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(54) Title: 2,3,4,7-TETRAHYDRO-INDOLO[2,3-C]QUINOLINE COMPOUNDS

(57) Abstract: The present invention pertains to 2,3,4,7-tetrahydro-indolo[2,3-c]quinoline compounds, as well as the resulting pharmaceutical compositions, and their use in the treatment or prophylaxis of diseases alleviated by inhibition of type 5 phosphodiesterases. Furthermore, the present invention pertains to the methods of manufacturing these 2,3,4,7-tetrahydro-indolo[2,3-c]quinoline compounds.

Description

2,3,4,7-tetrahydro-indolo[2,3-c]quinoline compounds

Field of application of the invention

The invention relates to 2,3,4,7-tetrahydro-indolo[2,3-c]quinoline compounds, and their use, as well as the resulting pharmaceutical compositions and uses thereof in the treatment or prophylaxis of diseases alleviated by inhibition of type 5 phosphodiesterases.

Background of the Invention

6-Benzyl-3,3-dimethyl-2,3,4,7-tetrahydro-indolo[2,3-c]quinolin-1-one is described in Khimiya Geterotsiklicheskikh Soedinenii (1985) 3, 363-6 without mentioning any pharmaceutical activity thereof. WO02/064590 and EP1953159 disclose nitrogen-containing heterocyclic PDE5 inhibiting compounds. WO2008027182 discloses indoloquinoline compounds as calcium channel blockers. US4014883 discloses derivatives of 7H-indolo[2,3-c]quinolin-6(5H)-one and 7H-indolo[2,3-c]quinoline useful as anti-tumor agents. SU753093 discloses 1-Methyl- 3,4-(delta-2,2-dimethyl- 4-oxotetrahydro-benzo)indolo(2,3-c)-pyridine hydrochloride with tranquillising activity.

It is an object of the present invention to provide novel compounds and pharmaceutical compositions which may be used in the treatment or prophylaxis of diseases alleviated by inhibition of type 5 phosphodiesterases.

A further object of the present invention is to provide a method of manufacture of the compounds and compositions of the present invention.

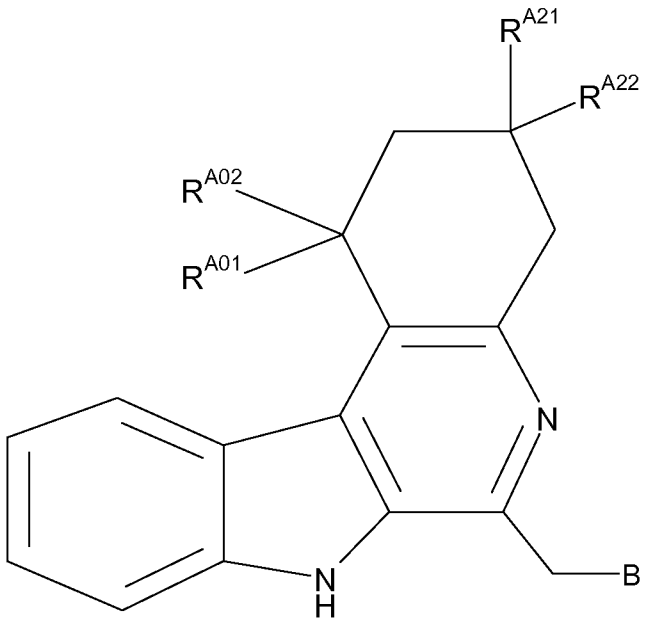
It is a further object of the present invention to provide a method for treating diseases alleviated by inhibition of the type 5 phosphodiesterase in a subject in need thereof.

Description of the invention

It has now been found that the 2,3,4,7-tetrahydro-indolo[2,3-c]quinoline compounds, which are described in detail below, have surprising and advantageous properties, making them especially useful in the treatment and prophylaxis of diseases alleviated by inhibition of type 5 phosphodiesterases.

The compounds of the present invention are characterized by Formula (I) as specified in the following.

The invention thus relates to compounds of Formula (I)



(I)

wherein

R^{A01} is selected from the group consisting of hydrogen, hydroxy and $NR^{A03}R^{A04}$;

R^{A02} is hydrogen; or

R^{A01} and R^{A02} combine to form an oxo group;

R^{A03} and R^{A04} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

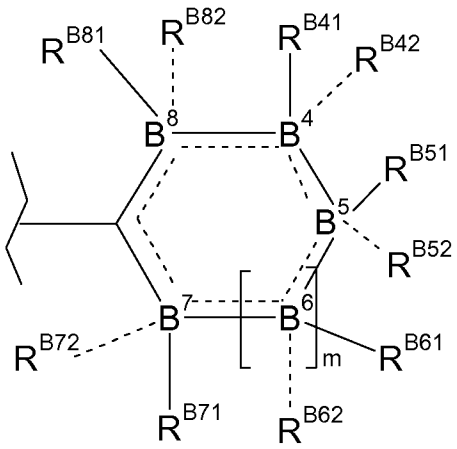
-C(O)H and $-C(O)-C_{1-6}$-alkyl,

wherein the $-C(O)-C_{1-6}$-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{A21} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

R^{A22} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

B is



wherein
m is 0 or 1;

the dotted lines signify 0, 1, 2 or 3 covalent π-bonds that may or may not be conjugated and which may each be located between any two adjacent ring atoms, with the proviso that each ring atom participates in no more than one covalent π-bond;

B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group consisting of C, N, O and S;
with the proviso that the fragment B does not represent a group selected from pyridine, pyrimidine, pyrrole, pyrazine and imidazole, each of which may optionally be substituted;

wherein R^{B41} and R^{B42} are each independently selected from the members of the groups (g1) and (g2) as defined below:

(g1) hydrogen, halogen, C_{1-3}-alkoxy,
wherein the C_{1-3}-alkoxy is not substituted,
NO_2 and NH_2;

(g2) hydroxy, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-3}-alkoxy,

wherein the C_{1-3}-alkoxy is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{4-6}-alkoxy,

wherein the C_{4-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B43},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B44}R^{B45}$, and

a lone pair; or

R^{B41} and R^{B42} combine to form an oxo-group;

wherein one of the substituents R^{B41} and R^{B42} is absent in case the dotted lines signify a covalent π-bond between B^4 and one of the adjacent ring atoms;

R^{B43} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B44} and R^{B45} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B46}; or

R^{B44} and R^{B45} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B47}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^4 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B46} is selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B43},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B43},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B48}R^{B49}$;

R^{B47} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B48} and R^{B49} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B51} and R^{B52} are each independently selected from the members of the groups (h1) and (h2) as defined below:

(h1) hydrogen, halogen, hydroxy, C_{1-3}-alkyl,
wherein the C_{1-3}-alkyl is not substituted,
C_{1-3}-alkoxy,
wherein the C_{1-3}-alkoxy is not substituted,
NO_2, NH_2, -NH-C(O)-C_{1-2}-alkyl, -NH-C(O)-NH_2 and a methoxy group,
wherein the methoxy group is substituted by 2 or 3 fluorine atoms; or
one of R^{B41} and R^{B42} and one of R^{B51} and R^{B52} combine to form a group selected from -O-CH_2-O-, -O-CH_2-CH_2- and -CH_2-CH_2-O-;

(h2) C_{1-3}-alkyl,
wherein the C_{1-3}-alkyl is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,
C_{4-6}-alkyl,
wherein the C_{4-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy,
C_{1-3}-alkoxy,
wherein the C_{1-3}-alkoxy is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,
C_{4-6}-alkoxy,
wherein the C_{4-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,
C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,
-O-C_{3-6}-cyclyl,
wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B53},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B54}R^{B55}$ and

a lone pair; or

R^{B51} and R^{B52} combine to form an oxo-group;

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms;

R^{B53} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B54} and R^{B55} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B56}; or

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B56} is selected from the group consisting of

C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B53},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B53},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

$NR^{B58}R^{B59}$;

R^{B57} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B58} and R^{B59} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B61} and R^{B62} are each independently selected from the members of the groups (i1) and (i2) as defined below:

(i1) hydrogen and halogen;

(i2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B63},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B64}R^{B65}$ and

a lone pair;

wherein one of the substituents R^{B61} and R^{B62} is absent in case the dotted lines signify a covalent π-bond between B^6 and one of the adjacent ring atoms;

R^{B63} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B64} and R^{B65} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B66}; or

R^{B64} and R^{B65} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B67}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^6 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B66} is selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxyl, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B63},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B63},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatoms selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B68}R^{B69}$;

R^{B67} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B67} and R^{B68} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxyl;

wherein R^{B71} and R^{B72} are each independently selected from the members of the groups (j1) and (j2) as defined below:

(j1) hydrogen and halogen;

(j2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B73},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B74}R^{B75}$ and

a lone pair; or

R^{B71} and R^{B72} combine to form an oxo-group;

wherein one of the substituents R^{B71} and R^{B72} is absent in case the dotted lines signify a covalent π-bond between B^7 and one of the adjacent ring atoms;

R^{B73} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B74} and R^{B75} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B76}; or

R^{B74} and R^{B75} combine to form a 3- to 7-membered heterocycle,

wherein 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B77}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^7 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B76} is selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B73},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B73},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B78}R^{B79}$;

R^{B77} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B78} and R^{B79} are each independently selected from the groups consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B81} and R^{B82} are each independently selected from the members of the groups (k1) and (k2) as defined below:

(k1) hydrogen and halogen;

(k2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B83},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B84}R^{B85}$ and

a lone pair; or

R^{B81} and R^{B82} combine to form an oxo-group;

wherein one of the substituents R^{B81} and R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^8 and one of the adjacent ring atoms;

R^{B83} is selected from the groups consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-C_{1-6}-alkyl,
wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B84} and R^{B85} are each independently selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-R^{B86}; or
R^{B84} and R^{B85} combine to form a 3- to 7-membered heterocycle,
wherein 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,
wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B87}, O and S, and
wherein, in case the atoms adjacent to the N which binds to B^8 are carbon atoms, said carbon atoms independently are optionally substituted by an oxo-group;

R^{B86} is selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
3- to 7-membered heterocyclyl,
wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and
wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B83},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B83},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B88}R^{B89}$;

R^{B87} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B88} and R^{B89} are each independently selected from the groups consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

with the proviso that, in case m is 1, B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 3 conjugated covalent π-bonds, one of each of the pairs of substituents R^{B41} and R^{B42}, R^{B51} and R^{B52}, R^{B61} and R^{B62}, R^{B71} and R^{B72}, R^{B81} and R^{B82} is absent, respectively, and at least one of the remaining substituents is selected from the members of the groups (g2), (h2), (i2), (j2) and (k2) as defined above;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

Special embodiments of the present application are described in the following.

