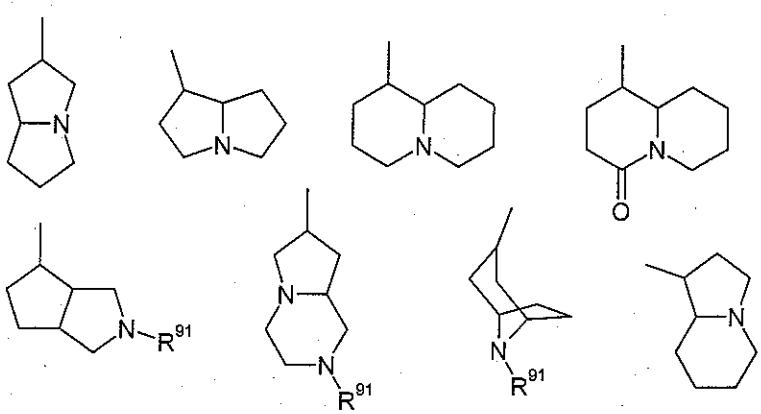
M O, S, N(R50), CO, SO, SO_2, preferably O, S, N(R50), CO, SO_2, particularly preferably O, N(R50), very particularly preferably O;

m 1, 2, 3, 4, 5, 6, preferably 1, 2, 3, 4, particularly preferably 1, 2;

R48, R49, R50

independently of one another H, (C_1-C_6)-alkyl, aryl, particularly preferably H, alkyl;

Q



R91 H, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R92), $(CR93R94_{O'}$-R95, $CO(CR93R94)_{p'}$-R96;

R92 H, (C_1-C_8)-alkyl;

R93, R94

independently of one another H, (C_1-C_8)-alkyl, OH, (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6;

R95, R96

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH;

R97, R98, R99, R100, R103, R104

independently of one another H, (C_1-C_8)-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further

heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, (C_1-C_8)-alkyl;

or

R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

the N-oxides thereof and the physiologically tolerated salts thereof.

The invention relates to compounds of the formula I in the form of their racemates, enantiomer-enriched mixtures and pure enantiomers and to their diastereomers and mixtures thereof.

The compounds of the formula I are distinguished by improved metabolic stability with at the same time high activity compared with compounds of similar structure.

The alkyl, alkenyl and alkynyl radicals in the substituents R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24, R25, R26, R27, R28, R29, R30, R31, R32, R33, R34, R35, R36, R37, R38, R39, R40, R41, R42, R43, R44, R45, R46, R47, R48, R49, R50, R90, R91, R92, R93, R94, R95, R96, R97, R98, R99, R100, R101, R102, R103, R104, R105, R106, R107, R108, R109, R110, R111, R112, R113, R114, R115, R116, R117, R118, R119, R120, R121, R122, R123, R124, R125, R126 and R86R127 may be either straight-chain, branched and/or optionally substituted by substituents such as aryl, heteroaryl, alkoxy or halogen. This also applies if the alkyl, alkenyl and alkynyl radicals are part of another group, e.g. part of an alkoxy group (such as (C_1-C_4)-alkoxy-(C_1-C_4-alkyl)). Suitable halogens are fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine, particularly preferably fluorine.

Examples of alkyl groups are: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Included therein are both the n isomers of these radicals and branched isomers such as isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl etc. Unless described otherwise, the term alkyl additionally includes alkyl radicals which are unsubstituted or optionally substituted by one or more further radicals, for example 1, 2, 3 or 4 identical or different radicals such as aryl, heteroaryl, (C_1-C_4)-alkoxy or halogen. It is moreover possible for the additional substituents to occur in any position of the alkyl radical. The alkyl radicals are preferably unsubstituted, unless defined otherwise.

Cycloalkyl means for the purposes of the present application cycloalkyl and cycloalkyl-alkyl (alkyl which is in turn substituted by cycloalkyl), with cycloalkyl having at least 3 carbon atoms. Examples of cycloalkyl radicals are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. Polycyclic ring systems are also possible where appropriate, such as decalinyl, norbornanyl, bornanyl or adamantanyl. The cycloalkyl radicals may be unsubstituted or optionally substituted by one or

more further radicals as detailed by way of example above for the alkyl radicals. The cycloalkyl radicals are preferably unsubstituted, unless defined otherwise.

Examples of alkenyl and alkynyl groups are: vinyl, 1-propenyl, 2-propenyl (allyl), 2-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, ethynyl, 2-propynyl (propargyl), 2-butynyl or 3-butynyl.

Cycloalkenyl means for the purposes of the present application cycloalkenyl radicals and cycloalkenyl-alkyl radicals (alkyl which is substituted by cycloalkenyl) which comprise at least three carbon atoms. Examples of cycloalkenyl are: cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

The alkenyl radicals and cycloalkenyl radicals may have one to three conjugated or unconjugated double bonds (that is also alk-dienyl and alk-trienyl radicals), preferably one double bond in a straight or branched chain. The same applies to the triple bonds in alkynyl radicals. The alkenyl and alkynyl radicals may be unsubstituted or optionally substituted by one or more further radicals as detailed by way of example for the alkyl radicals above. The alkenyl and alkynyl raadicals are preferably unsubstituted, unless defined otherwise.

Aryl refers in the present invention to radicals derived from monocyclic or bicyclic aromatic systems comprising no ring heteroatoms. Where the systems are not monocyclic, the term aryl includes for the second ring also the saturated form (perhydro form) or the partially unsaturated form (for example the dihydro form or tetrahydro form) where the respective forms are known and stable. The term aryl also includes in the present invention for example bicyclic radicals in which both the rings are aromatic and bicyclic radicals in which only one ring is aromatic. Examples of aryl are:

phenyl, naphthyl, indanyl, 1,2-dihydronaphthenyl, 1,4-dihydronaphthenyl, indenyl or 1,2,3,4-tetrahydronaphthyl. The aryl radicals are preferably unsubstituted, unless defined otherwise. Aryl is particularly preferably phenyl or naphthyl.

Heteroaryl radicals mean radicals derived from monocyclic or bicyclic aromatic systems which comprise ring heteroatoms, preferably N, O or S. Otherwise, that stated concerning aryl radicals applies to the heteroaryl radicals.

A "tricyclic system" means structures having 3 rings which are connected together by more than one bond. Examples of such systems are fused systems having 3 rings and spirocyclic systems having a fused-on ring system.

The bivalent carbo- or heterocyclic ring structure E also includes structures which are linked via one and the same atom to the two adjacent groups K and X.

A polycyclic group means for the purposes of the present application a group derived from spiranes, fused ring systems or bridged ring systems. Spiranes are distinguished by two rings having only one carbon atom in common and the ring planes of the two rings being perpendicular to one another. In the fused ring systems, two rings are linked together so that they have two atoms in common. This type of linkage involves an "*ortho* fusion". Bridged ring systems are ring systems which have a bridge of carbon atoms and/or heteroatoms between two nonadjacent atoms of a ring.

A "chemically reasonable radical" means for the purposes of the present invention a radical which is stable at room temperature and atmospheric

pressure. For the purposes of the present invention, a "chemically reasonable radical" preferably means in the definitions of the groups L, X and K in the compounds of the formula (I) groups of the formula $(CR48R49)_m$ (in the definition of L) $(CR19R20)_y$ (in the definition of X) or $(CR33R34)_z$ (in the definition of K) which have no heteroatom–heteroatom linkages between the individual (CR48R49), (CR19R20) or (CR33R34) groups.

The compounds of the formula I may have one or more centers of asymmetry. The compounds of the formula I may therefore exist in the form of their racemates, enantiomer-enriched mixtures, pure enantiomers, diastereomers and mixtures of diastereomers. The present invention encompasses all these isomeric forms of the compounds of the formula I. These isomeric forms may be obtained by known methods, even if not expressly described in some cases.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion, such as, for example,

trifluoro acetate, likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

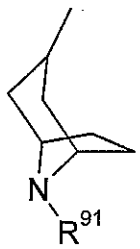
The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

If radicals or substituents may occur more than once in the compounds of the formula I, they may all have the stated meanings independently of one another and be identical or different.

L in the compounds of the formula I according to the invention preferably has the following meanings:

L a group of the formula $(CR48R49)_m$ in which one or more (CR48R49) groups may be replaced by M to result in a chemically reasonable radical, where L is O if Q is



,

M O, S, N(R50), CO, SO, SO_2, preferably O, S, N(R50), CO, SO_2, particularly preferably O, N(R50), very particularly preferably O;

m 1, 2, 3, 4, 5, 6, preferably 1, 2, 3, 4, particularly preferably 1, 2;

R48, R49, R50

independently of one another H, $(C_1$-$C_6)$-alkyl, aryl, preferably H, $(C_1$-$C_6)$-alkyl, particularly preferably H.

The symbols in the compounds of the formula I preferably have the following meanings:

A, B, D, G

independently of one another N, C(R3) or groups A and B or D and G are each C(R3) and form together an ortho-phenylene

unit to result overall in a 1,4-disubstituted naphthalene system; preferably independently of one another N or C(R3), where the total number of nitrogen atoms in the ring is 0 - 2, preferably 0 or 1, particularly preferably A, B, D and G are C(R3);

R3 H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, N(R4)(R5), SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15); preferably H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15), particularly preferably H, F, Cl, CF_3, CN, (C_1-C_6)-alkyl, $(C(R13)(R14))_x$-O(R15); very particularly preferably H, F, (C_1-C_6)-alkyl; further preferably H, F, CH_3; especially preferably H;

R4, R5, R6, R7, R8

independently of one another H, (C_1-C_8)-alkyl;

or

R4 and R5, R6 and R7

independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R9, R12

independently of one another H, (C_1-C_8)-alkyl;

R13, R14

H;

R15 H, (C_1-C_6)-alkyl;

x 0, 1, 2, preferably 0, 1, particularly preferably 1;

R1 H, (C_1-C_8)-alkyl;

X N(R16), a bond, (R17)C=C(R18), C≡C, CH_2-CH_2, YCH_2, CH_2Y, preferably N(R16), a bond;

Y O, S, N(R21);

R16, R17, R18

independently of one another H, (C_1-C_8)-alkyl;

R21 H, (C_1-C_8)-alkyl;

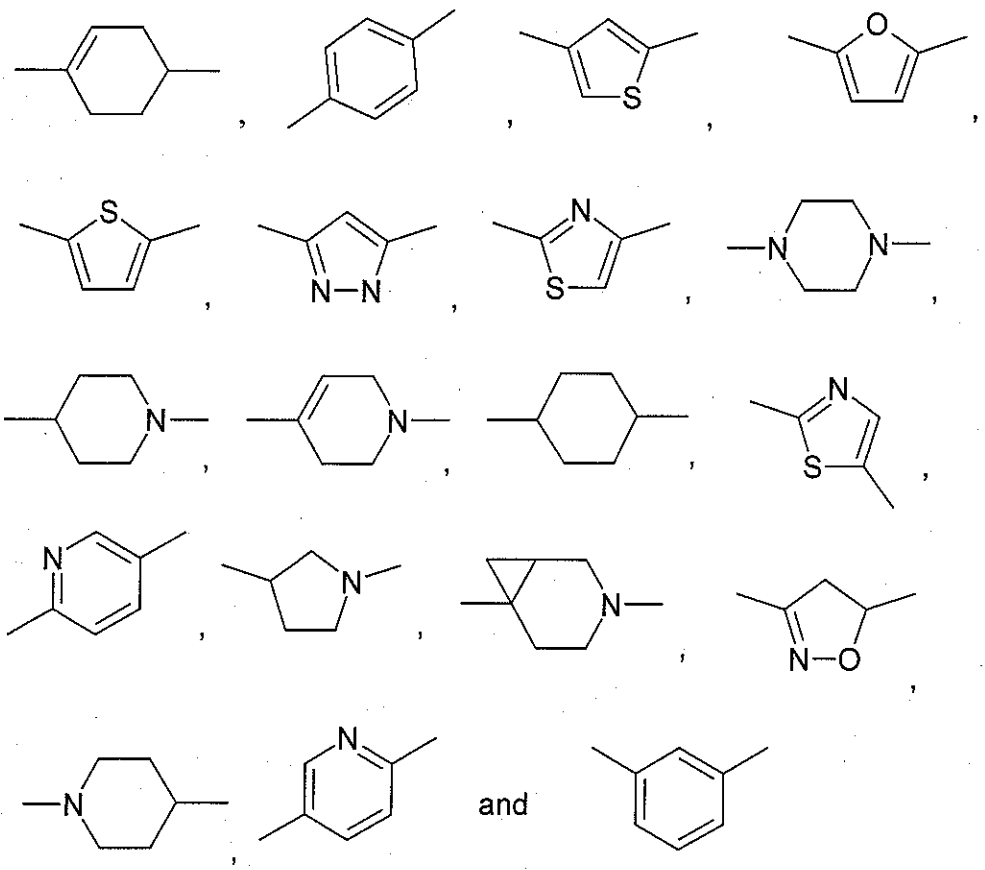
E 3-8 membered bivalent carbo- or heterocyclic ring structure having 0-4 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, O-(C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkenyl, (C_2-C_6)-alkynyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R22)(R23), SO_2-CH_3, N(R26)CO(R27), $N(R28)SO_2(R29)$, CO(R30) and be mono- or bicyclic, where E is not a tetrazol-5-yl group;

preferably 5-7 membered bivalent carbo- or heterocyclic ring structure having 0-3 heteroatoms from the group of N, O and S,

which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R22)(R23), SO_2-CH_3, N(R26)CO(R27), CO(R30) and be mono- or bicyclic;

particularly preferably 5-7 membered bivalent carbo- or heterocyclic ring structure having 0-2 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, N(R22)(R23), SO_2-CH_3, CO(R30), preferably H, F, Cl, Br, OH CF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

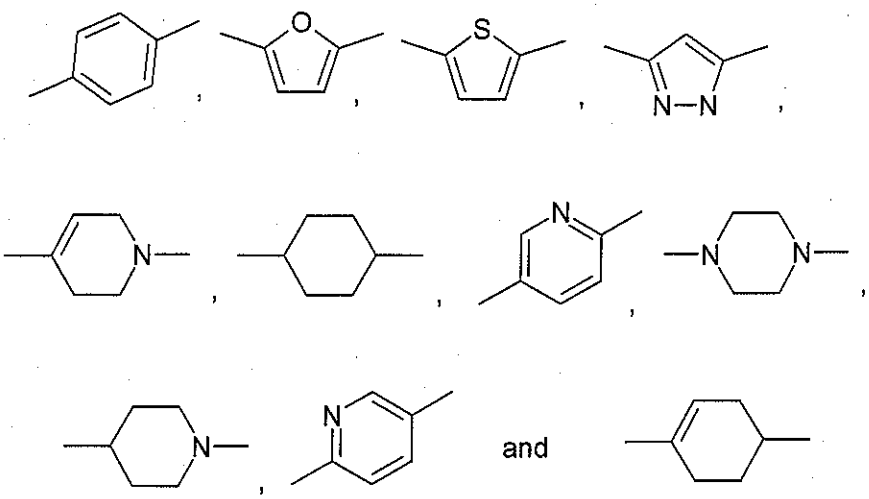
e.g. E is selected from the group consisting of



which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-

alkenyl, N(R22)(R23), SO_2-CH_3, CO(R30), preferably H, F, Cl, Br, OH, CF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

preferably



which may optionally have the aforementioned substituents;