According to one embodiment of the present invention, R^{A01} is $NR^{A03}R^{A04}$, wherein R^{A03} and R^{A04} has the same meanings as defined above, or preferably below.

According to another embodiment of the present invention, R^{A03} and R^{A04} are each independently selected from the group consisting of

hydrogen, -C(O)H and $-C(O)-C_{1-6}$-alkyl,

wherein the $-C(O)-C_{1-6}$-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy.

According to another embodiment of the present invention, m is 0.

According to another embodiment of the present invention, m is 1.

According to another embodiment of the present invention, m is 0 or 1.

According to another embodiment of the present invention, the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, the dotted lines signify 2 covalent π-bonds.

According to another embodiment of the present invention, the dotted lines signify 3 covalent π-bonds.

According to another embodiment of the present invention, B^5 is a sulfur atom.

According to another embodiment of the present invention, B^7 is a sulfur atom.

According to another embodiment of the present invention, R^{B41} and R^{B42} are each independently selected from the members of the groups (g1a) and (g2a) as defined below:

(g1a) hydrogen,

(g2a) C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy, and

a lone pair,

wherein one of the substituents R^{B41} and R^{B42} is absent in case the dotted lines signify a covalent π-bond between B^4 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1a) and (h2a) as defined below:

(h1a) hydrogen, C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is not substituted,

(h2a) C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

$NR^{B54}R^{B55}$ and

a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1a) and (h2a) as defined below:

(h1a) hydrogen, C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is not substituted,

(h2a) C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S,

$NR^{B54}R^{B55}$ and

a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to yet another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1b) and (h2b) as defined below:

(h1b) hydrogen, C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is not substituted,

(h2b) C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has a sulfur atom in its ring,

$NR^{B54}R^{B55}$ and

a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to another embodiment of the present invention, R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group.

According to another embodiment of the present invention, R^{B54} and R^{B55} are each independently selected from the group consisting of

hydrogen and -C(O)-R^{B56},

wherein R^{B56} has the same meaning as defined above, or preferably below.

According to yet another embodiment of the present invention, R^{B56} is C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy.

According to yet another embodiment of the present invention, R^{B56} is cyclopropenyl.

According to another embodiment of the present invention, R^{B61} and R^{B62} are each independently selected from the members of the groups (i1a) and (i2a) as defined below:

(i1a) hydrogen,

(i2a) C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

wherein one of the substituents R^{B61} and R^{B62} is absent in case the dotted lines signify a covalent π-bond between B^6 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B61} and R^{B62} are hydrogen wherein one of the substituents R^{B61} and R^{B62} is absent in case the dotted lines signify a covalent π-bond between B^6 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B71} and R^{B72} are each independently selected from the members of the groups (j1a) and (j2a) as defined below:

(j1a) hydrogen,

(j2a) NO_2 and C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

wherein one of the substituents R^{B71} and R^{B72} is absent in case the dotted lines signify a covalent π-bond between B^7 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B71} and R^{B72} are each independently selected from the members of the groups (j1a) and (j2a) as defined below:

(j1a) hydrogen,

(j2a) NO_2

wherein one of the substituents R^{B71} and R^{B72} is absent in case the dotted lines signify a covalent π-bond between B^7 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B81} and R^{B82} are each independently selected from the members of the groups (k1a) and (k2a) as defined below:

(k1a) hydrogen,

(k2a) NO_2 and C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

wherein one of the substituents R^{B81} and R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^8 and one of the adjacent ring atoms.

According to another embodiment of the present invention, m is 1 and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, R^{B81} and R^{B82} are hydrogen wherein one of the substituents R^{B81} and R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^8 and one of the adjacent ring atoms.

According to another embodiment of the present invention, m is 1, each of B^4, B^5, B^6, B^7 and B^8 are a carbon atom and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, m is 1, each of B^4, B^5, B^6, B^7 and B^8 is a carbon atom, the dotted lines signify 0 covalent π-bonds and each of R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B61}, R^{B62}, R^{B71}, R^{B72}, R^{B81} and R^{B82} is hydrogen.

According to another embodiment of the present invention, m is 1 and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, m is 0 or 1 and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, m is 0 or 1, each of B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 0 covalent π-bonds or at least one of B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group constisting of N, O, S and the the dotted lines signify 0, 1, 2, 3 covalent π-bonds with the proviso that each ring atom participates in no more than one covalent π-bond and with the proviso that the fragment B does not represent a group selected from pyridine, pyrimidine, pyrrole, pyrazine and imidazole, each of which may optionally be substituted wherein one of the substituents R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B61}, R^{B62}, R^{B71}, R^{B72}, R^{B81}, R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^4, B^5, B^6, B^7 and B^8 one of the adjacent ring atoms and wherein R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B61}, R^{B62}, R^{B71}, R^{B72}, $R^{B81}$and R^{B82} have the meaning mentioned above or below.
According to another embodiment of the present invention, m is 0 or 1, each of B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 0 covalent π-bonds or at least one of B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group constisting of N, O, S and the the dotted lines signify 0, 1, 2, 3 covalent π-bonds.

According to another embodiment of the present invention, m is 0, each of B^4, B^5, B^7 and B^8 are a carbon atom and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, m is 0, each of B^4, B^5, B^7 and B^8 is a carbon atom, the dotted lines signify 0 covalent π-bonds and each of R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B71}, R^{B72}, R^{B81} and R^{B82} is hydrogen.

According to another embodiment of the present invention, m is 0 or 1, each of B^4, B^5, B^7 and B^8 are a carbon atom and the dotted lines signify 0 covalent π-bonds.

According to another embodiment of the present invention, m is 0 or 1, each of B^4, B^5, B^7 and B^8 is a carbon atom, the dotted lines signify 0 covalent π-bonds and each of R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B71}, R^{B72}, R^{B81} and R^{B82} is hydrogen.

According to another embodiment of the present invention, m is 0, at least one of B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group constisting of N, O, S.

According to another embodiment of the present invention, m is 0 or 1, at least one of B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group constisting of N, O, S.

According to another embodiment of the present invention, m is 0, B^7 is a sulfur atom, each of B^4, B^5 and B^8 are a carbon atom and the dotted lines signify 2 covalent π-bonds that are conjugated.

According to yet another embodiment of the present invention, m is 0, B^7 is a sulfur atom, each of B^4, B^5 and B^8 are a carbon atom, the dotted lines signify 2 covalent π-bonds that are conjugated, each of R^{B41}, R^{B51}, R^{B81} and is hydrogen, R^{B42}, $R^{B52}$and R^{B82} are absent and R^{B71} and R^{B72} each represent a lone pair.

According to yet another embodiment of the present invention, R^{A01} is selected from the group consisting of hydrogen, hydroxy and $NR^{A03}R^{A04}$;

R^{A02} is hydrogen; or

R^{A01} and R^{A02} combine to form an oxo group;

R^{A03} and R^{A04} are hydrogen;

R^{A21} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

R^{A22} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

According to yet another embodiment of the present invention, R^{B41} and R^{B42} are each independently selected from the members of the groups (g1a) and (g2a) as defined below:

(g1a) hydrogen,

(g2a) C_{1-6}-alkyl,

a lone pair,

wherein one of the substituents R^{B41} and R^{B42} is absent in case the dotted lines signify a covalent π-bond between B^4 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1a) and (h2a) as defined below:

(h1a) hydrogen,

(h2a) C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S,

$NR^{B54}R^{B55}$ and

a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to yet another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1b) and (h2b) as defined below:

(h1b) hydrogen,

(h2b) C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has a sulfur atom in its ring,

$NR^{B54}R^{B55}$ and

a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to another embodiment of the present invention, R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group.

According to another embodiment of the present invention, R^{B54} and R^{B55} are each independently selected from the group consisting of

-C(O)-R^{B56} and

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group and

wherein R^{B56} and R^{B57} have the same meaning as defined above or below.

According to another embodiment of the present invention, R^{B54} and R^{B55} are each independently selected from the group consisting of

-C(O)-R^{B56} and

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group and

wherein R^{B56} has the same meaning as defined above or below.

According to yet another embodiment of the present invention, R^{B56} is C_{3-6}-cyclyl,

According to yet another embodiment of the present invention, R^{B56} is cyclopropenyl.

According to yet another embodiment of the present invention, R^{A01} is selected from the group consisting of hydrogen, hydroxy and $NR^{A03}R^{A04}$;

R^{A02} is hydrogen; or

R^{A01} and R^{A02} combine to form an oxo group;

R^{A03} and R^{A04} are hydrogen;

R^{A21} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

R^{A22} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

According to yet another embodiment of the present invention, R^{B41} and R^{B42} are each independently selected from the members of the groups (g1a) and (g2a) as defined below:

(g1a) hydrogen,

(g2a) C_{1-6}-alkyl,
a lone pair,

wherein one of the substituents R^{B41} and R^{B42} is absent in case the dotted lines signify a covalent π-bond between B^4 and one of the adjacent ring atoms.

According to another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1a) and (h2a) as defined below:

(h1a) hydrogen,

(h2a) C_{1-13}-heteroaryl,
wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S,
$NR^{B54}R^{B55}$ and
a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and
wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to yet another embodiment of the present invention, R^{B51} and R^{B52} are each independently selected from the members of the groups (h1b) and (h2b) as defined below:

(h1b) hydrogen,

(h2b) C_{1-13}-heteroaryl,
wherein the C_{1-13}-heteroaryl has a sulfur atom in its ring,
$NR^{B54}R^{B55}$ and
a lone pair,

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms, and

wherein R^{B54} and R^{B55} have the same meanings as defined above, or preferably below.

According to another embodiment of the present invention, R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group.

According to another embodiment of the present invention, R^{B54} and R^{B55} are each independently selected from the group consisting of

$-C(O)-R^{B56}$ and

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group and

wherein R^{B56} and R^{B57} have the same meaning as defined above or below.

According to another embodiment of the present invention, R^{B54} and R^{B55} are each independently selected from the group consisting of

$-C(O)-R^{B56}$ and

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group and

wherein R^{B56} has the same meaning as defined above or below.

According to yet another embodiment of the present invention, R^{B56} is C_{3-6}-cyclyl,

According to yet another embodiment of the present invention, R^{B56} is cyclopropenyl.

According to yet another embodiment of the present invention, R^{A01} is selected from the group consisting of hydrogen, hydroxy and $NR^{A03}R^{A04}$;

R^{A02} is hydrogen; or

R^{A01} and R^{A02} combine to form an oxo group;

R^{A03} and R^{A04} are hydrogen;

R^{A21} and R^{A22} are C_{1-3}-alkyl;

m is 0 or 1;

the dotted lines signify 0, 1, 2 or 3 covalent π-bonds that may or may not be conjugated and which may each be located between any two adjacent ring atoms, with the proviso that each ring atom participates in no more than one covalent π-bond;

B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group consisting of C, N, O and S;
with the proviso that the fragment B does not represent a group selected from pyridine, pyrimidine, pyrrole, pyrazine and imidazole, each of which may optionally be substituted;

wherein R^{B41} and R^{B42} are each independently selected from the members of the groups (g1) and (g2) as defined below:

(g1) hydrogen;

(g2) C_{1-6}-alkyl,

wherein R^{B51} and R^{B52} are each independently selected from the members of the groups (h1) and (h2) as defined below:

(h1) hydrogen;

(h2) C_{1-13}-heteroaryl,
wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and
$NR^{B54}R^{B55}$ and
a lone pair; or

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms;

R^{B54} and R^{B55} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

-C(O)-R^{B56}; or

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B56} is C_{3-6}-cyclyl,

wherein R^{B61} and R^{B62} are each hydrogen; wherein one of the substituents R^{B61} and R^{B62} is absent in case the dotted lines signify a covalent π-bond between B^6 and one of the adjacent ring atoms;

wherein R^{B71} and R^{B72} are each independently selected from the members of the groups (j1) and (j2) as defined below:

(j1) hydrogen;

(j2) NO_2,

wherein one of the substituents R^{B71} and R^{B72} is absent in case the dotted lines signify a covalent π-bond between B^7 and one of the adjacent ring atoms;

wherein R^{B81} and R^{B82} are hydrogen, wherein one of the substituents R^{B81} and R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^8 and one of the adjacent ring atoms;

with the proviso that, in case m is 1, B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 3 conjugated covalent π-bonds, one of each of the pairs of substituents R^{B41} and R^{B42}, R^{B51} and R^{B52}, R^{B61} and R^{B62}, R^{B71} and R^{B72}, R^{B81} and R^{B82} is absent, respectively, and at least one of the remaining substituents is selected from the members of the groups (g2), (h2), and (j2) as defined above;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

According to yet another embodiment of the present invention, the compounds of Formula (I) are selected from the group consisting of
6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(3-methylbenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(2-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-[4-(2-thienyl)benzyl]-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
1-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}pyrrolidine-2,5-dione;
N-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-amine;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
N-{4-[(1-Hydroxy-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide;
(1S)-6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
(1S)-3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;

Wherever two substituents in the present invention bind to the same atom and the list of meanings of these substituents includes hydrogen, one of the substituents may be hydrogen and the other may have a meaning as defined.

In addition to the compounds exemplified herein and the specific substituent combinations mentioned above, the present invention expressly pertains to all compounds that can be derived from each and every combination of the specific meanings of substituents and other variable groups characterized above as embodiments of the present invention, with the proviso that, in case m is 1, B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 3 conjugated covalent π-bonds, one of each of the pairs of substituents R^{B41} and R^{B42}, R^{B51} and R^{B52}, R^{B61} and R^{B62}, R^{B71} and R^{B72}, R^{B81} and R^{B82} is absent, respectively, and at least one of the remaining substituents is selected from the members of the groups (g2), (g2a), (h2), (h2a), (h2b), (i2), (i2a), (j2), (j2a), (k2) and (k2a) as defined above.

The term **"halogen"** used in the specification of the present application means a fluorine atom, a chlorine atom and a bromine atom, wherein a fluorine atom is more preferred.

The term **"C_{1-6}-alkyl"** used in the specification of the present application indicates linear or branched alkyl groups having 1 to 6 carbon atoms. Among these, linear or branched alkyl groups having 1 to 4 carbon atoms (C_{1-4}-alkyl) are preferred, linear or branched alkyl groups having 1 to 3 carbon atoms (C_{1-3}-alkyl) are more preferred and alkyl groups having 1 to 2 carbon atoms (C_{1-2}-alkyl) are still more preferred. In the same way, the term **"C_{4-6}-alkyl"** used in the specification of the present invention indicates linear or branched alkyl groups having 4 to 6 carbon atoms. Examples of the above-defined alkyl groups include a methyl group, an ethyl group, an n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, a 1,1-dimethylpropyl group, a 1,2-dimethylpropyl group, a 2,2-dimethylpropyl group, a 1-ethylpropyl group, a 2-ethylpropyl group, a 1-methyl-2-ethylpropyl group, a 1-ethyl-2-methylpropyl group, a 1,1,2-trimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1-ethylbutyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 2-ethylbutyl group or a n-hexyl group. More preferred examples of the alkyl groups having 1 to 6 carbon atoms are a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group and a sec-butyl group, and still more preferred examples are a methyl group, an ethyl group, a n-propyl group, an isopropyl group and an isobutyl group, wherein a methyl group is particularly preferred.

The term **"C_{1-6}-alkoxy"** used in the specification of the present invention indicates alkoxy groups having 1 to 6 carbon atoms, wherein alkoxy groups having 1 to 3 carbon atoms (C_{1-3}-alkoxy) are preferred. Examples of the C_{1-6}-alkoxy group include a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a n-pentoxy group, an isopentoxy group, a sec-pentoxy group, a 3-methylpentoxy group, an n-hexoxy group, a 1,1-dimethylpropoxy group, a 1,2-dimethylpropoxy group, a 2,2-dimethylpropyloxy group, a 2-ethylpropoxy group, a 1-methyl-2-ethylpropoxy group, a 1-ethyl-2-methylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1,2-trimethylpropoxy group, a 1,1-dimethylbutoxy group, a 1,2-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 2,3-dimethylbutoxy group, a 1,3-dimethylbutyloxy group, a 2-ethylbutoxy group, a 1,3-dimethylbutoxy group, a 2-methylpentoxy group, a 3-methylpentyloxy group, a hexyloxy group, wherein a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy group and a tert-butoxy group are preferred, and a methoxy group, ethoxy group, isopropoxy group and a isobutoxy group are more preferred.

The term **"C_{3-6}-cyclyl"** used in the specification of the present invention indicate cycloalkyl groups having 3 to 6 carbon atoms. Examples of the C_{3-6}-cyclyl groups include a cyclopropyl group, a

cyclobutyl group, a cyclopentyl group and a cyclohexyl group, wherein a cyclopropyl group and a cyclopentyl group are preferred.

The term **"3- to 7-membered heterocyclyl"** includes ring structures analogous to carbocyclic groups in which one or more of the carbon atoms in the ring is replaced by an atom other than carbon, for example, nitrogen, sulfur, or oxygen. Heterocyclic groups may be saturated or unsaturated. Preferable examples include an oxiranyl group, an aziridinyl group, an oxetanyl group, an acetidyl group, a pyrrolidinyl group, a pyrrolinyl group, a pyrrolidonyl group, a tetrahydrofuranyl group, tetrahydrothiophenyl group, a tetrahydropyranyl group, a piperidinyl group, a piperazinyl group, an imidazolinyl group, a pyrazolidinyl group, an imidazolidinyl group, a morpholinyl group, a thiomorpholinyl group, an imidazolinyl group, an oxazolinyl group and the like.

The term **"3- to 7-membered heterocycle"** used in the specification of the present invention indicates a monocyclic 3- to 7-membered non-aromatic heterocyclic group which contains a nitrogen atom and optionally one or more hetero atoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom. The preferable example includes an aziridinyl group, an acetidyl group, a pyrrolidinyl group, a pyrrolinyl group, a piperidinyl group, a piperazinyl group, a piperazine-2,3-dione group, an imidazolinyl group, a pyrazolidinyl group, an imidazolidinyl group, a morpholinyl group, a thiomorpholinyl group, an imidazolinyl group, an oxazolinyl group, a pyrrolidine-2,5-dione group, a piperazine-2,3-dione group and the like. More preferred is a pyrrolidine-2,5-dione group.

The term **"C_{6-14}-aryl"** used in the specification of the present application means an aromatic hydrocarbon cyclic group which is constituted by 6 to 14 carbon atoms, such as a monocyclic group, a bicyclic group and a tricyclic group. Preferable examples are a phenyl group, an indenyl group, a naphthyl group, an azulenyl group, a heptalenyl group, an indacenyl group, an acenaphthyl group, a fluorenyl group, a phenalenyl group, a phenanthrenyl group and an anthracenyl group. Furthermore, the term **"C_{6-14}-aryl which is optionally substituted"** means an aromatic hydrocarbon cyclic group which is constituted by 6 to 14 carbon atoms, wherein the aromatic hydrocarbon cyclic group has the same meaning as defined above and is optionally substituted by one or more substituents. Examples of such substituents are hydroxy; C_{1-6}-alkyl, preferably methyl; C_{1-6}-alkoxy, preferably methoxy or ethoxy, more preferably methoxy; halogen, preferably fluoro and chloro, more preferably fluoro; nitro; and methylendioxo. The C_{6-14}-aryl may be substituted by one of these substituents, but may also be substituted by two or more of these substituents which may be the same or may be different from each other.

The term **"C_{1-13}-heteroaryl"** used in the specification of the present application refers to aromatic groups having 1 to 13 carbon atoms and one or more heteroatoms selected from N, O and S. Preferred embodiments of such groups can be characterized as "5- to 14-membered heteroaryl" which

indicates a monocyclic, bicyclic or tricyclic 5- to 14-membered aromatic heterocyclic group which contains one or more heteroatoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom. In the present invention a 5- to 10-membered heteroaryl may preferably be used, and a 5 to 6 membered heteroaryl is more preferred.