R22, R23, R26, R28

independently of one another H, (C_1-C_8)-alkyl;

or

R22 and R23

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R27, R29, R30

independently of one another H, (C_1-C_8)-alkyl;

K a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, N-SO_2, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, preferably a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, particularly preferably OCH_2, CH_2O, N(R36)CO, CON(R37), $(C(R38)(R39))_2$, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, very particularly preferably OCH_2, CH_2O, CON(R37), C≡C, SCH_2;

v 1, 2, 3, preferably 2;

R31, R32, R35, R36, R37, R38, R39

independently of one another H, $(C_1$-$C_8)$-alkyl;

R2 $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, a 3 to 10-membered mono-, bi-, tri- or spirocyclic ring which may include 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_8)$-alkyl, $(C_0$-$C_2)$-alkylene-aryl, oxo, CO(R41), CON(R42)(R43), hydroxy, N(R45)CO$(C_1$-$C_6)$-alkyl, N(R46)(R47) or SO_2CH_3; preferably $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, a 3 to 10-membered mono- or bicyclic ring which may include 0 to 2 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_8)$-alkyl, oxo, CO(R41), CON(R42)(R43), N(R45)CO$(C_1$-$C_6)$-alkyl or SO_2CH_3;

R41, R42, R43, R45, R46, R47

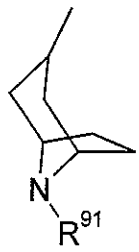
independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R42 and R43, R46 and R47

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

L a group of the formula $(C(R48)(R49))_m$ in which 0 or 1 member may be replaced by an element from the group of O, N(R50), preferably O, where L is O if Q is



,

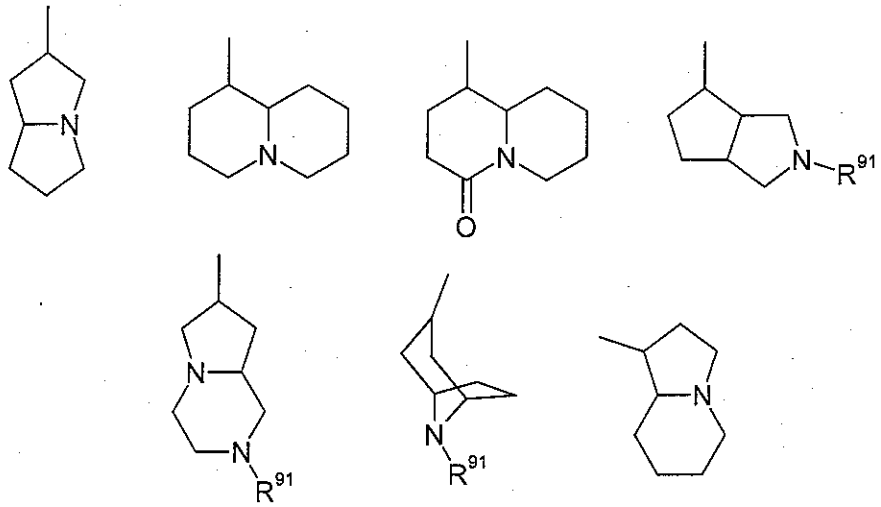
m 1, 2, 3, 4, preferably 1 or 2;

R48, R49

H;

R50 H, (C_1-C_8)-alkyl, preferably H;

Q



R91 H, $(C_1\text{-}C_4)$-alkoxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, $(C_1\text{-}C_6)$-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, $(C_1\text{-}C_8)$-alkyl;

R93, R94

independently of one another H, $(C_1\text{-}C_8)$-alkyl, OH, $(C_3\text{-}C_8)$-cycloalkyl, $(C_1\text{-}C_4)$-alkoxy-$(C_1\text{-}C_4)$-alkyl, preferably H, $(C_1\text{-}C_8)$-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-$(C_1\text{-}C_8)$-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, $(C_1\text{-}C_8)$-alkyl, O-$(C_1\text{-}C_8)$-alkyl, CO(R104), oxo,

OH; preferably independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 heteroatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, (C_1-C_8)-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, (C_1-C_8)-alkyl;

or

R120 and R121, R124 and R125

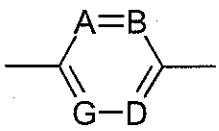
form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further

heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur.

Particularly preferred compounds of the formula I are those in which

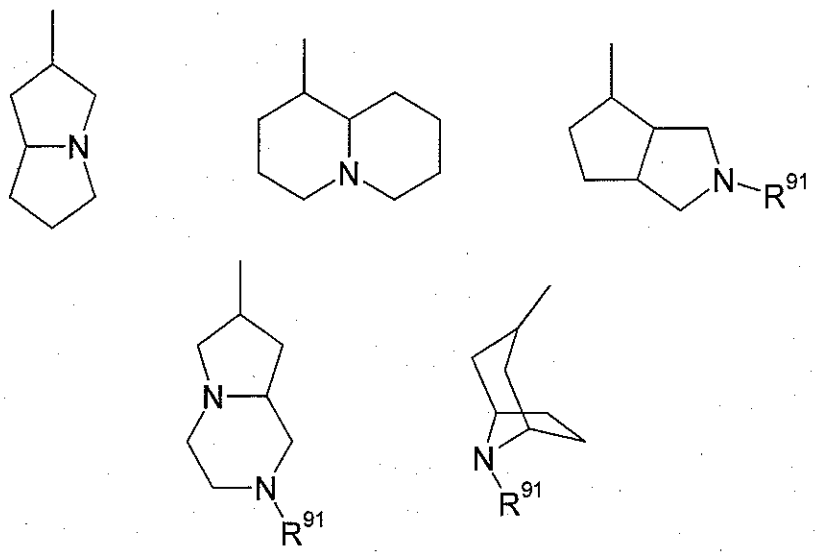
A, B, D, G are independently of one another N or C(R3), and the total number of nitrogen atoms in this ring is 0-2, preferably 0 or 1, particularly preferably O.

In the compounds of the formula, the linkage between the group Q and the group



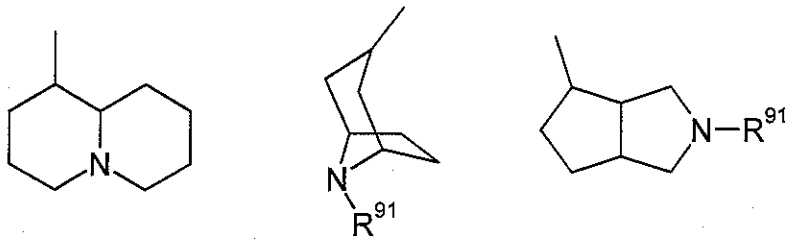
preferably takes place via a heteroatom, particularly preferably O or N, very particularly preferably O of the linker L.

The group Q in the compounds of the formula I particularly preferably has the following meanings:



,

preferably



R91 H, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, (C_1-C_6)-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, (C_1-C_8)-alkyl;

R93, R94

independently of one another H, (C_1-C_8)-alkyl, OH, (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, preferably H, (C_1-C_8)-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to

2 heteroatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, O-$(C_1$-$C_8)$-alkyl, $(C_1$-$C_6)$-alkyl, CO(R112), oxo, OH, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

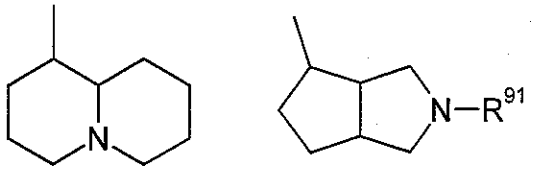
independently of one another H, $(C_1$-$C_8)$-alkyl;

or

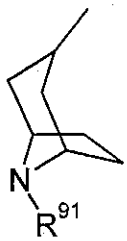
R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur.

In the compounds of the formula I, Q is very particularly preferably

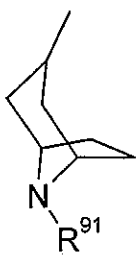


In a further very particularly preferred embodiment, Q has the following meaning:

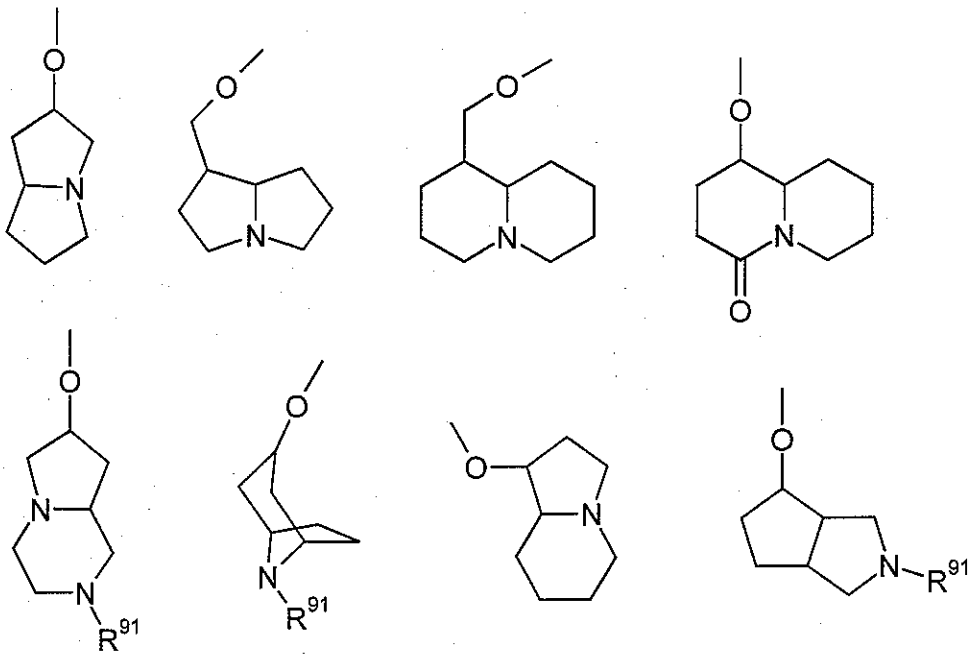


where R91 has the abovementioned meanings and L is O.

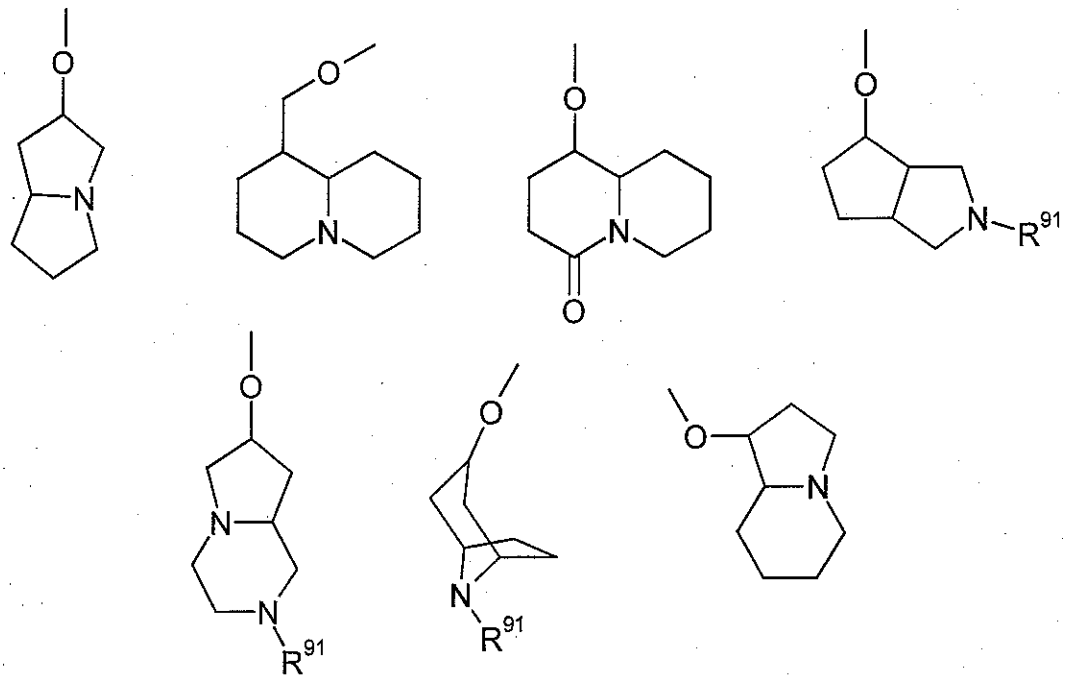
In the compounds of the formula I L is preferably O or CH_2O, particularly preferably O, where L is O if Q is



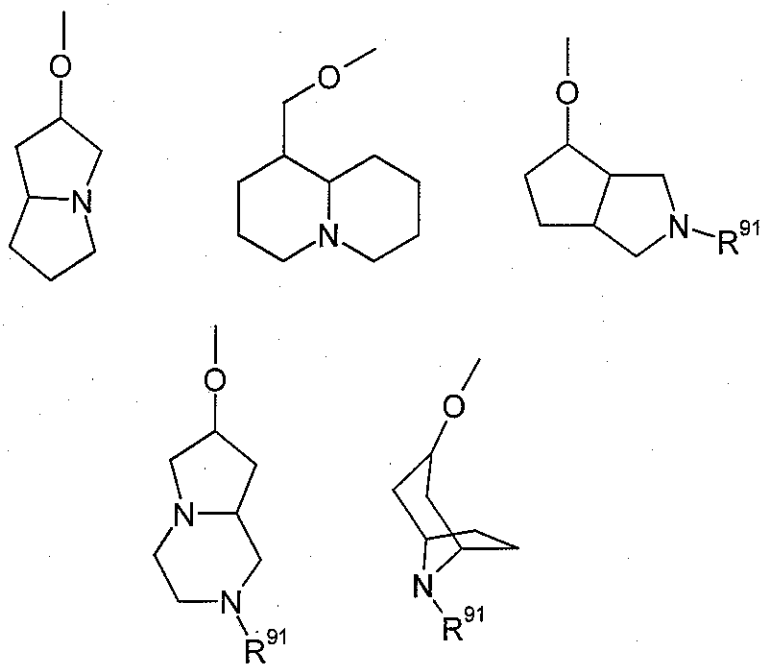
Compounds of the formula I which are very particularly preferred are those in which L-Q has the following meanings:



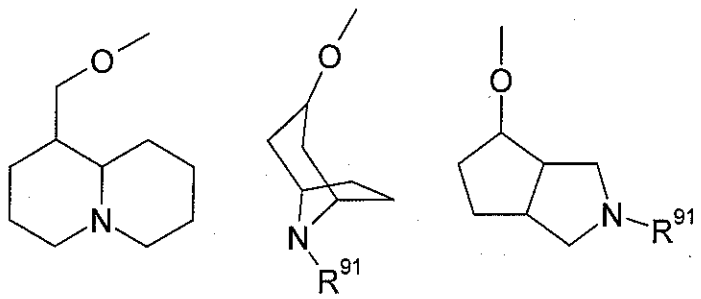
preferably



particularly preferably



very particularly preferably



R91 H, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, $(C_1$-$C_6)$-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, $(C_1$-$C_8)$-alkyl;

R93, R94

independently of one another H, (C_1-C_8)-alkyl, OH, (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, preferably H, (C_1-C_8)-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 heteroatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, (C_1-C_8)-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0

to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substitutents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

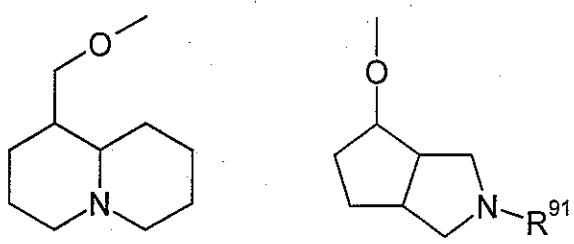
independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur.