Examples of the aromatic heterocyclic group include a pyrrolyl group, a pyridyl group, a pyridazinyl group, a pyrimidinyl group, a pyrazinyl group, a triazolyl group, a tetrazolyl group, a benzotriazolyl group, a pyrazolyl group, an imidazolyl group, a benzimidazolyl group, an indolyl group, an isoindolyl group, an indolizinyl group, a purinyl group, an indazolyl group, a quinolyl group, an isoquinolyl group, a quinolizinyl group, a phthalazinyl group, a naphthylidinyl group, a quinoxalinyl group, a quinazolinyl group, a cinnolinyl group, a pteridinyl group, an imidazotriazinyl group, a pyrazinopyridazinyl group, an acridinyl group, a phenanthridinyl group, a carbazolyl group, a carbolinyl group, a phenanthrolinyl group, a phenazinyl group, an imidazopyridinyl group, an imidazopyrimidinyl group, a pyrazolopyridinyl group, and the like; a thiophenyl group (thienyl group), a benzothiophenyl group (benzothienyl group) and the like; a furyl group, a pyranyl group, a cyclopentapyranyl group, a benzofuryl group, an isobenzofuryl group, a thiazolyl group, an isothiazolyl group, a benzothiazolyl group, a benzothiadiazolyl group, a phenothiazinyl group, an isoxazolyl group, a furazanyl group, a phenoxazinyl group, an oxazolyl group, an isooxazoyl group, a benzoxazolyl group, an oxadiazolyl group, a pyrazolooxazolyl group, an imidazothiazolyl group, a thienofuranyl group, a furopyrrolyl group, a pyridoxazinyl group and the like. Furthermore, the term **"C_{1-13}-heteroaryl which is optionally substituted"** means a monocyclic, bicyclic or tricyclic aromatic heterocyclic group, typically being a 5- to 14-membered aromatic heterocyclic group, which contains one or more heteroatoms selected from the group consisting of a nitrogen atom, a sulfur atom and an oxygen atom, wherein the 5- to 14-membered aromatic heterocyclic group is substituted by one or more substituents. Examples of such substituents are hydroxy; C_{1-6}-alkyl, preferably methyl; C_{1-6}-alkoxy, preferably methoxy or ethoxy, more preferably methoxy; halogen, preferably fluoro and chloro, more preferably fluoro; nitro; and methylenedioxo. The 5- to 14-membered aromatic heterocyclic group may be substituted with only one of these substituents, but may also be substituted by two or more of these substituents which may be the same or may be different from each other. Among the above examples, a thiophenyl group is more preferred.

The above-mentioned C_{1-6}-alkyl group may be substituted with one or more substituents selected from the group consisting of fluoro, hydroxy, C_{1-6}-alkoxy, C_{3-6}-cyclyl and 3- to 7-membered heterocyclyl, wherein the C_{1-6}-alkoxy, C_{3-6}-cyclyl, 3- to 7-membered heterocyclyl, C_{6-14}-aryl and C_{1-13}-heteroaryl have the same meanings as defined above.

In case the C_{1-6}-alkyl group is substituted by at least one fluorine atom, the C_{1-6}-alkyl group can be any group as specified above with respect to the C_{1-6}-alkyl, unless specified otherwise. The

C_{1-6}-alkyl substituted by at least one fluorine atom is preferably a mono-, di-, tri-, polyfluoro or perfluoro substituted C_{1-6}-alkyl, wherein the mono-, tri- and perfluoro substituted C_{1-6}-alkyl groups are more preferred. Still more preferred are mono- and perfluoro substituted C_{1-6}-alkyl groups. Examples of these still more preferred mono- and perfluoro substituted C_{1-6}-alkyl groups are fluoromethyl, 1-fluoroethyl, 2-fluoroyethyl, 1-fluoro-isopropyl, 1-fluoro-n-propyl, 2-fluoro-isopropyl, 2-fluoro-n-propyl, 3-fluoro-n-propyl, trifluoromethyl, pentafluoroethyl, perfluoroisopropyl, perfluoro-n-propyl and perfluoroisobutyl.

In case the C_{1-6}-alkyl is substituted by at least one hydroxy, the C_{1-6}-alkyl group can be any group as specified above with respect to the C_{1-6}-alkyl, unless specified otherwise. The C_{1-6}-alkyl substituted by at least one hydroxy is preferably a C_{1-6}-alkyl group which is substituted by one or two hydroxy groups, more preferably a C_{1-3}-alkyl group which is substituted with one or two hydroxy groups, preferably one hydroxy group. Examples of such C_{1-3}-alkyl groups substituted with at least one hydroxy group includes hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-isopropyl, 2-hydroxy-isopropyl, 1-hydroxy-n-propyl, 2-hydroxy-n-propyl and 3-hydroxy-n-propyl, wherein a hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-isopropyl and 2-hydroxy-n-propyl are still more preferred, and hydroxymethyl is particularly preferred.

In case the C_{1-6}-alkyl group is substituted by at least one C_{1-6}-alkoxy, the C_{1-6}-alkyl group can be any group as specified above with respect to C_{1-6}-alkyl, unless specified otherwise. Similarly, the C_{1-6}-alkoxy group can be any group as specified above for C_{1-6}-alkoxy, unless specified otherwise. The C_{1-6}-alkyl is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom, and the C_{1-6}-alkoxy is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom. Further preferred is that the C_{1-6}-alkyl is substituted one C_{1-6}-alkoxy. Particlulary preferred are a methoxymethyl group and a 2-methoxyethyl group.

In case the C_{1-6}-alkyl group is substituted by at least one C_{3-6}-cyclyl, the C_{1-6}-alkyl group can be any group as specified above with respect to C_{1-6}-alkyl, unless specified otherwise. Similarly, the C_{3-6}-cyclyl group can be any group as specified above for C_{3-6}-cyclyl, unless specified otherwise. The C_{1-6}-alkyl is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom, and the C_{3-6}-cyclyl is preferably a ring having 3 to 5 carbon ring atoms. Further preferred is that the C_{1-6}-alkyl is substituted one C_{3-6}-cyclyl. Particluarly preferred is a cyclopropylmethyl group.

In case the C_{1-6}-alkyl group is substituted by at least one 3- to 7-membered heterocyclyl, the C_{1-6}-alkyl group can be any group as specified above with respect to C_{1-6}-alkyl, unless specified otherwise. Similarly, the 3- to 7-membered heterocyclyl group can be any group as specified above for 3- to 7-membered heterocyclyl, unless specified otherwise. The C_{1-6}-alkyl is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom, and the 3- to 7-membered heterocyclyl is preferably a 5 or 6-membered heterocyclyl having one heteroatom in its ring selected from N, O or S, more preferably a 5-membered heterocyclyl having an oxygen atom in its ring. Further preferred is that the C_{1-6}-alkyl is substituted by one 3- to 7-membered heterocyclyl.

The above-mentioned C_{1-6}-alkoxy group may be substituted with one or more substituents selected from the group consisting of fluoro, hydroxy, C_{1-6}-alkoxy and C_{3-6}-cyclyl, wherein the C_{1-6}-alkoxy and C_{3-6}-cyclyl have the same meanings as defined above.

In case the C_{1-6}-alkoxy group is substituted by at least one fluorine atom, the C_{1-6}-alkoxy group can be any group as specified above with respect to C_{1-6}-alkoxy, unless specified otherwise. It is preferably a mono-, di-, tri-, polyfluoro or perfluoro substituted C_{1-6}-alkoxy, wherein the mono-, tri- and perfluoro substituted C_{1-6}-alkoxy groups are more preferred. More preferred are mono- and perfluoro substituted C_{1-6}-alkoxy groups. Examples of these more preferred mono- and perfluoro substituted C_{1-6}-alkoxy groups are fluoromethoxy, 1-fluoroethoxy, 2-fluoroyethoxy, 1-fluoro-isopropoxy, 1-fluoro-n-propoxy, 2-fluoro-isopropoxy, 2-fluoro-n-propoxy, 3-fluoro-n-propoxy, trifluoromethoxy, pentafluoroethoxy, perfluoroisopropoxy, perfluoro-n-propoxy and perfluoroisobutoxy.

In case the C_{1-6}-alkoxy group is substituted by at least one hydroxy, the C_{1-6}-alkoxy group can be any group as specified above with respect to C_{1-6}-alkoxy, unless specified otherwise. It is preferably a C_{1-6}-alkoxy group which is substituted by one or two hydroxy groups, more preferably a C_{1-3}- alkoxy group which is substituted with one or two hydroxy groups, preferably one hydroxy group. Examples of such C_{1-3}- alkoxy groups substituted with at least one hydroxy group include hydroxymethoxy, 1-hydroxyethoxy, 2-hydroxyethoxy, 1-hydroxy-isopropoxy, 2-hydroxy-isopropoxy, 1-hydroxy-n-propoxy, 2-hydroxy-n-propoxy and 3-hydroxy-n-propoxy, wherein a hydroxymethoxy, 2-hydroxyethoxy, 2-hydroxy-isopropoxy and 2-hydroxy-n-propoxy are still more preferred, and hydroxymethoxy is particularly preferred.

In case the C_{1-6}-alkoxy group is substituted by at least one another C_{1-6}-alkoxy, both C_{1-6}-alkoxy groups can be any group as specified above with respect to C_{1-6}-alkoxy. The first mentioned C_{1-6}-

alkoxy is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, more preferably 1 carbon atom, and the other C_{1-6}-alkoxy is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom. Further preferred is that the first mentioned C_{1-6}-alkoxy is substituted by one other C_{1-6}-alkoxy. Particulary preferred are a methoxymethoxy group, a ethoxymethoxy group, a 2-methoxyethoxy group and a 2-ethoxyethoxy group.

In case the C_{1-6}-alkoxy group is substituted by at least one C_{3-6}-cyclyl, the C_{1-6}-alkoxy group can be any group as specified above with respect to C_{1-6}-alkoxy, unless specified otherwise. Similarly, the C_{3-6}-cyclyl group can be any group as specified above for C_{3-6}-cyclyl, unless specified otherwise. The C_{1-6}-alkoxy is preferably a group having 1 to 3 carbon atoms, more preferably a group having 1 or 2 carbon atoms, still more preferably 1 carbon atom, and the C_{3-6}-cyclyl is preferably a ring having 3 to 5 carbon ring atoms. Further preferred is that the C_{1-6}-alkoxy is substituted by one C_{3-6}-cyclyl. Particluarly preferred is a cyclopropylmethoxy group.

The above-mentioned C_{3-6}-cyclyl group may be substituted by one or more substituents selected from the group consisting of fluoro and hydroxy.

In case the C_{3-6}-cyclyl group is substituted by one or more fluoro, the C_{3-6}-cyclyl group can be any group as specified above with respect to C_{3-6}-cyclyl, unless specified otherwise. The C_{3-6}-cyclyl group substituted by one or more fluoro is preferably a mono-, di-, tri-, polyfluoro or perfluoro substituted C_{3-6}-cyclyl, wherein the mono-, di- and perfluoro substituted C_{3-6}-cyclyl groups are more preferred. Still more preferred are mono- and perfluoro substituted C_{3-6}-cyclyl groups.

In case the C_{3-6}-cyclyl group is substituted by one or more hydroxy, the C_{3-6}-cyclyl group can be any group as specified above with respect to C_{3-6}-cyclyl, unless specified otherwise. The C_{3-6}-cyclyl group substituted by one or more hydroxy is preferably a mono- or dihydroxy substituted C_{3-6}-cyclyl, wherein monohydroxy substituted C_{3-6}-cyclyl groups are more preferred.

The above-mentioned 3- to 7-membered heterocyclyl group may be substituted with one or more substituents selected from the group consisting of fluoro, hydroxy, hydrogen, C_{1-6}-alkyl and –C(O)-C_{1-6}-alkyl.

In case the 3- to 7-membered heterocyclyl group is substituted by one or more substituents selected from fluoro and hydroxy, this/these substituent(s) preferably bind to a ring carbon atom.

In case the 3- to 7-membered heterocyclyl group is substituted by one or more fluoro, the 3- to 7-membered heterocyclyl group can be any group as specified above with respect to 3- to 7-membered heterocyclyl, unless specified otherwise. The 3- to 7-membered heterocyclyl group substituted by one or more fluoro is preferably a mono-, di-, tri-, polyfluoro or perfluoro substituted 3- to 7-membered heterocyclyl, wherein the mono-, di- and perfluoro substituted 3- to 7-membered heterocyclyl groups are more preferred. Still more preferred are mono- and perfluoro substituted 3- to 7-membered heterocyclyl groups.

In case the 3- to 7-membered heterocyclyl group is substituted by one or more hydroxy, the 3- to 7-membered heterocyclyl group can be any group as specified above with respect to 3- to 7-membered heterocyclyl, unless specified otherwise. The 3- to 7-membered heterocyclyl group substituted by one or more hydroxy is preferably a mono- or dihydroxy substituted 3- to 7-membered heterocyclyl, wherein monohydroxy substituted 3- to 7-membered heterocyclyl groups are more preferred.

In case the 3- to 7-membered heterocyclyl group is substituted by one or more substituents selected from hydrogen, C_{1-6}-alkyl and –C(O)-C_{1-6}-alkyl, the 3- to 7-membered heterocyclyl group can be any group as specified above with respect to 3- to 7-membered heterocyclyl, unless specified otherwise. Similarly the C_{1-6}-alkyl group and the C_{1-6}-alkyl moiety of the –C(O)-C_{1-6}-alkyl group can be any group as specified above with respect to the substituted or unsubstituted C_{1-6}-alkyl. It is preferred that the substituent(s) hydrogen, C_{1-6}-alkyl and –C(O)-C_{1-6}-alkyl bind to a nitrogen ring atom. It is more preferred that the substituent –C(O)-C_{1-6}-alkyl is –C(O)-CH_3 and –C(O)-CH_2OH.

The above-mentioned 3- to 7-membered heterocycle may be substituted with one or more substituents selected from the group consisting of fluoro, hydroxy, C_{1-6}-alkoxy, amide, hydrogen, C_{1-6}-alkyl and -C(O)-C_{1-6}-alkyl.

In case the 3- to 7-membered heterocycle is substituted by one or more substituents selected from fluoro, hydroxy, C_{1-6}-alkoxy and amide, this/these substituent(s) preferably bind to a ring carbon atom.

In case the 3- to 7-membered heterocycle is substituted by one or more fluoro, the 3- to 7-membered heterocycle can be any group as specified above with respect to 3- to 7-membered heterocycle, unless specified otherwise. The 3- to 7-membered heterocycle substituted by one or more fluoro is preferably a mono-, di-, tri-, polyfluoro or perfluoro substituted 3- to 7-membered heterocycle, wherein a mono-, di- and perfluoro substituted 3- to 7-membered heterocycle is more preferred. Still more preferred are mono- and perfluoro substituted 3- to 7-membered heterocycles.

In case the 3- to 7-membered heterocycle is substituted by one or more hydroxy, the 3- to 7-membered heterocycle can be any group as specified above with respect to 3- to 7-membered heterocycle, unless specified otherwise. The 3- to 7-membered heterocycle substituted by one or more hydroxy is preferably a mono- or dihydroxy substituted 3- to 7-membered heterocycle, wherein monohydroxy substituted 3- to 7-membered heterocycles are more preferred.

In case the 3- to 7-membered heterocycle is substituted by one or more substituents selected from hydrogen, C_{1-6}-alkyl and –C(O)-C_{1-6}-alkyl, the 3- to 7-membered heterocycle can be any group as specified above with respect to 3- to 7-membered heterocycle, unless specified otherwise. Similarly the C_{1-6}-alkyl group and the C_{1-6}-alkyl moiety of the –C(O)-C_{1-6}-alkyl group can be any group as specified above with respect to the substituted or unsubstituted C_{1-6}-alkyl. It is preferred that the substituent(s) hydrogen, C_{1-6}-alkyl and –C(O)-C_{1-6}-alkyl bind to a nitrogen ring atom. It is more preferred that the substituent –C(O)-C_{1-6}-alkyl is –C(O)-CH_3 and –C(O)-CH_2OH.

It is to be understood that the invention covers all tautomers of the compounds of formula (I), a salt thereof, an N-oxide of the tautomeric compound or the salt thereof, a stereoisomer of the tautomeric compound, the salt, the N-oxide of the stereoisomer of the tautomeric compound or the N-oxide of the salt thereof.

It is to be understood that the invention covers all combinations of substituent groups referred to hereinabove. In particular, the invention covers all combinations of preferred groups described herein.

Salts of the compounds according to the invention, the N-oxides thereof, the stereoisomers of the salts and the N-oxides thereof include all inorganic and organic acid addition salts and salts with bases, especially all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases, particularly all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases customarily used in pharmacy.

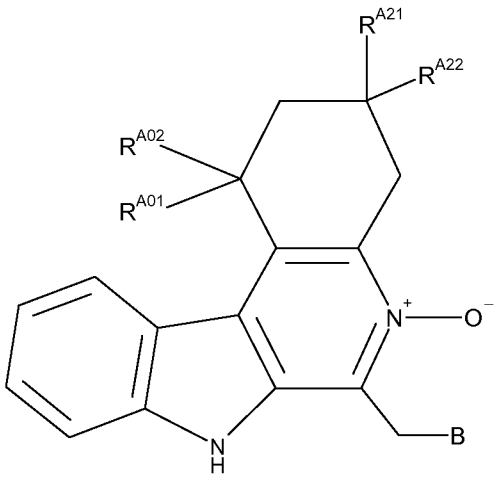
Examples of acid addition salts include, but are not limited to, hydrochlorides, hydrobromides, phosphates, nitrates, sulfates, acetates, trifluoroacetates, citrates, gluconates including D-gluconates and L-gluconates, glucuronates including D-glucuronates and L-glucuronates, benzoates, 2-(4-hydroxybenzoyl)benzoates, butyrates, salicylates, sulfosalicylates, maleates, laurates, malates including L-malates and D-malates, lactates including L-lactates and D-lactates, fumarates, succinates, oxalates, tartarates including L-tartarates, D-tartarates and meso-tartarates, stearates, benzenesulfonates (besilates), toluenesulfonates (tosilates), methanesulfonates (mesilates), laurylsulfonates, 3-hydroxy-2-naphthoates, lactobionates (salts of 4-O-beta-D-galactopyranosyl-D-gluconic acid), galactarates, embonates and ascorbates.

Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, ammonium, meglumine and guanidinium salts.

The salts include water-insoluble and, particularly, water-soluble salts.

The compounds according to the invention, the salts thereof, the N-oxides of the compounds and the salts thereof and the stereoisomers of the compounds, salts, N-oxides of the compounds and N-oxides of the salts thereof may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are, therefore, all solvates of the compounds of formula (I), the salts thereof, the N-oxides of the compounds and the salts thereof and the stereoisomers of the compounds, salts, N-oxides of the compounds and N-oxides of the salts thereof. Hydrates are a preferred example of said solvates.

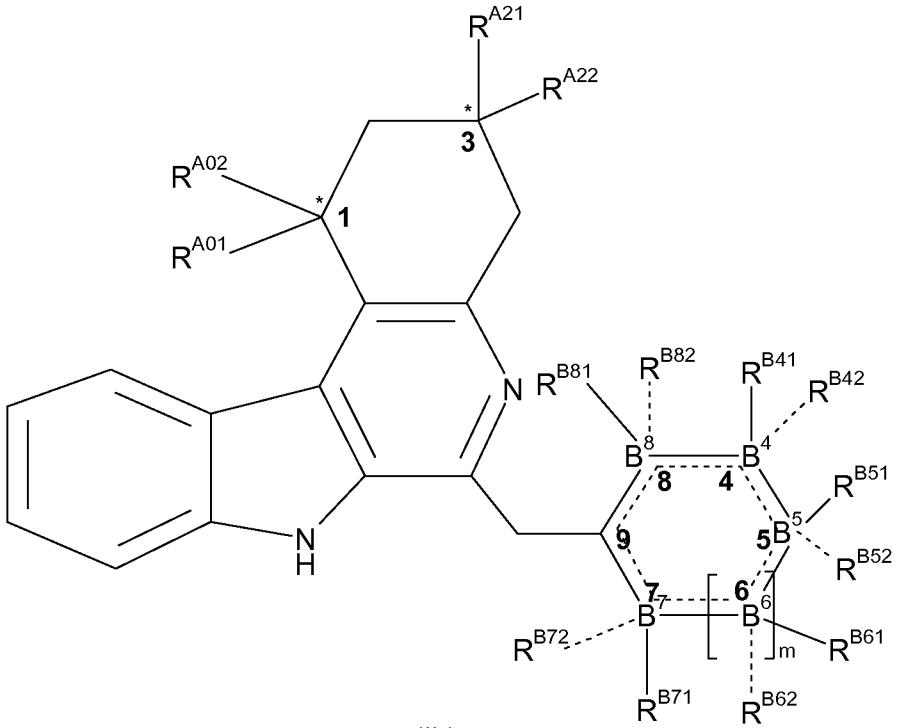
The N-oxides of the compounds according to the invention, the salts thereof, the stereoisomers of the compounds and the salts thereof include compounds, wherein the nitrogen atom of the pyridine moiety is oxidized, as illustrated by formula (Ia) below:



(Ia)

The compounds according to the invention, the salts thereof, the N-oxides of the compounds and the salts thereof include stereoisomers. In case R^{A01} being a hydroxy group, R^{A02} being hydrogen and R^{A21} and R^{A22} representing identical groups, the compounds according to the invention, the salts thereof, the N-oxides of the compounds and the salts thereof have one stereogenic center. In case R^{A01} and R^{A02} being hydrogen or R^{A01} and R^{A02} combining to form an oxo group and R^{A21} and R^{A22} representing different groups, the compounds according to the invention, the salts thereof, the N-oxides of the compounds and the salts thereof have one stereogenic center. In case R^{A01} being a hydroxy group, R^{A02} being hydrogen and R^{A21} and R^{A22} representing different groups, the com-

pounds according to the invention, the salts thereof, the N-oxides of the compounds and the salts thereof have two stereogenic centers. Likewise, in case of both substituents R^{Bx1} and R^{By2}, wherein x = y and x, y = 4, 5, 6, 7 or 8, exist and are different from one another, the corresponding atoms B_x may be stereogenic centers. Moreover, C9 (number refers to the atoms indicated in formula (Ib)) may be a stereogenic center. Each of said stereogenic centers may have the absolute configuration R or the absolute configuration S (according to the rules of Cahn, Ingold and Prelog). Accordingly, the stereoisomers (1R), (1S), (3R), (3S), (4R), (4S), (5R), (5S), (6R), (6S), (7R), (7S), (8R), (8S), (9R), (9S), wherein the numbers refer to the atoms indicated in formula (Ib) below,



(Ib)

the salts thereof, the N-oxides of the stereoisomers and the salts thereof are part of the invention. Accordingly, in the case of the presence of two stereocenters, all of the possible 20160 stereoisomers, e.g. (1R,3R), (1R,3S), (1S,3R), (1S,3S) or (1R,9R), (1R,9S), (1S,9R), (1S,9S), wherein the numbers refer to the atoms indicated in formula (Ib), the salts thereof, the N-oxides of the stereoisomers and the salts thereof are part of the invention.

Accordingly, in the case of the presence of three or more stereocenters, all of the possible stereoisomers, the salts thereof, the N-oxides of the stereoisomers and the salts thereof are part of the invention.

In a preferred embodiment, the invention relates to stereoisomers of formula (Ib) having the configuration (1R) or (1S), with the carbon atom at position number 3 not being an asymmetric carbon atom.

The invention further includes all mixtures of the stereoisomers mentioned above independent of the ratio, including the racemates.

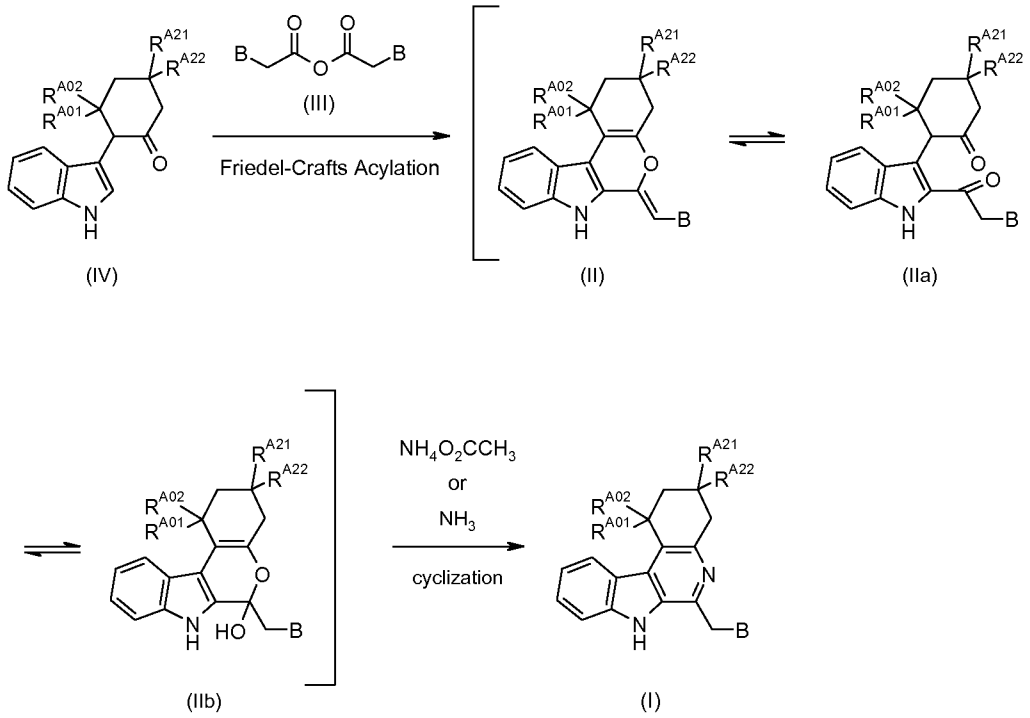
Some of the compounds, salts thereof, N-oxides of the compounds and the salts thereof, stereoisomers of the compounds, salts, N-oxides of the compounds and N-oxides of the salts thereof according to the invention may exist in different crystalline forms (polymorphs) which are within the scope of the invention.

Furthermore, derivatives of the compounds of formula (I), the salts thereof, the N-oxides of the compounds or the salts thereof, stereoisomers of the compounds, salts, N-oxides of the compounds or N-oxides of the salts thereof which are converted into compound (I) or a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof in a biological system (bioprecursors or pro-drugs) are covered by the invention. Said biological system is e.g. a mammalian organism, particularly a human subject. The bioprecursor is, for example, converted into the compound of formula (I), a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof by metabolic processes.

The compounds according to the invention can be prepared as follows.

As shown in reaction scheme 1, a compound of formula (I) can be obtained by reacting a compound of formula (II) or (IIa) or (IIb) or a mixture thereof with ammonia in an appropriate solvent, e.g. acetonitrile, preferably under microwave heating. The compound of formula (II) or (IIa) or (IIb) or a mixture thereof can be prepared by cyclization of a compound of formula (IV) with a compound of formula (III) in the presence of a strong inorganic acid, e.g. perchloric acid, in a suitable solvent, e.g. nitromethane.

Reaction scheme 1:

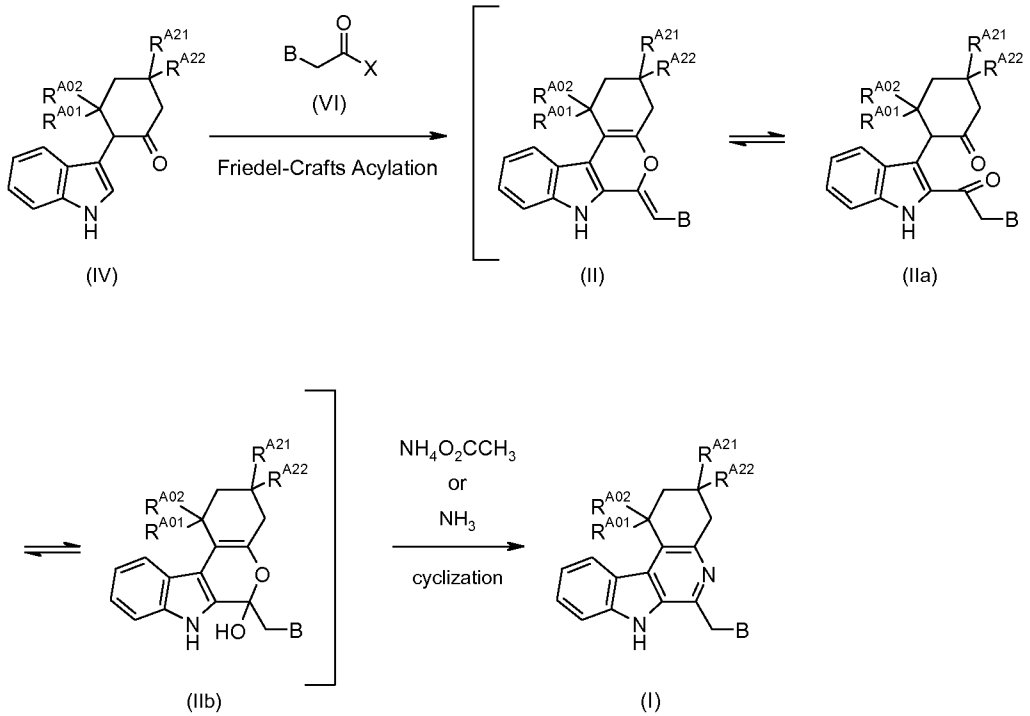


Compounds of formula (III) are commercially available or can be obtained according to procedures known in the art.

In an alternative procedure, as illustrated in reaction scheme 2, a compound of formula (IV) can be reacted with a compound of formula (VI), in which X is a suitable leaving group, e.g. halogen, such as chlorine, or a conjugate base of an acid, such as trifluoroacetate, in a Friedel-Crafts acylation reaction in the presence of an appropriate Lewis acid, e.g. zinc chloride, boron trifluoride etherate or orthophosphoric acid, in a suitable solvent, e.g. dichloromethane, dichloroethane, diethylether, toluene, nitromethane and/or chlorobenzene, to give the corresponding compound of formula (II) or (IIa) or (IIb) or a mixture thereof. Said Friedel-Crafts acylation reaction can be based on, for example, work of Duval et al. [see e.g. Tetrahedron Letters 45, 5411 (2004)]. The compound of formula (II) or (IIa) or (IIb) or a mixture thereof can be subjected to a cyclization condensation reaction with ammonium acetate in an appropriate solvent, e.g. acetic acid, preferably at elevated temperature, and / or a cyclization condensation reaction with ammonia in an appropriate solvent, e.g. methanol, preferably at elevated temperature, to give a corresponding compound of formula (I). In some cases it may be convenient to perform both the Friedel-Crafts acylation reaction and the cyclization condensation reaction in one pot.