In a particularly preferred embodiment of the present invention, the group L-Q in the compounds of the formula I is



In a further preferred embodiment, the group L-Q in the compounds of the formula I is



where R91 has the abovementioned meanings.

The present invention further relates to compounds of the formula I in which

A, B, D, G

are independently of one another N or C(R3), and the total number of nitrogen atoms in this ring is 0-2, preferably 0 or 1, particularly preferably 0;

where the other symbols in formula I have already been defined above.

In a preferred embodiment, the present application relates to compounds of the formula I

in which the meanings are

A, B, D, G

C(R3);

R3 H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, N(R4)(R5), SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15); preferably H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, SO_2-CH_3,

CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15), particularly preferably H, F, Cl, CF_3, CN, $(C_1$-$C_6)$-alkyl, $(C(R13)(R14))_x$-O(R15); very particularly preferably H, F, $(C_1$-$C_6)$-alkyl; further preferably H, F, CH_3; especially preferably H;

R4, R5, R6, R7, R8

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R4 and R5, R6 and R7

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

R9, R12

independently of one another H, $(C_1$-$C_8)$-alkyl;

R13, R14

H;

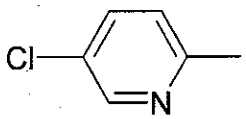
R15 H, $(C_1$-$C_6)$-alkyl;

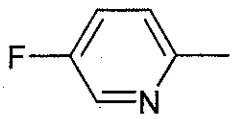
x 0, 1, 2, preferably 0, 1, particularly preferably 1.

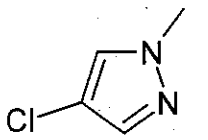
In a further preferred embodiment, A, B, G and D in the compounds of the formula I are CH.

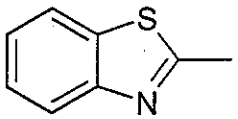
R2 is preferably selected from the group consisting of:

n-propyl, n-butyl, iso-butyl, iso-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohex-(1)-enyl, phenyl, p-fluorophenyl, p-chlorophenyl, p-bromophenyl, p-tolyl, p-methoxyphenyl, p-trifluoromethylphenyl,



,


,


,


.

K is preferably selected from the group consisting of:

O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, preferably OCH_2, CH_2O, N(R36)CO, CON(R37), $(C(R38)(R39))_2$, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, particularly preferably OCH_2, CH_2O, CON(R37), C≡C, SCH_2; where

v 1, 2, 3, preferably 2;

R31, R32, R35, R36, R37, R38, R39

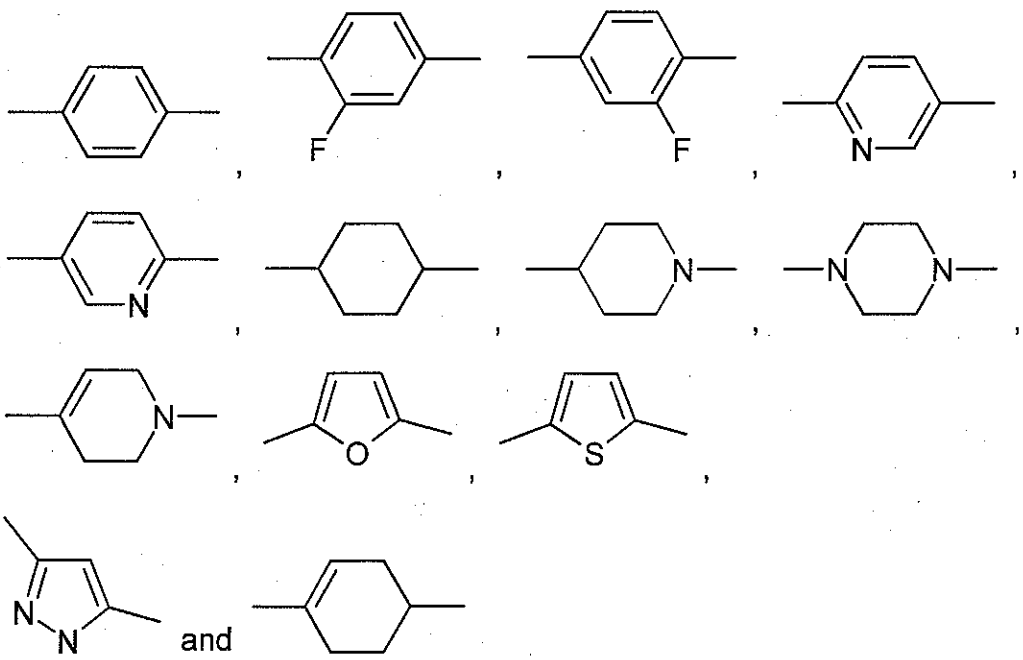
are independently of one another H, $(C_1$-$C_8)$-alkyl.

X is preferably selected from the group consisting of bond and N(R16), in which R16 is H or $(C_1$-$C_8)$-alkyl, particularly preferably bond and NH.

The group E in the compounds of the formula I is defined above. According to the above definitions of E it is possible for E to be for example a five- or

six-membered ring. If the group E is a five-membered ring then the groups K and X in the compounds of the formula I are in a preferred embodiment disposed in positions 1 and 3 of the five-membered ring. If the group E is a six-membered ring then the groups K and X are in a preferred embodiment disposed in positions 1 and 4 (i.e. in para position relative to one another) of the six-membered ring.

E is particularly preferably selected from the group consisting of:



This invention further relates to the use of compounds of the formula I and their pharmaceutical compositions as MCH receptor ligands. The MCH receptor ligands of the invention are particularly suitable as modulators of the activity of the MCH1R.

The role of MCH in regulating the energy balance has now been well documented (Qu, D. et al. Nature 1996, 380, 243-7; Shimada, M. et al. Nature 1998, 396, 670-4; Chen, Y et al. Endocrinology 2002, 143, 2469-77; Endocrinology 2003, 144, 4831-40; Review: G. Hervieu, Expert Opin. Ther. Targets 2003, 7, 495-511).

There are also indications that MCH antagonists can have a beneficial influence on centrally related disorders such as, for example, depressions (Borowsky, B. et al. Nature Medicine 2002, 8, 825-30; Review: G. Hervieu, Expert Opin. Ther. Targets 2003, 7, 495-511).

Compounds of this type are particularly suitable for the treatment and/or prevention of

1. Obesity

2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith.

   Particular aspects in this connection are

   - hyperglycemia,
   - improvement in insulin resistance,
   - improvement in glucose tolerance,
   - protection of the pancreatic ß cells
   - prevention of macro- and microvascular disorders

3. Dyslipidemias and the sequelae thereof such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:

   - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations
   - low HDL cholesterol concentration

4. Various other conditions which may be associated with the metabolic

syndrome, such as:

- thromboses, hypercoagulable and prothrombotic stages (arterial and venous)
- high blood pressure
- heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Psychiatric indications such as

- depressions
- anxiety states
- disturbances of the circadian rhythm
- affection disorders
- schizophrenia
- addictive disorders

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of bodyweight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the

active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable

tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one or more surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally

contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formula I are distinguished by beneficial effects on lipid metabolism, and they are particularly suitable for weight reduction and for maintaining a reduced weight after weight reduction has taken place in mammals and as anorectic agents. The compounds are distinguished by their low toxicity and their few side effects. The compounds can be employed alone or in combination with other weight-reducing or anorectic active ingredients. Further anorectic active ingredients of this type are

mentioned, for example, in the Rote Liste, chapter 01 under weight-reducing agents/appetite suppressants, and may also include active ingredients which increase the energy turnover of the organism and thus lead to weight reduction or else those which influence the general metabolism of the organism in such a way that an increased calorie intake does not lead to an enlargement of the fat depots and a normal calorie intake leads to a reduction of the fat depots of the organism. The compounds are suitable for the prophylaxis and, in particular, for the treatment of excessive weight or obesity. The compounds are further suitable for the prophylaxis and, in particular, for the treatment of type II diabetes, of arteriosclerosis and for normalizing lipid metabolism and for the treatment of high blood pressure.

Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, beneficial effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
10. active ingredients for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.

They can be combined with the compounds of the invention of the formula I in particular for a synergistic improvement in the effect. Administration of the active ingredient combination can take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation.

Examples which may be mentioned are:

Antidiabetics

Suitable antidiabetics are disclosed for example in the Rote Liste 2001, chapter 12 or the USP Dictionary of USAN and International Drug Names,

US Pharmacopeia, Rockville 2003. Antidiabetics include all insulins and insulin derivatives, such as, for example, Lantus® (see www.lantus.com) or Apidra®, and other fast-acting insulins (see, US 6,221,633), GLP-1 receptor modulators, as described in WO 01/04146 or else such as those disclosed in WO 98/08871 of Novo Nordisk A/S for example.

The orally effective hypoglycemic active ingredients include, preferably, sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, oral GLP-1 agonists, DPP-IV inhibitors, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism and lead to a change in the blood lipid composition, compounds which reduce food intake or food absorption, PPAR and PXR modulators and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with substances which influence hepatic glucose production such as, for example, glycogen phosphorylase inhibitors (see: WO 01/94300, WO 02/096864, WO 03/084923, WO 03/084922, WO 03/104188).

In one embodiment, the compounds of the formula I are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment, the compounds of the formula I are administered in

combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with a biguanide such as, for example, metformin.

In a further embodiment, the compounds of the formula I are administered in combination with a meglitinide such as, for example, repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione such as, for example, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment, the compounds of the formula I are in combination with a DPPIV inhibitor as described, for example, in WO98/19998, WO99/61431, WO99/67278, WO99/67279, WO01/72290, WO 02/38541, WO03/040174, in particular P 93/01 (1-cyclopentyl-3-methyl-1-oxo-2-pentanammonium chloride), P-31/98, LAF237 (1-[2-[3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021 ((2S, 4S)-4-fluoro-1-[[(2-hydroxy-1,1-dimethylethyl)amino]-acetyl]pyrrolidine-2-carbonitrile monobenzenesulfonate).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPARgamma agonist such as, for example, rosiglitazone, pioglitazone.

In one embodiment, the compounds of the formula I are administered in combination with compounds with an inhibitory effect on SGLT-1 and/or 2, as disclosed directly or indirectly for example in PCT/EP03/06841,

PCT/EP03/13454 and PCT/EP03/13455.

In one embodiment, the compounds of the formula I are administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In one embodiment, the compounds of the formula I are administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Lipid modulators

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA-reductase inhibitor, such as lovastatin, fluvastatin, pravastatin, simvastatin, ivastatin, itavastatin, atorvastatin, rosuvastatin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897, US 6,277,831, EP 0683 773, EP 0683 774).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine or colesevelam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor as described for example in WO 0250027, or ezetimibe, tiqueside,

pamaqueside.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see, for example, US 6,342,512).

In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Hoechst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPARalpha agonist.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate such as, for example, fenofibrate, gemfibrozil, clofibrate, bezafibrate.

In one embodiment of the invention, the compounds of the formula I are administered in combination with nicotinic acid or niacin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, e.g. CP- 529, 414

(torcetrapib).

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor such as, for example, implitapide.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP-citrate lyase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist.

Antiobesity agents

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor such as, for example,

orlistat.

In one embodiment, the further active ingredient is fenfluramine or dexfenfluramine.

In another embodiment, the further active ingredient is sibutramine.

In another embodiment, the further active ingredient is rimonabant.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.: Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}amide; hydrochloride (CGP 71683A), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochlorides (SB-334867-A)), CB1 antagonists/inverse agonists, H3 antagonists/inverse agonists (e.g. 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol; hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), BRS3

agonists, galanin antagonists, ghrelin antagonists, MCH antagonists, mGluR5 antagonists, opioid antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tertiary butyl ester (WO 01/85695)), CNTF, CNTF derivatives (e.g. Axokine), TRH agonists (see, for example, EP 0 462 884), uncoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR-β agonists.

In one embodiment of the invention, the further active ingredient is leptin.

In one embodiment, the further active ingredient is dexamphetamine, amphetamine, mazindole or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having effects on the coronary circulation and the vascular system, such as, for example, ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin-renine system, calcium antagonists, beta blockers etc.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having an antiinflammatory effect.

In one embodiment, the compounds of the formula I are administered in combination with medicaments which are employed for cancer therapy and cancer prevention.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

The activity of the compounds was tested as follows:

Cloning of the cDNA for the human MCH receptor, preparation of a recombinant HEK293 cell line which expresses the human MCH receptor, and functional measurements with the recombinant cell line took place in analogy to the description by Audinot et al. (J. Biol. Chem. 276, 13554-13562, 2001). A difference from the reference was, however, the use of the plasmid pEAK8 from EDGE Biosystems (USA) for the construction of the expression vector. The host used for the transfection was a transformed HEK cell line named "PEAK Stable Cells" (likewise from EDGE Biosystems). Functional measurements of the cellular calcium flux after addition of agonist (MCH) in the presence of ligand of the invention took place with the aid of the FLIPR apparatus from Molecular Devices (USA), using protocols of the apparatus manufacturer.

Biological test model

The anorectic effect was tested on female NMRI mice. After withdrawal of feed for 17 hours, the test product was administered by gavage. The animals were housed singly with free access to drinking water and were offered condensed milk 30 minutes after administration of the product. The condensed milk consumption was determined every half hour for 7 hours, and the general wellbeing of the animals was observed. The measured milk consumption was compared with the vehicle-treated control animals.

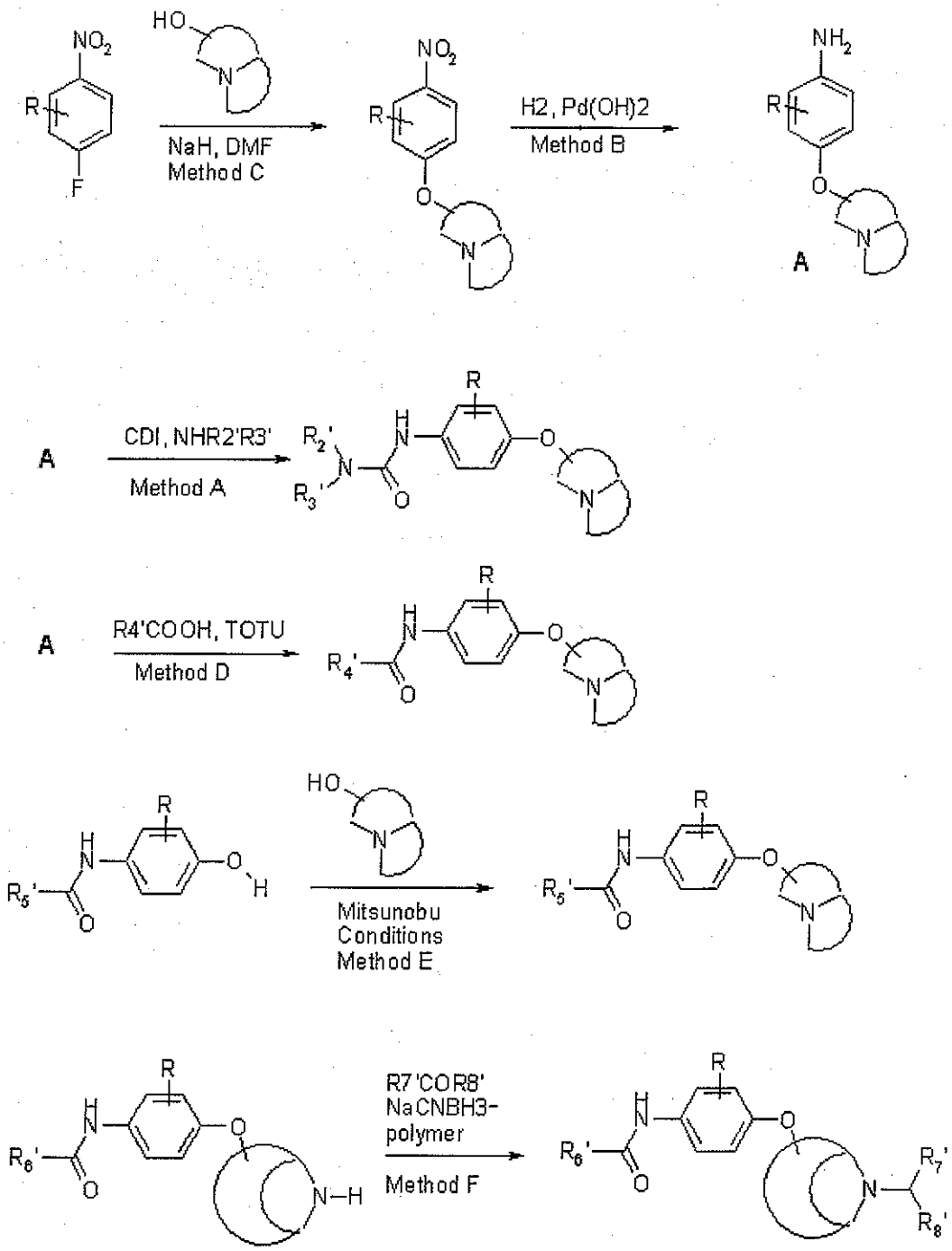
Table 1: Anorectic effect relating to compounds of the formula I, measured as the reduction in the cumulative milk consumption of treated compared with control animals.

Example	Oral dose [mg/kg]	Reduction in cumulative milk consumption as % of the control
2	30	73
37	30	24

The examples and preparation methods detailed below serve to illustrate the invention without, however, restricting it.

Preparation Methods

The compounds of the invention of the formula I can be prepared with the aid of reactions known in principle. For example, the compounds were obtained according to the following general reaction schemes.



Descriptions of the general methods used are to be found by way of example at the following places:

Methods A, B and C in Example 1;

Method D in Example 2;

Method E in Example 5;

Method F in Example 78.

Examples

General explanations

a) Mode of drawing the structural formulae

Only non-hydrogen atoms are depicted for clarity in the structural formulae of the examples given.

b) Salt forms

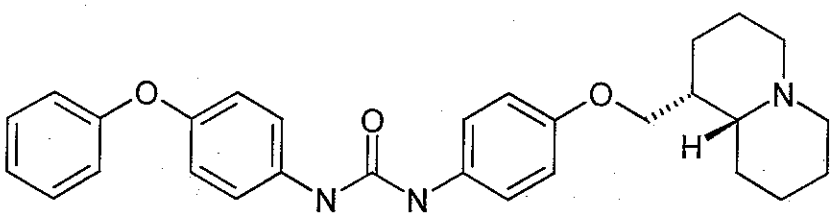
Many of the compounds of the invention are bases and can form salts with appropriately strong acids. In particular, after purification of the compounds by HPLC chromatography using a trifluoroacetic acid-containing mobile phase they may be in the form of hydrotrifluoroacetates. These can be converted into the free bases shown by simple treatment of a solution of the salts for example with sodium carbonate solution.

c) Units of the characterizing data

The unit of the stated molecular weights is "g/mol". Peaks observed in the mass spectrum are indicated as integral quotient of the molar molecular ion mass and of the charge on the molecular ion (m/z).

Example 1

1-{4-[(1R, 9aR)-1-(Octahydroquinolizin-1-yl)methoxy]phenyl}-3-(4-phenoxy-phenyl)urea



Method A

A solution of 4-phenoxyaniline (185 mg) in DMF (1 ml) was added dropwise to a solution, cooled to 0°C, of carbonyldiimidazole (162 mg) in DMF (1 ml). After 30 minutes, 4-[(1R, 9aR)-1-(octahydroquinolizin-1-yl)-methoxy]-phenylamine (289 mg) in DMF (1 ml) was added dropwise. The reaction solution was kept firstly at room temperature for 2 hours and then at 80°C for 30 minutes. The mixture was added dropwise to water (20 ml), and the resulting precipitate was filtered off with suction and washed with water. Alternatively, the product can also be extracted with ethyl acetate and purified after concentration by chromatography. The product with the molecular weight of 471.60 ($C_{29}H_{33}N_3O_3$); MS (ESI): 472 (M+H+) was obtained in this way.

4-[(1R, 9aR)-1-(Octahydroquinolizin-1-yl)-methoxy]phenylamine

Method B

A suspension of (1R, 9aR-1-(4-nitrophenoxymethyl)-octahydroquinolizine (800 mg) and palladium(II) hydroxide (20% on carbon; 0.15 g) in ethanol (30 ml) was vigorously stirred under a hydrogen atmosphere (atmospheric pressure) for 3 hours. The catalyst was then removed by filtration, and the filtrate was concentrated. The product with the molecular weight of 260.38 ($C_{16}H_{24}N_2O$); MS (ESI): 261 (M+H+) was obtained in this way.

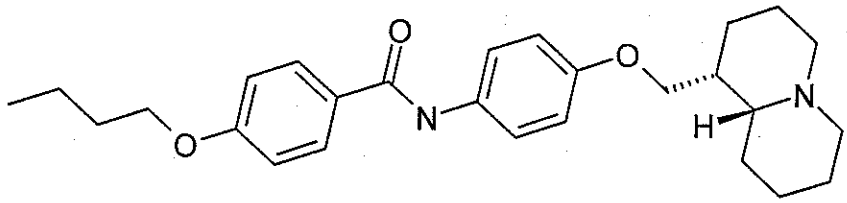
(1R,9aR)-1-(4-Nitrophenoxymethyl)octahydroquinolizine

Method C

(1R,9aR)-1-(Octahydroquinolizin-1-yl)methanol (2.5 g) was added to a suspension of sodium hydride (60% in oil, 710 mg) in DMF (20 ml) and, after gas evolution ceased, 4-fluoronitrobenzene (2.51 g) was added. After 2 hours, the reaction mixture was hydrolyzed with water and then partitioned between ethyl acetate and dilute hydrochloric acid. The aqueous phase was made alkaline with sodium hydroxide solution and extracted twice with ethyl acetate. The two ethyl acetate phases were combined, dried over magnesium sulfate and concentrated. The product with the molecular weight of 290.37 ($C_{16}H_{22}N_2O_3$); MS (ESI): 291 (M+H+) was obtained in this way.

Example 2

4-Butoxy-N-{4-[(1R,9aR)-1-(octahydroquinolizin-1-yl)methoxy]phenyl}-benzamide

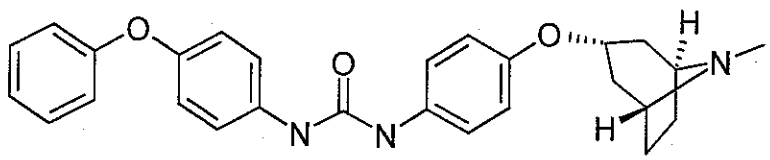


Method D

TOTU (78 mg) and ethyldiisopropylamine (31 mg), followed by 4-[(1R,9aR)-1-(octahydroquinolizin-1-yl)methoxy]phenylamine (62 mg), were added to a solution of 4-butoxybenzoic acid (46.4 mg) in DMF (2 ml) at 0°C. After a reaction time of three hours at room temperature, the mixture was diluted with sodium bicarbonate solution and ethyl acetate. After separation of the phases, the aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulfate and concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 436.60 (C27H36N2O3); MS (ESI): 437 (M+H+) was obtained in this way.

Example 3

1-[4-((1S*,3R*,5R*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenyl]-3-(4-phenoxyphenyl)urea



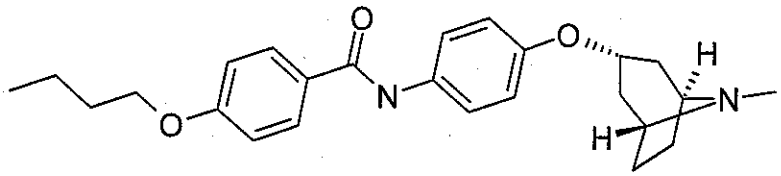
4-Phenoxyaniline was reacted by method A with 4-((1S*,3R*,5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenylamine. The product with the molecular weight of 443.55 (C27H29N3O3); MS (ESI): 444 (M+H+) was obtained in this way.

4-((1S*,3R*,5R*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenylamine

(1S*,3R*,5R*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-ol was reacted by method C and B with 4-fluoronitrobenzene and then hydrogenated. The product with the molecular weight of 232.33 ($C_{14}H_{20}N_2O$); MS (ESI): 233 (M+H+) was obtained in this way.

Example 4

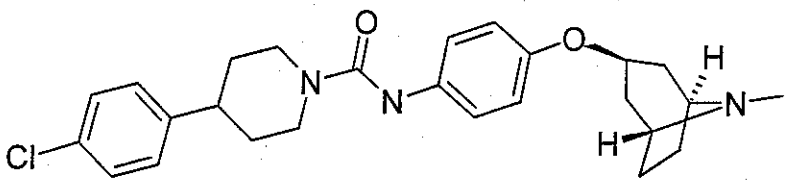
4-Butoxy-N-[4-((1S*,3R*,5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)-phenyl]benzamide



4-Butoxybenzoic acid was reacted by method D with 4-((1S*,3R*,5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenylamine. The product with the molecular weight of 408.55 ($C_{25}H_{32}N_2O_3$); MS (ESI): 409 (M+H+) was obtained in this way.

Example 5

4-(4-Chlorophenyl)piperidine-1-carboxylic acid [4-((1S*,3S*,5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenyl]amide



Method E

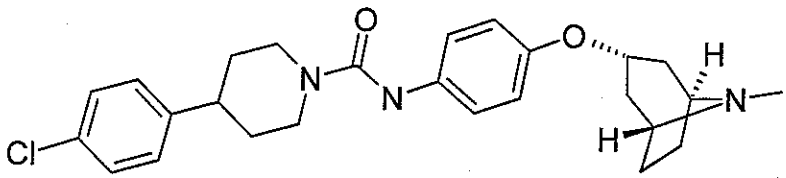
Di-tert-butyl azodicarboxylate (69.5 mg) was added to a stirred suspension of triphenylphosphine (polymer, 80 mg) in dichloromethane (3 ml) at 0°C and, after 5 minutes, a mixture of tropine, 4-(4-chlorophenyl)piperidine-1-carboxylic acid (4-hydroxyphenyl)amide (100 mg) and dichloromethane (3 ml) was added. After 12 hours at room temperature, the polymer was filtered off with suction and the filtrate was concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 454.02 ($C_{26}H_{32}ClN_3O_2$); MS (ESI): 454 (M+H+) was obtained in this way.

4-(4-Chlorophenyl)piperidine-1-carboxylic acid (4-hydroxyphenyl)amide

Carbonyldiimidazole (1.48 g) was added to a solution of 4-aminophenol (1.0 g) in DMF (10 ml) at 0°C. After 10 minutes, a mixture of 4-(4-chlorophenyl)piperidine (hydrochloride; 2.13 g), Hünig's base (1.18 g) and DMF (10 ml) was added. After two hours, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated. The product with the molecular weight of 330.82 (C18H19ClN2O2); MS (ESI): 331 (M+H+) was obtained in this way.

Example 6

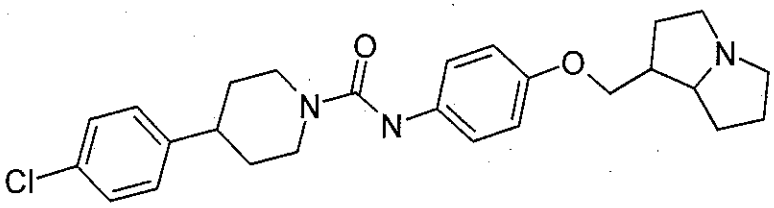
4-(4-Chlorophenyl)piperidine-1-carboxylic acid [4-((1S*, 3R*, 5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenyl]amide



4-(4-Chlorophenyl)piperidine was reacted by method A with [4-((1S*, 3R*, 5R*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)phenyl]amide. The product with the molecular weight of 454.02 (C26H32ClN3O2); MS (ESI): 454 (M+H+) was obtained in this way.

Example 7

4-(4-Chlorophenyl)piperidine-1-carboxylic acid [4-(4-oxooctahydroquinolizin-1-yloxy)phenyl]amide



4-(4-Chlorophenyl)piperidine was reacted by method E with (hexahydropyrrolizin-1-yl)methanol. The product with the molecular weight of 454.02 (C26H32ClN3O2); MS (ESI): 454 (M+H+) was obtained in this way.

(Hexahydropyrrolizin-1-yl)methanol

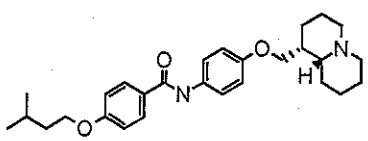
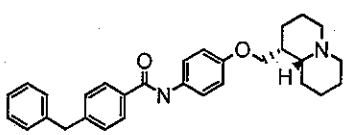
Lithiumaluminumhydride (0.3 g) was added to a solution of hexahydropyrrolizine-1-carboxylic acid ethyl ester (0.97 g) in THF (3 ml). After 12 hours, the reaction mixture was diluted with diethyl ether and hydrolyzed by cautious addition of water (0.7 ml). The resulting precipitate was filtered off and the filtrate was concentrated. The product with the molecular weight of 141.21 (C8H15NO); MS (ESI): 142 (M+H+) was obtained in this way.