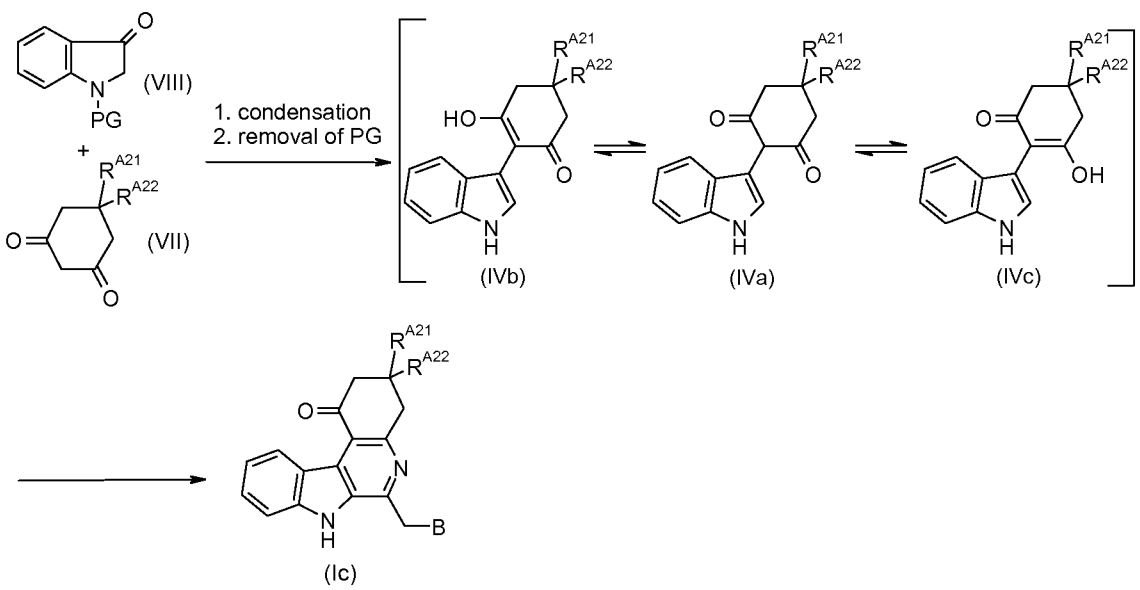
Compounds of formula (VI) are commercially available or can be obtained according to procedures known in the art.

Reaction scheme 2:



As shown in reaction scheme 3, a compound of formula (IVa) or (IVb) or (IVc) or a mixture thereof are obtainable via an aldol-type condensation of a compound of formula (VIII), in which PG stands for a suitable temporary protecting group, e.g. acetyl, formyl, allyl or methoxycarbonyl, with a compound of formula (VII), and subsequent removal of PG. The compound of formula (IVa) or (IVb) or (IVc) or a mixture thereof can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Ic).

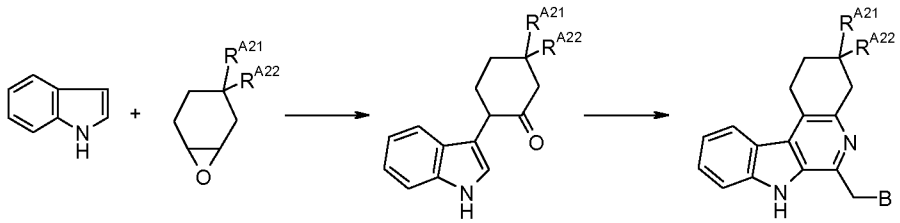
Reaction scheme 3:



Compounds of formulae (VIII) and (VII) are commercially available or can be obtained according to procedures known in the art.

Furthermore, a compound of formula (Id), in which R^{A01} and R^{A02} are hydrogen, can be obtained as shown in reaction scheme 4. In particular, indole (IX) can be reacted with a compound of formula (X) in an art-known nucleophilic substitution reaction [see e.g. Heterocycles 31 (8), 1497-1504 (1990)]. The thus obtained hydroxy-compound can be oxidized in a manner known to the skilled person, e.g. according to a Swern oxidation [see e.g. Tetrahedron 47, 8653 (1991)] or a variant thereof using trifluoroacetic anhydride as activator [see e.g. J. Org. Chem. 41, 957 (1976)] or by utilizing sulfur trioxide pyridine complex as oxidizing agent [see e.g. Organic Process Research & Development 10, 163 (2006)], to give the corresponding compound of formula (XI). The compound of formula (XI) can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Id).

Reaction scheme 4:

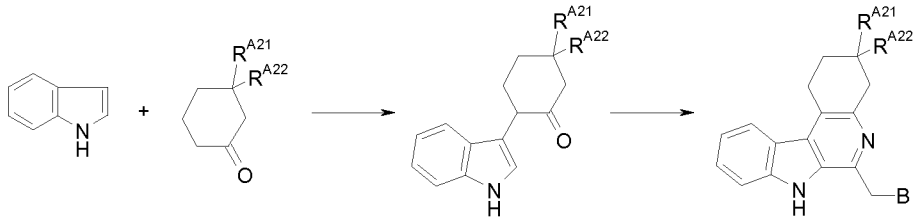


(IX) (X) (XI) (Id)

Indole (IX) is commercially available, the compounds of formula (X) are known, commercially available or can be obtained according to known procedures.

Alternatively, a compound of formula (Id), in which R^{A01} and R^{A02} are hydrogen, can be obtained as illustrated in reaction scheme 5. In a first step, indole (IX) is reacted with a compound of formula (XII) in an art-known oxidative coupling reaction [see e.g. JACS 129, 12857 (2007)], in the presence of a suitable base, e.g. lithium diisopropylamide or lithium hexamethyldisilazide, and a suitable oxidation agent, e.g. copper(II)-2-ethylhexanoate. The thus obtained compound of formula (XI) can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Id).

Reaction scheme 5:

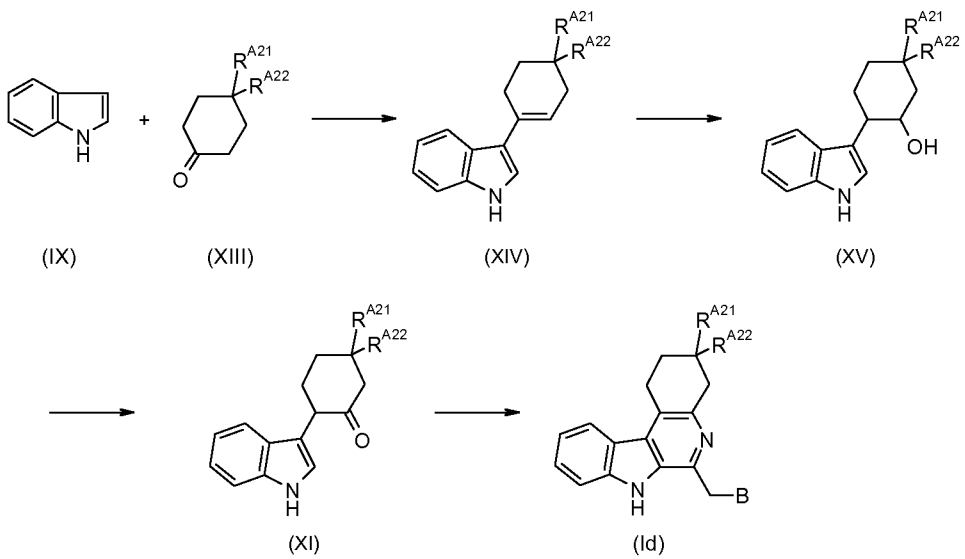


(IX) (XII) (XI) (Id)

Indole (IX) is commercially available, the compounds of formula (XII) are known, commercially available or can be obtained according to known procedures.

Moreover, a compound of formula (Id) can be obtained as illustrated in reaction scheme 6. In a first step, indole (IX) is reacted with a compound of formula (XIII) in an art-known condensation reaction in the presence of a base, e.g. pyrrolidine or potassium hydroxide [see e.g. Bioorganic & Medicinal Chemistry Letters 17, 3099 (2007)]. The thus obtained unsaturated compound of formula (XVI) can be hydroxylated in a hydroboration – oxidation reaction known to the person skilled in the art, e.g. by using borane and sodium hydroxide / hydrogen peroxide [see e.g. Bioorganic & Medicinal Chemistry Letters 16, 3524 (2006)]. The resulting hydroxy-compound (XV) can be oxidized in a manner known to the skilled person, e.g. according to a Swern oxidation [see e.g. Tetrahedron 47, 8653 (1991)] or a variant thereof using trifluoroacetic anhydride as activator [see e.g. J. Org. Chem. 41, 957 (1976)] or by utilizing sulfur trioxide pyridine complex as oxidizing agent [see e.g. Organic Process Research & Development 10, 163 (2006)], to give the corresponding compound of formula (XI). The compound of formula (XI) can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Id).

Reaction scheme 6:



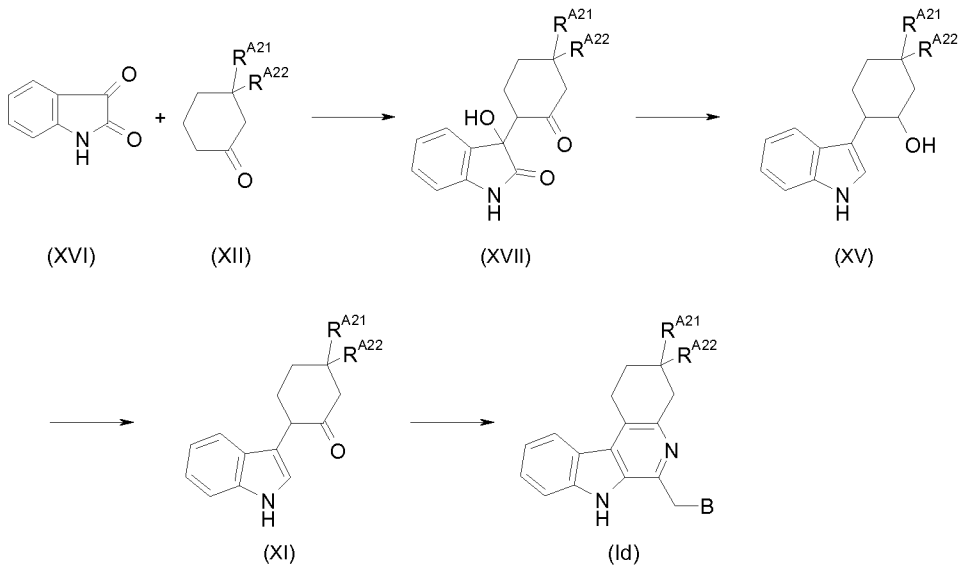
(IX) (XIII) (XIV) (XV)

(XI) (Id)

Indole (IX) is commercially available, compounds of formula (XIII) are known, commercially available or can be obtained according to known procedures.