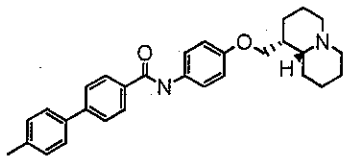
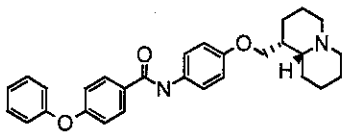
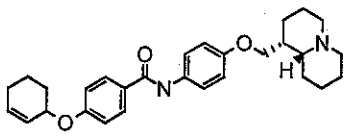
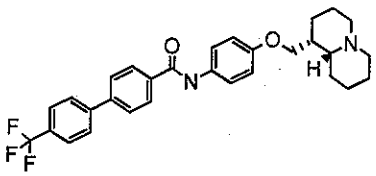
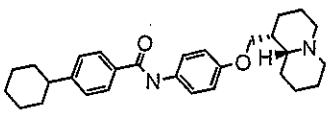
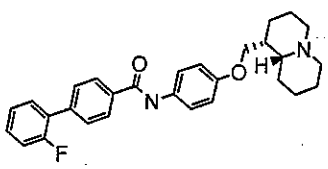
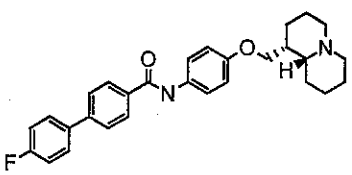
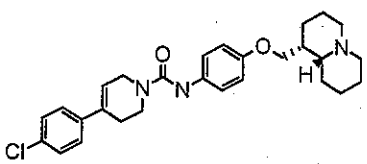
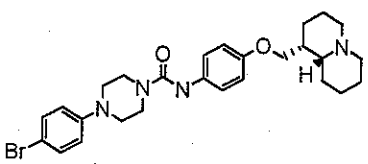
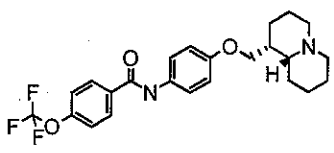
Hexahydropyrrolizine-1-carboxylic acid ethyl ester

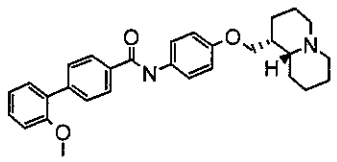
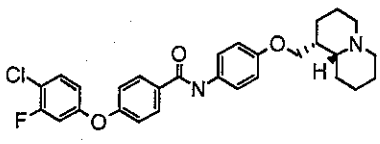
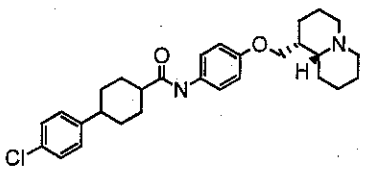
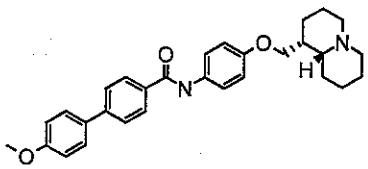
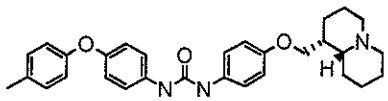
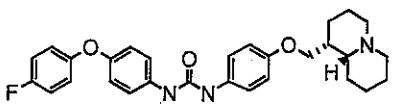
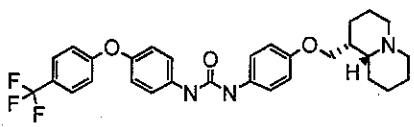
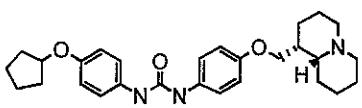
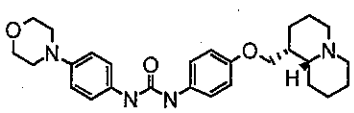
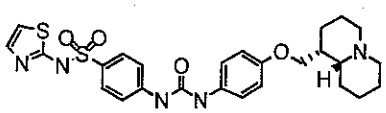
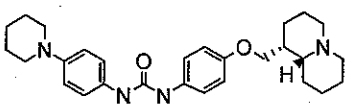
A mixture of rac-proline (1.15 g), ethyl acrylate (1.20 g), toluene (80 ml) and paraformaldehyde (3.6 g) was heated to reflux for 3 hours. The mixture was concentrated and the residue was filtered through silica gel. The product with the molecular weight of 183.25 (C10H17NO2); MS (ESI): 184 (M+H+) was obtained in this way.

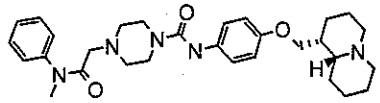
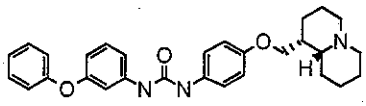
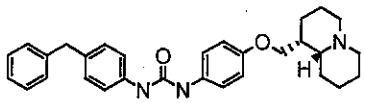
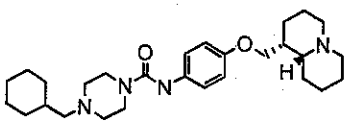
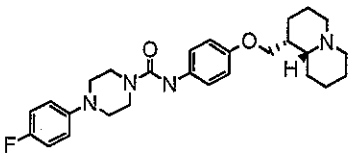
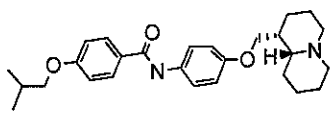
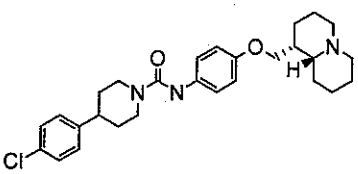
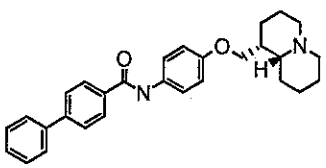
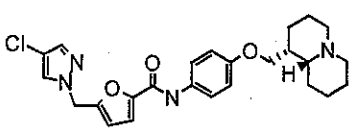
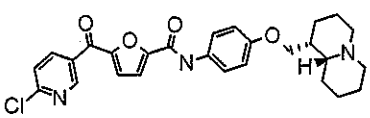
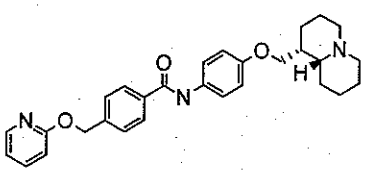
The compounds in Table 2a and Table 2b were obtained by method A (for ureas) or method D (for amides).

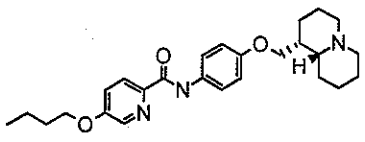
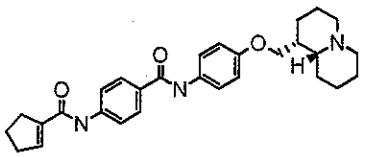
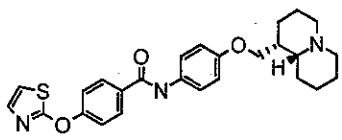
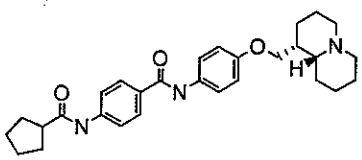
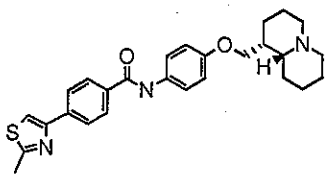
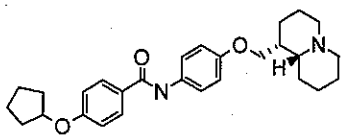
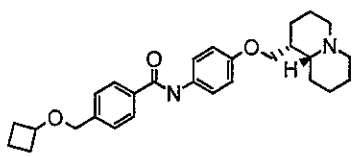
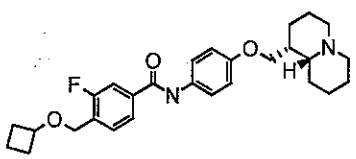
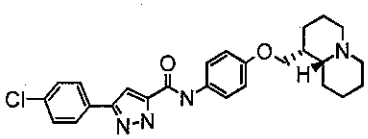
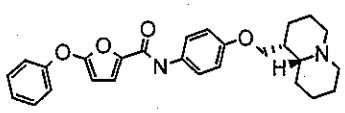
Table 2a.

Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS $[M+H]^+$
8		C28H38N2O3	450.63	451
9		C30H34N2O2	454.62	455

10		C30H34N2O2	454.62	455
11		C29H32N2O3	456.59	457
12		C29H36N2O3	460.62	461
13		C30H31F3N2O2	508.59	509
14		C29H38N2O2	446.64	447
15		C29H31FN2O2	458.58	459
16		C29H31FN2O2	458.58	459
17		C28H34ClN3O2	480.06	480
18		C27H35BrN4O2	527.51	528
19		C24H27F3N2O3	448.49	449

20		C30H34N2O3	470.62	471
21		C29H30ClFN2O3	509.03	509
22		C29H37ClN2O2	481.08	481
23		C30H34N2O3	470.62	471
24		C30H35N3O3	485.63	486
25		C29H32FN3O3	489.60	490
26		C30H32F3N3O3	539.60	540
27		C28H37N3O3	463.63	464
28		C27H36N4O3	464.61	465
29		C26H31N5O4S2	541.70	542
30		C28H38N4O2	462.64	463

31		C30H41N5O3	519.69	520
32		C29H33N3O3	471.60	472
33		C30H35N3O2	469.63	470
34		C28H44N4O2	468.69	469
35		C27H35FN4O2	466.60	467
36		C27H36N2O3	436.60	437
37		C28H36ClN3O2	482.07	482
38		C29H32N2O2	440.59	441
39		C25H29ClN4O3	468.99	469
40		C27H28ClN3O4	493.99	494
41		C29H33N3O3	471.60	472

42		C26H35N3O3	437.59	438
43		C29H35N3O3	473.62	474
44		C26H29N3O3S	463.60	464
45		C29H37N3O3	475.64	476
46		C27H31N3O2S	461.63	462
47		C28H36N2O3	448.61	449
48		C28H36N2O3	448.61	449
49		C28H35FN2O3	466.60	467
50		C26H29ClN4O2	465.00	465
51		C27H30N2O4	446.55	447

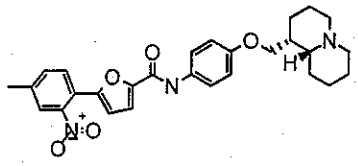
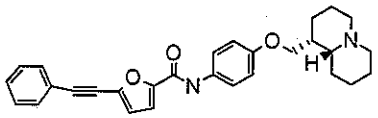
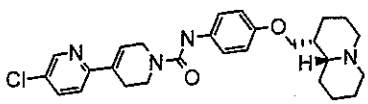
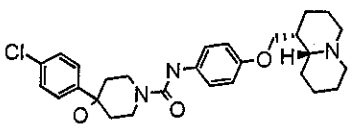
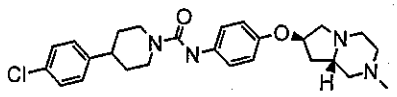
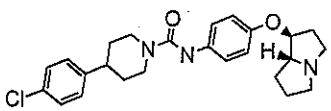
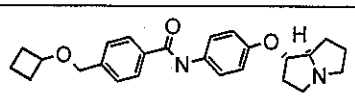
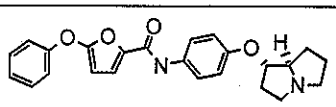
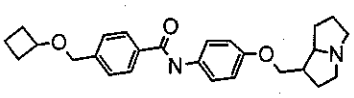
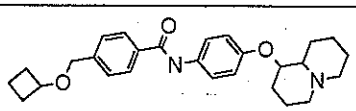
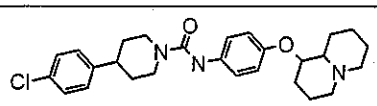
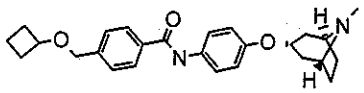
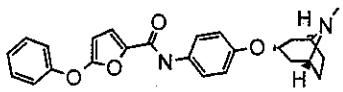
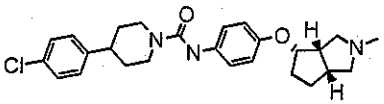
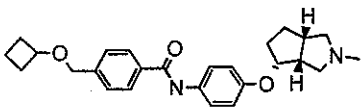
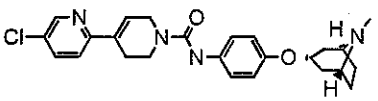
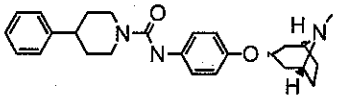
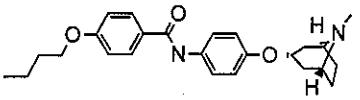
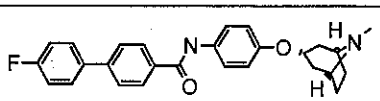
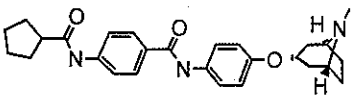
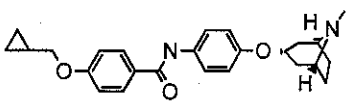
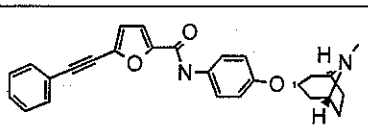
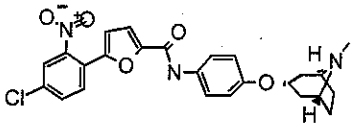
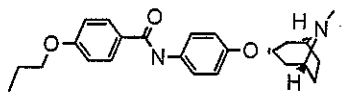
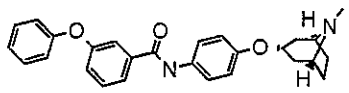
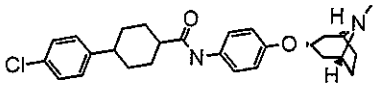
52		C28H31N3O5	489.58	490
53		C29H30N2O3	454.57	455
54		C27H33ClN4O2	481.04	482
55		C28H36ClN3O3	498.07	498

Table 2b.

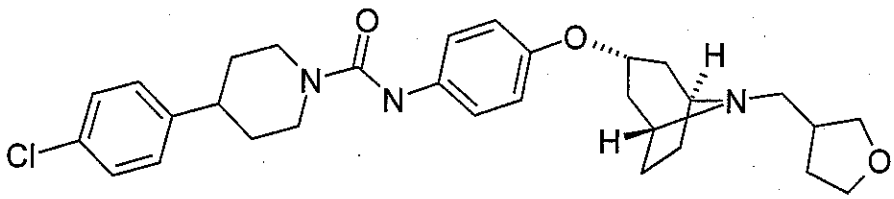
Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS $[M+H]^+$
56		C26H33ClN4O2	469.03	469
57		C25H30ClN3O2	439.99	440
58		C25H30N2O3	406.53	407
59		C24H24N2O4	404.47	405
60		C26H32N2O3	420.56	421
61		C27H34N2O3	434.58	435

62		C27H34ClN3O2	468.04	468
63		C26H32N2O3	420.56	421
64		C25H26N2O4	418.50	419
65		C26H32ClN3O2	454.02	454
66		C26H32N2O3	420.56	421
67		C25H29ClN4O2	452.99	453
68		C26H33N3O2	419.57	420
69		C25H32N2O3	408.55	409
70		C27H27FN2O2	430.53	431
71		C27H33N3O3	447.58	448
72		C25H30N2O3	406.53	407
73		C27H26N2O3	426.52	427

74		C25H24ClN3O5	481.94	482
75		C24H30N2O3	394.52	395
76		C27H28N2O3	428.54	429
77		C27H33ClN2O2	453.03	453

Example 78

4-(4-Chloro-phenyl)-piperidine-1-carboxylic acid {4-((1S*,3R*,5R*)-[8-(tetrahydrofuran-3-ylmethyl)-8- aza-bicyclo[3.2.1]oct-3-yloxy]-phenyl}-amide



Method F

A mixture of 4-(4-Chloro-phenyl)-piperidine-1-carboxylic acid [4-((1S*,3R*,5R*)-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenyl]-amide (50 mg), tetrahydrofuran-3-carbaldehyde (10 mg), acetic acid (7 mg), THF (2 ml) was mixed with sodium cyanoborohydride (polymer-bound); 0.12 mmol) and stirred for 12 h. The polymer was filtered off with suction and the filtrate was concentrated. The residue was purified by preparative HPLC. The product with the molecular weight of 524.11 (C30H38ClN3O3); MS (ESI): 524 (M+H+) was obtained in this way.

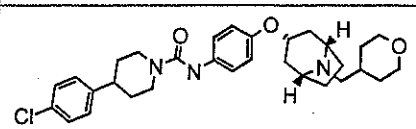
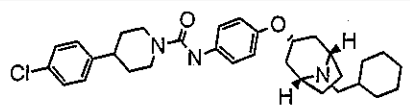
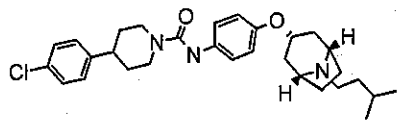
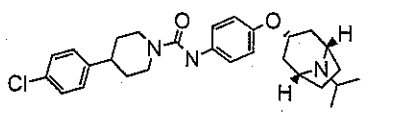
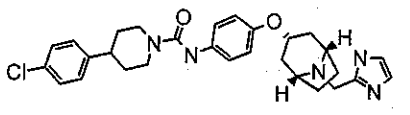
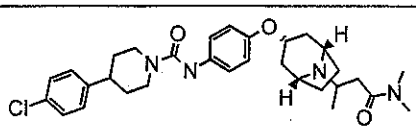
4-(4-Chloro-phenyl)-piperidine-1-carboxylic acid [4-((1S*,3R*,5R*)-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenyl]-amide

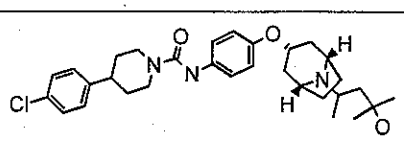
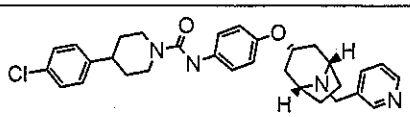
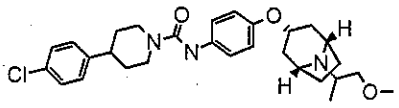
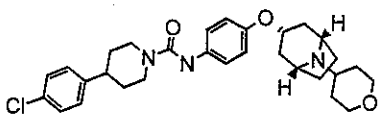
(1S*,3R*,5R*)-8-azabicyclo[3.2.1]octan-3-ol was protected by a standard process (di-tert-butyl dicarbonate, sodium hydroxide, THF/water) and the

resulting carbonate was first reacted with 4-fluoronitrobenzene and then hydrogenated by methods C and B. The resulting aniline ((1S,3R,5R)-3-(4-Amino-phenoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester) was reacted by method A with 4-(4-chlorophenyl)piperidine and finally the amine was liberated with trifluoroacetic acid in dichloromethane. The product with the molecular weight of 439.99 (C25H30ClN3O2); MS (ESI): 440 (M+H+) was obtained in this way.

The examples in table 3 were obtained by reacting 4-(4-chloro-phenyl)-piperidine-1-carboxylic acid[4-((1S*,3R*,5R*)-8-aza-bicyclo[3.2.1]oct-3-yloxy)-phenyl]-amide with the appropriate carbonyl compounds by method F.

Table 3.

Ex. No.	Structure	Molecular formula	Molecular weight	ESI-MS $[M+H]^+$
79		C31H40ClN3O3	538.14	538
80		C32H42ClN3O2	536.16	536
81		C30H40ClN3O2	510.13	510
82		C28H36ClN3O2	482.07	482
83		C29H34ClN5O2	520.08	520
84		C31H41ClN4O3	553.15	553

85		C31H42ClN3O3	540.15	540
86		C31H35ClN4O2	531.10	531
87		C29H38ClN3O3	512.10	512
88		C30H38ClN3O3	524.11	524

Synthesis of starting materials which cannot be purchased

4-(Cyclopentanecarbonylamino)benzoic acid

4-Aminobenzoic acid ethyl ester was reacted by method E with cyclopentanecarboxylic acid, and the resulting ester was hydrolyzed by boiling with sodium hydroxide in aqueous ethanol. The product with the molecular weight of 233.27 (C13H15NO3); MS (ESI): 234 (M+H+) was obtained in this way.

4-[(Cyclopent-1-enecarbonyl)amino]benzoic acid can be obtained analogously.

4-Cyclobutoxymethylbenzoic acid

Sodium hydride (50% in oil; 0.42 g) was cautiously added to a solution of cyclobutanol (0.7 g) in DMF (8 ml). After gas evolution ceased, 4-bromomethylbenzoic acid methyl ester (1.0 g) was added. After 4 hours, the mixture was partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. The ester obtained as crude product was hydrolyzed by boiling with sodium hydroxide in aqueous ethanol. The product with the molecular weight of 206.24 (C12H14O3); MS (ESI): 207 (M+H+) was obtained in this way.

4-Cyclobutoxymethyl-3-fluorobenzoic acid

Sodium hydride (50% in oil; 1.63 g) was cautiously added to a solution of cyclobutanol (2.7 g) in DMF (12 ml). After gas evolution ceased, 4-bromo-1-bromomethyl-2-fluorobenzene (10 g) was added at 0°C. After 6 hours at room temperature, the mixture was cautiously hydrolyzed and then partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. 4-Bromo-1-cyclobutoxymethyl-2-fluorobenzene was obtained as crude product in this way.

n-Butyllithium (1.6 M in hexane; 7.0 ml) was added to a solution of 4-bromo-1-cyclobutoxymethyl-2-fluorobenzene (2.6 g) in THF (50 ml) at -78°C. After 15 minutes, dry ice (4.4 g) was added. After warming to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The aqueous phase was acidified and again extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated. The product with the molecular weight of 224.23 ($C_{12}H_{13}FO_3$); MS (ESI): 225 ($M+H^+$) was obtained in this way.

4-(Pyridin-2-yloxymethyl)benzoic acid

A mixture of 2-fluoropyridine (1.6 g), 4-bromobenzyl alcohol (3.08 g), potassium tert-butoxide (2.03 g) and N-methylpyrrolidone (12.8 ml) was heated at 100°C by microwave irradiation for one minute. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated. 2-(4-Bromobenzyloxy)pyridine was obtained in this way.

n-Butyllithium (1.6 M in hexane; 11.4 ml) was added to a solution of 2-(4-bromobenzyloxy)pyridine (4.2 g) in THF (120 ml) at –78°C. After 15 minutes, dry ice (7 g) was added. After warming to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The aqueous phase was acidified and again extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated. The product with the molecular weight of 229.24 ($C_{13}H_{11}NO_3$); MS (ESI): 230 ($M+H^+$) was obtained in this way.

5-Butoxypyridine-2-carboxylic acid

Sodium hydride (50% in oil, 250 mg) was added to 5-hydroxypyridine-2-carboxylic acid benzhydryl ester (2.0 g) dissolved in DMF (20 ml) and, after gas evolution ceased, 1-bromobutane (0.72 g) was added. The mixture was heated at 90°C for 6 hours. It was diluted with water and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated. The residue was hydrogenated in analogy to method B. The product with the molecular weight of 195.22 (C10H13NO3); MS (ESI): 196 (M+H+) was obtained in this way.

5-Chloro-1',2',3',6'-tetrahydro-[2,4']bipyridinyl

Butyllithium (15% in hexane; 7.6 ml) was added dropwise to a solution of 2-bromo-5-chloropyridine (2.0 g) in diethyl ether (50 ml) at –78°C and, after one hour, a solution of N-tert-butoxycarbonyl-4-piperidinone (2.1 g) in diethyl ether (10 ml) was added dropwise. After 30 minutes, water was cautiously added, and the mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was treated with thionyl chloride (3 g) for 24 hours, and the concentrated reaction solution was purified by preparative HPLC. The product with the molecular weight of 194.67 (C10H11ClN2); MS(ESI): 195 (M+H+) was obtained in this way.

4-Cyclopentyloxyaniline

A mixture of 4-nitrophenol (63.7 g), bromocyclopentane (68.2 g), potassium carbonate (63.3 g) and DMF (300 ml) was heated at 80°C for 24 hours. Cooling was followed by dilution with water and extraction with ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and concentrated. The residue was hydrogenated by method B. The product with the molecular weight of 177.25 (C11H15NO); MS (ESI): 178 (M+H+) was obtained in this way.

Starting from the appropriate cyclic amino alcohols, reaction with 4-fluoronitrobenzene by method C and subsequent hydrogenation resulted in the following anilines:

4-((S)-2-Benzyl-2-aza-bicyclo[2.2.2]oct-6-yloxy)-phenylamine;

4-((7R,8aS)-2-Methyl-octahydro-pyrrolo[1,2-a]pyrazin-7-yloxy)-phenylamine;

4-[(4R*,5S*)-(1-Aza-bicyclo[3.3.1]non-4-yl)oxy]-phenylamine;

4-[(1R*,7aS*)-(Hexahydro-pyrrolizin-1-yl)oxy]-phenylamine;

4-(Octahydro-quinolizin-1-yloxy)-phenylamine and

4-((3aS*,4S*,6aR*)-2-Methyl-octahydro-cyclopenta[c]pyrrol-4-yloxy)-phenylamine.

The required cyclic amino alcohols were obtained by literature methods:

(7R,8aS)-2-Methyl-octahydro-pyrrolo[1,2-a]pyrazin-7-ol (J. Heterocyclic Chem. 1999, 27, 2181);

(4R*,5S*)-1-Aza-bicyclo[3.3.1]nonan-4-ol (lithium aluminum hydride reduction of 1-aza-bicyclo[3.3.1]nonan-4-one (J. Med. Chem. 2003, 46, 2216));

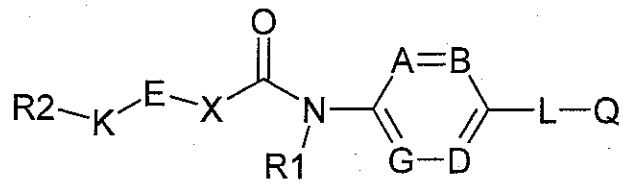
(1R*,7aS*)-Hexahydro-pyrrolizin-1-ol (Tetrahedron Lett. 1996, 52, 3757);

Octahydro-quinolizin-1-ol (J. Org. Chem. 1964, 29, 2248) and

(3aS*,4S*,6aR*)-2-Methyl-octahydro-cyclopenta[c]pyrrol-4-ol ((3aS*,4S*,6aR*)-2-Trityl-octahydro-cyclopenta[c]pyrrol-4-ol (Eur. J. Med. Chem. 1991, 26, 889) was heated in a mixture of formic acid and aqueous formaldehyde).

Claims

1. A compound of the formula I



I

in which the meanings are

A, B, D, G

independently of one another N, C(R3);

or

groups A and B or groups D and G are in each case C(R3) and form together a 5- or 6-membered carbocyclic or heterocyclic radical to result overall in a bicyclic system;

R3 H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_3-C_8)-cycloalkyl, O-(C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkenyl, (C_2-C_6)-alkynyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R4)(R5), SO_2-CH_3, COOH, COO-(C_1-C_6)-alkyl, CON(R6)(R7), N(R8)CO(R9), N(R10)SO_2(R11), CO(R12), $(CR13R14)_x$-O(R15);

R4, R5, R6, R7, R8, R10

independently of one another H, (C_1-C_8)-alkyl;

or

R4 and R5, R6 and R7

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R9, R11, R12

independently of one another H, (C_1-C_8)-alkyl, aryl;

R13, R14

independently of one another H, (C_1-C_8)-alkyl;

R15 H, (C_1-C_6)-alkyl, aryl;

x 0, 1, 2, 3, 4, 5, 6;

R1 H, (C_1-C_8)-alkyl, (C_3-C_6)-alkenyl, (C_3-C_6)-alkynyl;

X N(R16), O, a bond, (R17)C=C(R18), C≡C, a group of the formula $(CR19R20)_y$, in which one or two (CR19R20) groups may be replaced by Y to result in a chemically reasonable radical;

Y O, S, N(R21), C=O;

R16, R17, R18

independently of one another H, (C_1-C_8)-alkyl;

R19, R20

independently of one another H, (C_1-C_4)-alkyl, where R19 and R20 in the y groups may in each case have identical or different meanings;

y 1, 2, 3, 4, 5, 6;

R21 H, (C_1-C_8)-alkyl;

E 3-14 membered bivalent carbo- or heterocyclic ring structure having 0-4 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, I, OH, CF_3, CN, OCF_3, oxo, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_3-C_8)-cycloalkyl, O-(C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkenyl, O-(C_3-C_8)-cycloalkenyl, (C_2-C_6)-alkynyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R22)(R23), SO_2-CH_3, CON(R24)(R25), N(R26)CO(R27), N(R28)SO_2(R29), CO(R30) and be mono- or bicyclic, where E is not a tetrazol-5-yl group;

R22, R23, R24, R25, R26, R28

independently of one another H, (C_1-C_8)-alkyl, aryl;

or

R22 and R23, R24 and R25

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R27, R29, R30

independently of one another H, $(C_1$-$C_8)$-alkyl, aryl;

K a bond, C≡C, (R31)C=C(R32), a group of the formula $(CR33R34)_z$ in which one or more (CR33R34) groups may be replaced by Z to result in a chemically reasonable radical, preferably a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2;

v 1, 2, 3, 4;

R31, R32, R35, R36, R37, R38, R39

independently of one another H, $(C_1$-$C_8)$-alkyl;

Z O, S, N(R40), CO, SO, SO_2;

R33, R34

independently of one another H, $(C_1$-$C_8)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, hydroxy, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, where R38 and R39 in the z groups may in each case have identical or different meanings;

z 1, 2, 3, 4, 5, 6;

R40 H, $(C_1$-$C_8)$-alkyl;

R2 H, (C_1-C_8)-alkyl, (C_1-C_8)-alkoxy-(C_1-C_4)-alkyl, (C_3-C_8)-alkenyl, (C_3-C_8)-alkynyl, a 3 to 10-membered mono-, bi-, tri- or spirocyclic ring which may include 0 to 4 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, NO_2, CN, (C_1-C_6)-alkyl, O-(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_0-C_8)-alkylene-aryl, oxo, CO(R41), CON(R42)(R43), hydroxy, COO(R44), N(R45)CO(C_1-C_6)-alkyl, N(R46)(R47), SO_2CH_3, SCF_3 or S-(C_1-C_6)-alkyl, where R2 is not a tetrazol-5-yl group;

R41, R42, R43, R44, R45, R46, R47

independently of one another H, (C_1-C_8)-alkyl;

or

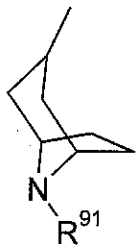
R42 and R43, R46 and R47

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

E, K and R2

together form a tricyclic system where the rings may independently of one another saturated, partially saturated or unsaturated and in each case comprise 3 – 8 ring atoms;

L a group of the formula $(CR48R49)_m$ in which one or more (CR48R49) groups may be replaced by M to result in a chemically reasonable radical, where L is O if Q is



where R91 is as defined below;

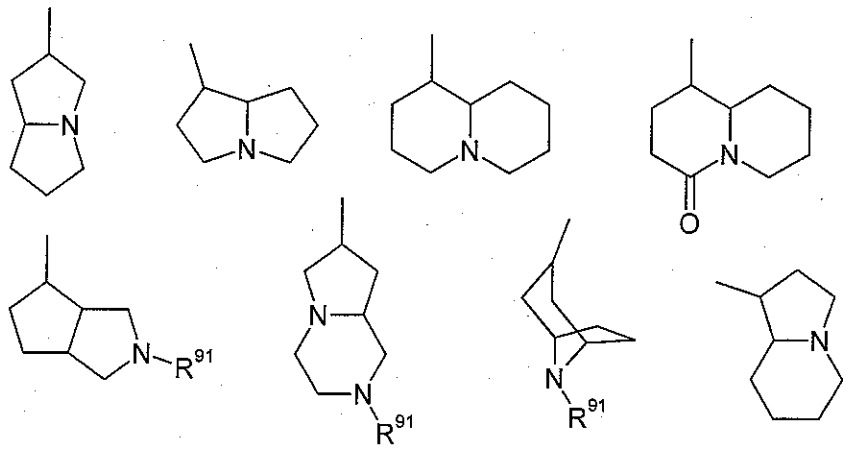
M O, S, N(R50), CO, SO, SO_2, preferably O, S, N(R50), CO, SO_2, particularly preferably O, N(R50), very particularly preferably O;

m 1, 2, 3, 4, 5, 6, preferably 1, 2, 3, 4, particularly preferably 1, 2;

R48, R49, R50

independently of one another H, (C_1-C_6)-alkyl, aryl;

Q



R91 H, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96;

R92 H, $(C_1$-$C_8)$-alkyl;

R93, R94

independently of one another H, $(C_1$-$C_8)$-alkyl, OH, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6;

R95, R96

independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH;

R97, R98, R99, R100, R103, R104

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further

heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q',r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, (C_1-C_8)-alkyl;

or

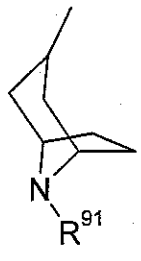
R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

the N-oxides thereof and the physiologically tolerated salts thereof.

2. A compound of the formula I as claimed in claim 1, in which the meanings are

L a group of the formula $(CR48R49)_m$ in which one or more (CR48R49) groups may be replaced by M to result in a chemically reasonable radical, where L is O if Q is



,

M O, S, N(R50), CO, SO, SO_2, preferably O, S, N(R50), CO, SO_2, particularly preferably O, N(R50), very particularly preferably O;

m 1, 2, 3, 4, 5, 6, preferably 1, 2, 3, 4, particularly preferably 1, 2;

R48, R49, R50

independently of one another H, (C_1-C_6)-alkyl, aryl, preferably H, (C_1-C_6)-alkyl, particularly preferably H.

3. A compound of the formula I as claimed in claim 1 or 2,

in which the meanings are

A, B, D, G

independently of one another N, C(R3) or groups A and B or D and G are each C(R3) and form together an ortho-phenylene unit to result overall in a 1,4-disubstituted naphthalene system; preferably independently of one another N or C(R3), where the total number of nitrogen atoms in the ring is 0 - 2, preferably 0 or 1, particularly preferably A, B, D and G are C(R3);

R3 H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_0-C_8)-alkylene-aryl, O-(C_0 - C_8)-alkylene-aryl, N(R4)(R5), SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15); preferably H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15), particularly preferably H, F, Cl, CF_3, CN, (C_1-C_6)-alkyl, $(C(R13)(R14))_x$-O(R15), very particularly preferably H, F, (C_1-C_6)-alkyl; further preferably H, F, CH_3; especially preferably H;

R4, R5, R6, R7, R8

independently of one another H, (C_1-C_8)-alkyl;

or

R4 and R5, R6 and R7

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R9, R12

independently of one another H, (C_1-C_8)-alkyl;

R13, R14

H;

R15 H, (C_1-C_6)-alkyl;

x 0, 1, 2, preferably 0, 1, particularly preferably 1;

R1 H, (C_1-C_8)-alkyl;

X N(R16), a bond, (R17)C=C(R18), C≡C, CH_2-CH_2, YCH_2, CH_2Y, preferably N(R16), a bond;

Y O, S, N(R21);

R16, R17, R18

independently of one another H, (C_1-C_8)-alkyl;

R21 H, (C_1-C_8)-alkyl;

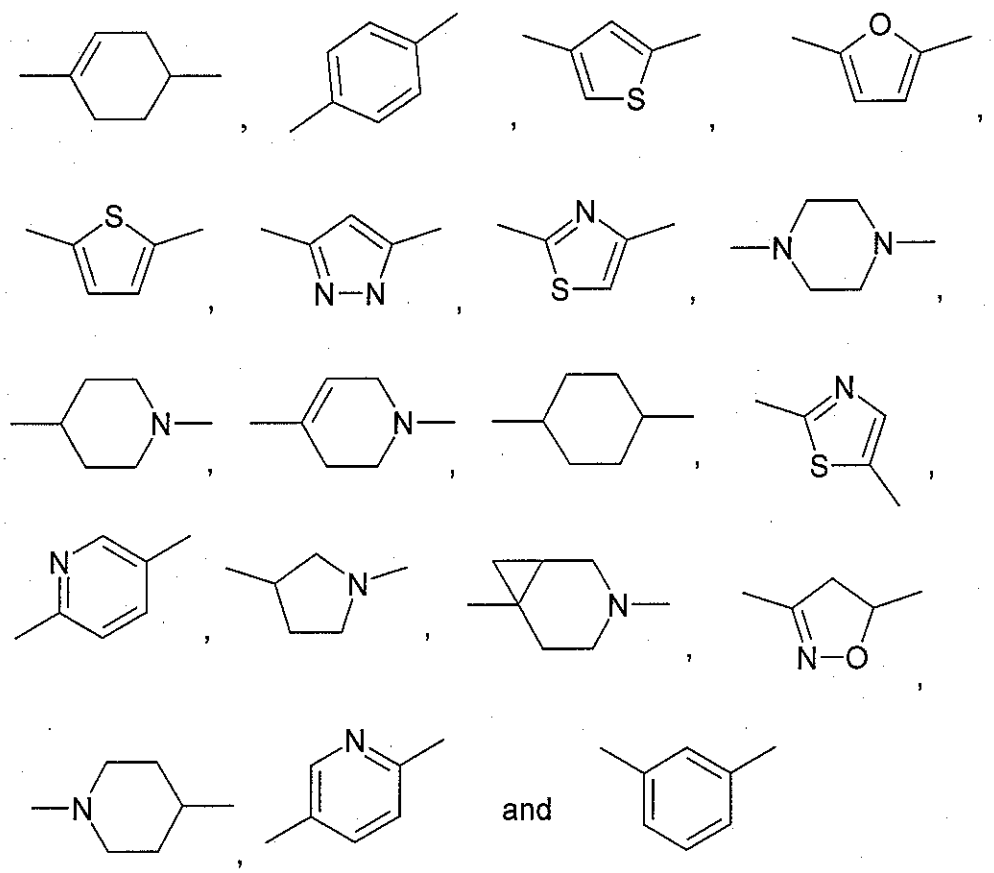
E 3-8 membered bivalent carbo- or heterocyclic ring structure having 0-4 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, O-(C_3-C_8)-cycloalkyl, (C_3-C_8)-cycloalkenyl, (C_2-C_6)-alkynyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, S-aryl, N(R22)(R23), SO_2-CH_3, N(R26)CO(R27), N(R28)SO_2(R29), CO(R30) and be mono- or bicyclic, where E is not a tetrazol-5-yl group;

preferably 5-7 membered bivalent carbo- or heterocyclic ring structure having 0-3 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, O-(C_0-C_8)-alkylene-aryl,

S-aryl, N(R22)(R23), SO_2-CH_3, N(R26)CO(R27), CO(R30) and be mono- or bicyclic;

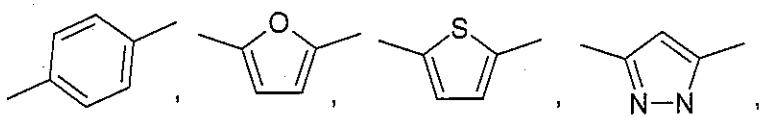
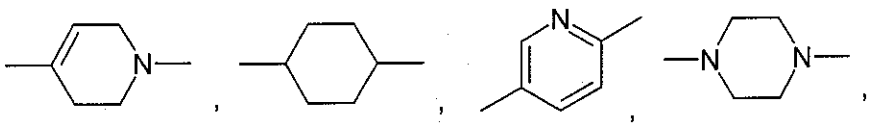
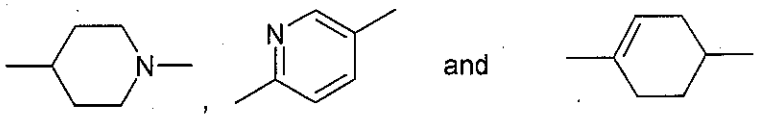
particularly preferably 5-7 membered bivalent carbo- or heterocyclic ring structure having 0-2 heteroatoms from the group of N, O and S, which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, N(R22)(R23), SO_2-CH_3, CO(R30), preferably H, F, Cl, Br, OH, CF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl,

e.g. E is selected from the group consisting of



which may optionally have substituents from the group of H, F, Cl, Br, OH, CF_3, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, N(R22)(R23), SO_2-CH_3, CO(R30), preferably H, F, Cl, Br, OH, CF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

preferably




and

which may optionally have the aforementioned substituents;

R22, R23

independently of one another H, (C_1-C_8)-alkyl;

or

R22 and R23

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R27, R29, R30

independently of one another H, (C_1-C_8)-alkyl;

K a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, N-SO_2, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, preferably a bond, O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$,

CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, particularly preferably OCH_2, CH_2O, N(R36)CO, CON(R37), $(C(R38)(R39))_2$, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, very particularly preferably OCH_2, CH_2O, CON(R37), C≡C, SCH_2;

v 1, 2, 3, preferably 2;

R31, R32, R35, R36, R37, R38, R39

independently of one another H, $(C_1$-$C_8)$-alkyl;

R2 $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, a 3 to 10-membered mono-, bi-, tri- or spirocyclic ring which may include 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_8)$-alkyl, $(C_0$-$C_2)$-alkylene-aryl, oxo, CO(R41), CON(R42)(R43), hydroxy, N(R45)CO$(C_1$-$C_6)$-alkyl, N(R46)(R47) or SO_2CH_3; preferably $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, a 3 to 10-membered mono- or bicyclic ring which may include 0 to 2 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_8)$-alkyl, oxo, CO(R41), CON(R42)(R43), N(R45)CO$(C_1$-$C_6)$-alkyl or SO_2CH_3;

R41, R42, R43, R45, R46, R47

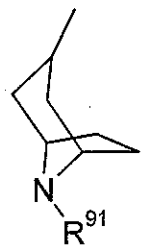
independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R42 and R43, R46 and R47

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

L a group of the formula $(C(R48)(R49))_m$ in which 0 or 1 member may be replaced by an element from the group of O, N(R50), preferably O, where L is O if Q is



,

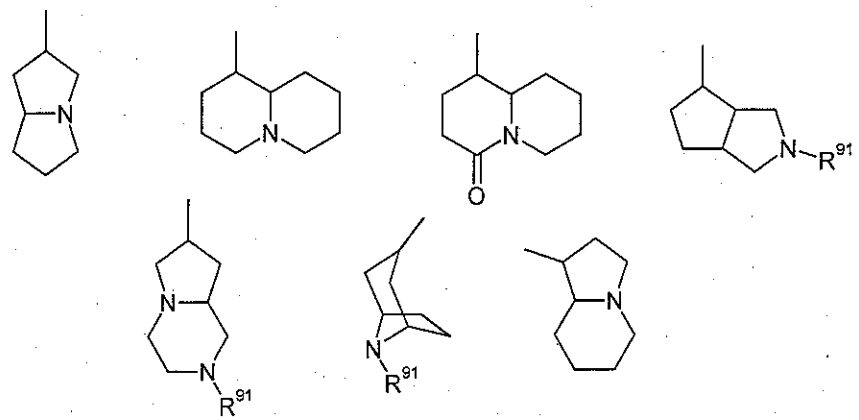
m 1, 2, 3, 4, preferably 1 or 2;

R48, R49

H;

R50 H, (C_1-C_8)-alkyl, preferably H;

Q



R91 H, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, $(C_1$-$C_6)$-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, $(C_1$-$C_8)$-alkyl;

R93, R94

independently of one another H, $(C_1$-$C_8)$-alkyl, OH, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$alkyl, preferably H, $(C_1$-$C_8)$-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 hetereoatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-$(C_1$-$C_8)$-alkyl, $(C_1$-$C_6)$-alkyl, CO(R112), oxo, OH, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, (C_1-C_8)-alkyl;

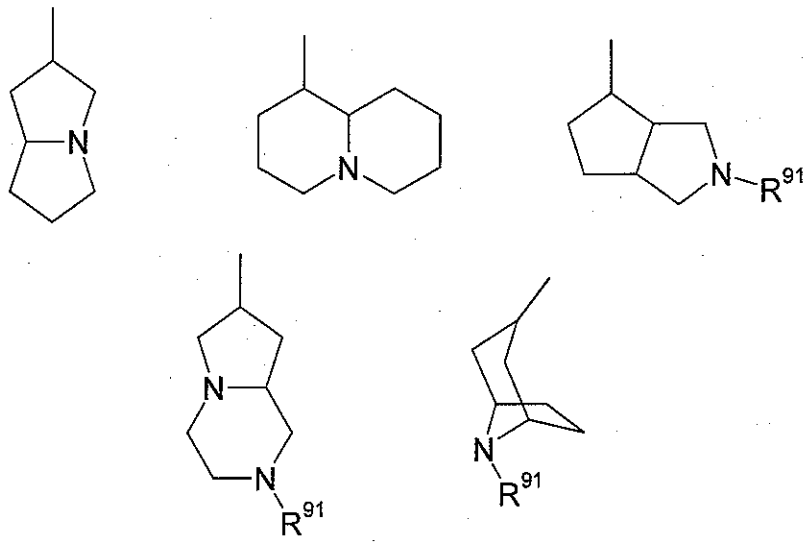
or

R120 and R121, R124 and R125

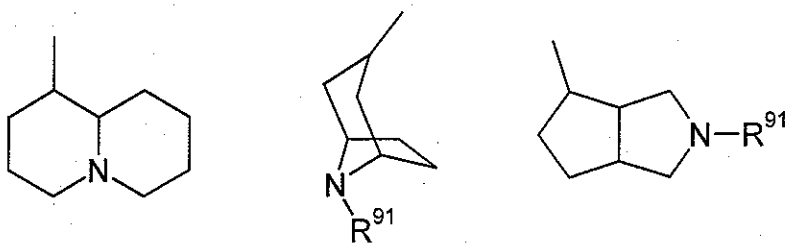
form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

the N-oxides thereof and the physiologically tolerated salts thereof.

4. A compound as claimed in claim 3, wherein Q has the following meanings:



preferably



R91 H, $(C_1\text{-}C_4)$-alkoxy-$(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, $(C_1\text{-}C_6)$-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, $(C_1\text{-}C_8)$-alkyl;

R93, R94

independently of one another H, (C_1-C_8)-alkyl, OH, (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkoxy-(C_1-C_4)alkyl, preferably H, (C_1-C_8)-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 heteroatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, (C_1-C_8)-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_{q'}$-R108, $CO(CR109R110)_{r'}$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

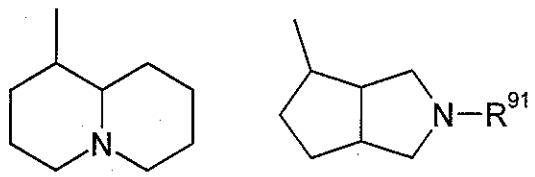
independently of one another H, (C_1-C_8)-alkyl;

or

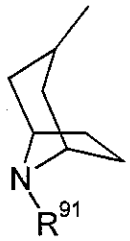
R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur.

5. A compound as claimed in claim 4, wherein Q has the following meanings



6. A compound as claimed in claim 4, in which Q has the following meaning:



R91 H, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, $(C_1$-$C_6)$-alkyl, $(CR93R94)_{o'}$-R95 ;

R92 H, $(C_1$-$C_8)$-alkyl;

R93, R94

independently of one another H, $(C_1$-$C_8)$-alkyl, OH, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$alkyl, preferably H, $(C_1$-C_8-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 heteroatoms selected

from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, CO(R105), $(CR106R107)_q$-R108, $CO(CR109R110)_r$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-$(C_1$-$C_8)$-alkyl, $(C_1$-$C_6)$-alkyl, CO(R112), oxo, OH, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-$(C_1$-$C_8)$-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, $(C_1$-$C_8)$-alkyl, O-$(C_1$-$C_8)$-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, $(C_1$-$C_8)$-alkyl;

or

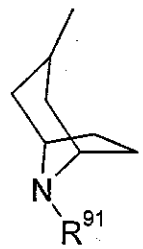
R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

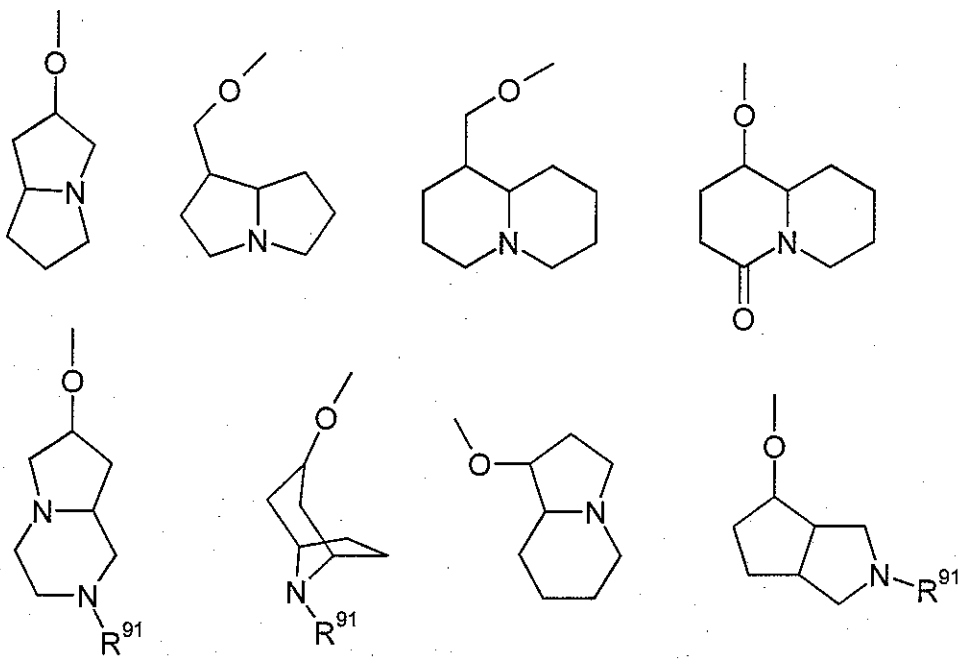
where in the compounds of the formula I

L is O.

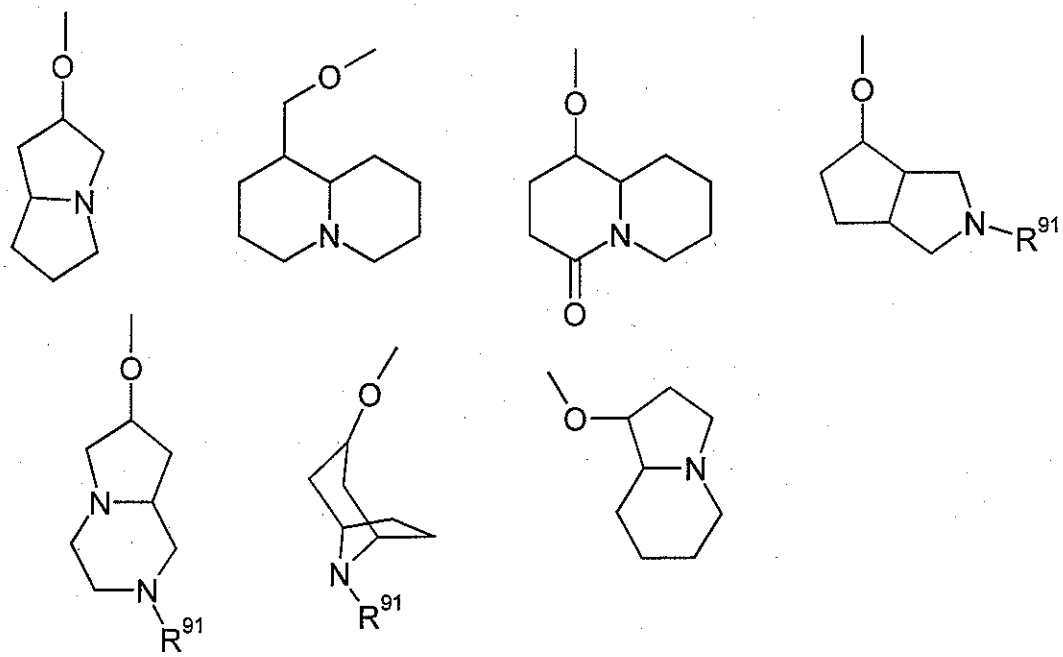
7. A compound as claimed in any of claims 1 to 5, wherein L is selected from O and CH_2O, preferably O, where L is O if Q is



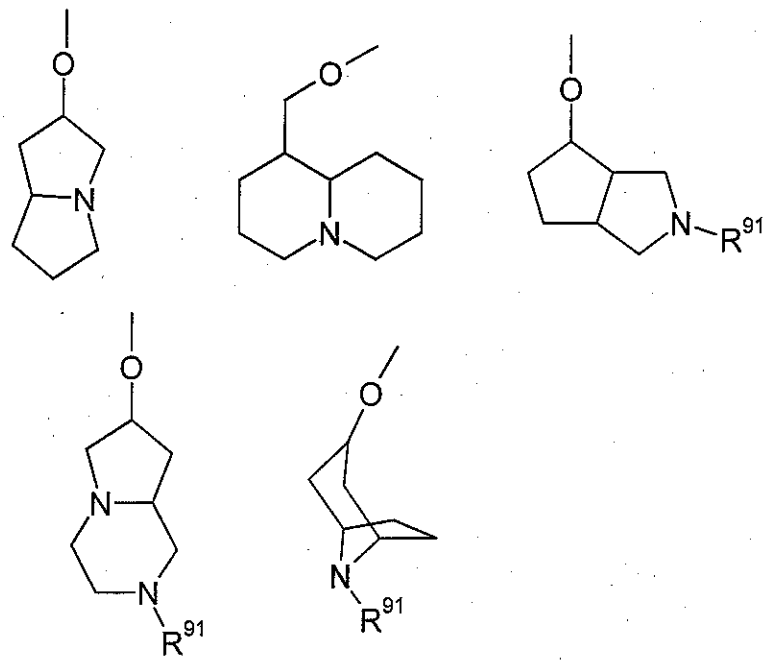
8. A compound as claimed in claim 7, in which the group L-Q has the following meanings:



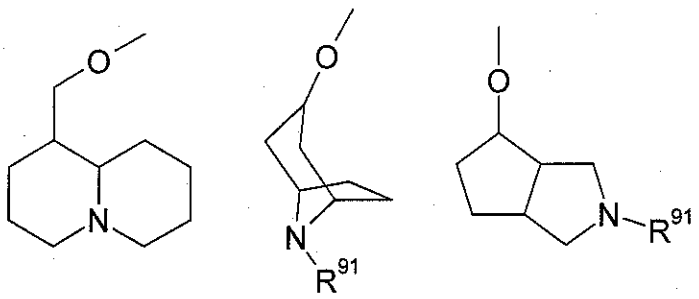
preferably



particularly preferably



very particularly preferably



R91 H, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R92), $(CR93R94)_{o'}$-R95, $CO(CR93R94)_{p'}$-R96; preferably H, (C_1-C_6)-alkyl, $(CR93R94)_{o'}$-R95;

R92 H, (C_1-C_8)-alkyl;

R93, R94

independently of one another H, (C_1-C_8)-alkyl, OH, (C_3-C_8)-cycloalkyl, (C_1-C_4)-alkoxy-(C_1-C_4)alkyl, preferably H, (C_1-C_8)-alkyl;

o', p' independently of one another 0, 1, 2, 3, 4, 5, 6, preferably 0, 1, 2, 3;

R95, R96

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), N(R99)CO(R100), N(R101)(R102), CO_2(R103), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-

alkyl, CO(R104), oxo, OH; preferably independently of one another OH, O-(C_1-C_8)-alkyl, CON(R97)(R98), a 4-6 membered ring system having 0 to 2 heteroatoms selected from the group of N and O, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R104), oxo, OH, the ring system particularly preferably being unsubstituted;

R97, R98, R99, R100, R103, R104

independently of one another H, (C_1-C_8)-alkyl;

or

R97 and R98

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R101, R102

independently of one another H, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, CO(R105), $(CR106R107)_q$-R108, $CO(CR109R110)_r$-R111; or R101 and R102 form together with the nitrogen atom to which they are bonded a 4 to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, comprises 0 to 3 additional heteroatoms selected from the group of N, O and S and may additionally be substituted by one or more of the following substituents: F, Cl, Br, CF_3, O-(C_1-C_8)-alkyl, (C_1-C_6)-alkyl, CO(R112), oxo, OH, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, CON(R113)(R114), N(R115)CO(R116), N(R117)(R118), CO_2(R119), SO_2Me;

R105, R106, R107, R108, R109, R110, R112, R113, R114, R115, R116, R117, R118, R119

independently of one another H, (C_1-C_8)-alkyl;

or

R117 and R118

form optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

q', r' independently of one another 0, 1, 2, 3, 4, 5, 6;

R108, R111

independently of one another OH, O-(C_1-C_8)-alkyl, CON(R120)(R121), N(R122)CO(R123), N(R124)(R125), CO_2(R126), SO_2Me, CN, a 3-10 membered ring system having 0 to 3 heteroatoms selected from the group of N, O and S, which may be substituted by one or more of the following substituents: F, Cl, Br, CF_3, (C_1-C_8)-alkyl, O-(C_1-C_8)-alkyl, CO(R127), oxo, OH;

R120, R121, R122, R123, R124, R125, R126, R127

independently of one another H, (C_1-C_8)-alkyl;

or

R120 and R121, R124 and R125

form independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1

further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur.

9. A compound of the formula I as claimed in any of claims 1 to 8, wherein

A, B, D, G

are independently of one another N or C(R3), and the total number of nitrogen atoms in this ring is 0-2, preferably 0 or 1, particularly preferably 0.

10. A compound of the formula I as claimed in any of claims 1 to 8,

in which the meanings are

K O, OCH_2, CH_2O, S, SO, SO_2, N(R35), N(R36)CO, CON(R37), $(C(R38)(R39))_v$, CO, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, preferably OCH_2, CH_2O, N(R36)CO, CON(R37), $(C(R38)(R39))_2$, (R31)C=C(R32), C≡C, SCH_2, SO_2CH_2, particularly preferably OCH_2, CH_2O, CON(R37), C≡C, SCH_2; where

v 1, 2, 3, preferably 2;

R31, R32, R35, R36, R37, R38, R39

are independently of one another H, (C_1-C_8)-alkyl.

11. A compound as claimed in any of claims 1 to 9,

in which the meanings are

A, B, D, G

C(R3);

R3 H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, O-(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_0-C_8)-alkylene-aryl, O-(C_0-C_8)-alkylene-aryl, N(R4)(R5), SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15); preferably H, F, Cl, Br, CF_3, CN, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, SO_2-CH_3, CON(R6)(R7), N(R8)CO(R9), CO(R12), $(CR13R14)_x$-O(R15), particularly preferably H, F, Cl, CF_3, CN, (C_1-C_6)-alkyl, $(C(R13)(R14))_x$-O(R15); very particularly preferably H, F, (C_1-C_6)-alkyl; further preferably H, F, CH_3; especially preferably H;

R4, R5, R6, R7, R8

independently of one another H, (C_1-C_8)-alkyl;

or

R4 and R5, R6 and R7

independently of one another optionally together with the nitrogen atom to which they are bonded a 5-6 membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms from the group of NH, N-(C_1-C_6)-alkyl, oxygen and sulfur;

R9, R12

independently of one another H, (C_1-C_8)-alkyl;

R13, R14

H;

R15 H, (C_1-C_6)-alkyl;

x 0, 1, 2, preferably 0, 1, particularly preferably 1.

12. A compound as claimed in any of claims 1 to 11, wherein X is bond or N(R16) in which R16 is H or (C_1-C_8)-alkyl.

13. A medicament comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 12.

14. A medicament comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 12 and one or more active ingredients which have beneficial effects on metabolic disturbances or disorders associated therewith.

15. A medicament comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 12 and one or more antidiabetics.

16. A medicament comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 12 and one or more lipid modulators.

17. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

18. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of disorders in which insulin resistance is involved.

19. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of diabetes mellitus and the sequelae associated therewith.

20. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of dyslipidemias and the sequelae thereof.

21. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of conditions associated with the metabolic syndrome.

22. The use of the compounds of the formula I as claimed in one or more of claims 1 to 12 for the treatment and/or prevention of obesity and sequelae associated therewith.

23. The use of the compounds as claimed in one or more of claims 1 to 12 in combination with at least one further active ingredient for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

24. The use of the compounds as claimed in one or more of claims 1 to 12 in combination with at least one further active ingredient for the treatment and/or prevention of disorders in which insulin resistance is involved.

25. A process for producing a medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 12, which comprises mixing the active ingredient with a pharmaceutically suitable carrier, and converting this mixture into a form suitable for administration