As an alternative approach, a compound of formula (Id) can be obtained as illustrated in reaction scheme 7. In a first step, isatine (XVI) is reacted with a compound of formula (XII) in an art-known aldol addition reaction [see e.g. Tetrahedron 58, 8399 (2002)]. The thus obtained hydroxy compound of formula (XVII) can be transformed into a compound of formula (XV) by using reductive agents, such as, for example, borane tetrahydrofuran complex or lithium aluminium hydride [see e.g. Tetrahedron 58, 8399 (2002)]. The resulting hydroxy-compound of formula (XV) can be oxidized in a manner known to the skilled person, e.g. according to a Swern oxidation [see e.g. Tetrahedron 47, 8653 (1991)] or a variant thereof using trifluoroacetic anhydride as activator [see e.g. J. Org. Chem. 41, 957 (1976)] or by utilizing sulfur trioxide pyridine complex as oxidizing agent [see e.g. Organic Process Research & Development 10, 163 (2006)], to give the corresponding compound of formula (XI). The compound of formula (XI) can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Id).

Reaction scheme 7:

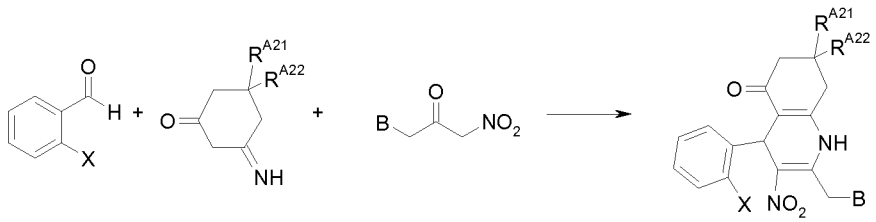


Isatine (XVI) is commercially available, compounds of formula (XII) are known, commercially available or can be obtained according to known procedures.

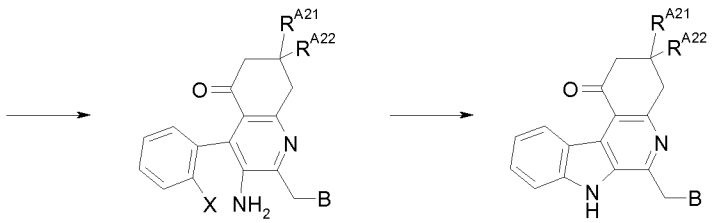
An alternative synthetic route to a compound of formula (Ic) is depicted in reaction scheme 8. Compounds of formulae (XVIII), (XIX) and (XX), with X being a leaving group, such as halogen, preferably bromine or chlorine, can be reacted in a multi-component unsymmetric Hantzsch reaction in the presence of catalytic amounts of acid, e.g. acetic acid, and amine, e.g. benzylamine [see e.g. Tetrahedron Letters 42, 4507 (2001) or Tetrahedron 63, 1946 (2007)]. The resulting nitrodihydropyridine of formula (XXI) can be converted to amino-pyridine of formula (XXII) either in two

steps (oxidation of dihydropyridine and reduction of nitro group) or, preferably, in one step by using, e.g., elementary iron in the presence of concentrated hydrochloric acid or elementary zinc in the presence of acetic acid. The final ring closing reaction to obtain a compound of formula (Ic) can be achieved by reacting a compound of formula (XXII) under nitrogen atmosphere with catalytic amounts of a suitable palladium source, e.g. tris(dibenzylideneacetone)dipalladium (0) or tetrakis(triphenylphosphine)palladium (0), and, if necessary, of a suitable phosphine ligand, in the presence of a suitable base, e.g. sodium tert-butoxide or sodium carbonate [see e.g. Bioorganic & Medicinal Chemistry Letters 17, 1043 (2007)].

Reaction scheme 8:



(XVIII) (XIX) (XX) (XXI)

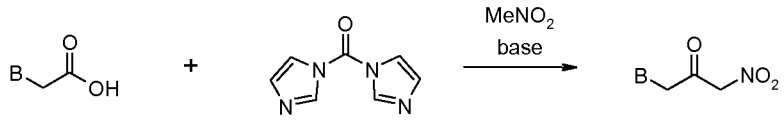


(XXII) (Ic)

Compounds of formulae (XVIII), (XIX) and (XX) are known, commercially available or can be obtained according to known procedures.

As an example, a compound of formula (XX) can be obtained, as shown in reaction scheme 9, by reacting the corresponding acids of formula (XXIII) with carbonyl diimidazole in the presence of nitromethane and a suitable base, e.g. potassium tertbutylate [see e.g. J. Am. Chem. Soc. 125, 157 (2003)].

Reaction scheme 9:

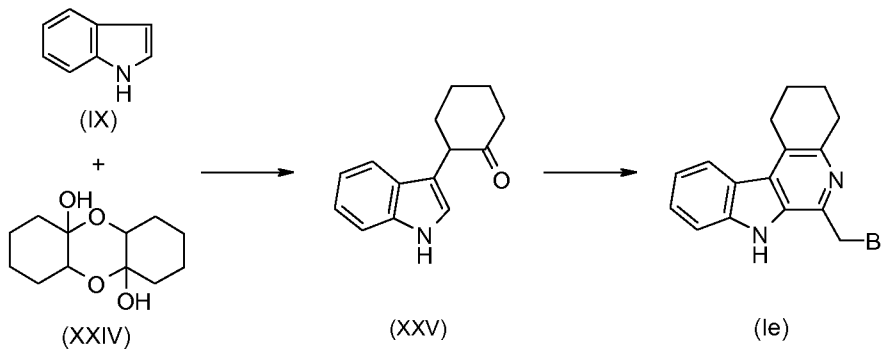


(XXIII) (XX)

Compounds of formula (XXIII) are known, commercially available or can be obtained according to known procedures.

Moreover, a compound of formula (Ie), in which R^{A01}, R^{A02}, R^{A21} and R^{A22} are hydrogen, can also be obtained by a condensation reaction as shown in reaction scheme 10. A compound of formula (IX) is, for example, reacted with a compound of formula (XXIV) in the presence of acetic acid and H_3PO_4, preferably at elevated temperature. The compound of formula (XXV) thus obtained can be reacted according to reaction scheme 1 or 2 [replacing compound (IV)] to give a compound of formula (Ie).

Reaction scheme 10:



Indole (IX) and 2-hydroxycyclohexanone dimer (XXIV) are known, commercially available or can be obtained according to known procedures.

Compounds of formula (I) can be converted into different compounds of formula (I) by methods known in the art. For example,

- a compound of formula (I), wherein R^{A01} is hydroxy and R^{A02} is hydrogen, can be prepared from a compound of formula (I), wherein R^{A01} and R^{A02} combine to form an oxo group, by reduction reaction, e.g. with the aid of a suitable reduction agent, such as sodium borohydride;
- a compound of formula (I), wherein R^{A01} is hydrogen and R^{A02} is hydrogen, can be prepared from a compound of formula (I), wherein R^{A01} and R^{A02} combine to form an oxo group, by reduction reaction, e.g. with the aid of a suitable reduction agent, such as hydrazine (e.g. according to a Wolff-Kishner reduction);
- a compound of formula (I), wherein R^{A01} is amino and R^{A02} is hydrogen can be prepared from a compound of formula (I), wherein the R^{A01} and R^{A02} combine to form an oxo group, by reductive amidation reaction, e.g. with the aid of a suitable amide, e.g. formamide, in combination with a suitable reduction agent, such as formic acid or ammonium formiate in a suitable solvent, e.g. formic acid, at elevated temperatures, preferably 140°C – 180°C, followed by amide hydrolysis

reaction, e.g. with the aid of a strong acid, such as hydrogen chloride, in a suitable solvent, such as methanol;

- a compound of formula (I), wherein R^{A01} is amino and R^{A02} is hydrogen can be prepared from a compound of formula (I), wherein the R^{A01} and R^{A02} combine to form an oxo group, by reductive amination reaction, e.g. with the aid of a suitable amine, e.g. benzylamine, in combination with a suitable reduction agent, such as sodium cyanoborohydride or sodium borohydride, in the presence of a suitable acid, e.g. acetic acid or p-toluenesulfonic acid, or a suitable Lewis acid, e.g. titanium(IV) tetraisopropyl oxide, in a suitable solvent, e.g. methanol, followed by hydrogenation, e.g. with the aid of a transition metal catalyst, such as palladium(0), in combination with a suitable hydrogen source, e.g. hydrogen gas or ammonium formiate, in a suitable solvent, such as methanol;
- a compound of formula (I), wherein R^{A01} is mono- or di-C_{1-6}-alkylamino, and R^{A02} is hydrogen can be prepared from a compound of formula (I), wherein the R^{A01} and R^{A02} combine to form an oxo group, by reductive amination reaction, e.g. with the aid of a suitable amine, e.g. methylamine or diethylamine, in combination with a suitable reduction agent, such as sodium cyanoborohydride or sodium borohydride, in the presence of a suitable acid, e.g. acetic acid or p-toluenesulfonic acid, or a suitable Lewis acid, e.g. titanium(IV) tetraisopropyl oxide, in a suitable solvent, e.g. methanol;
- a compound of formula (I), wherein R^{A01} is carbonylamino-, e.g. –NH-C(O)-C_{1-6}-alkyl, wherein said C_{1-6}-alkyl may be substituted as defined above, and R^{A02} is hydrogen, can be prepared e.g. from a compound of formula (I), wherein R^{A01} is amino and R^{A02} is hydrogen, by reaction with an appropriate carboxylic acid chloride, e.g. C_{1-6}-alkylC(O)Cl, wherein said C_{1-6}-alkyl may be substituted as defined above, or carboxylic anhydride, e.g. $(C_{1-6}\text{-alkyl-C(O)})_2O$, wherein said C_{1-6}-alkyl may be substituted as defined above, in the presence of a base, e.g. triethylamine, pyridine or potassium carbonate, or with an appropriate carboxylic acid, e.g. C_{1-6}-alkylC(O)OH, wherein said C_{1-6}-alkyl may be substituted as defined above, in the presence of a dehydrating agent, e.g. dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, a suitable base, e.g. triethylamine or diisopropylethylamine, and, optionally, a suitable additive reagent, such as 1-hydroxybenzotriazole;
- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) a nitro group can be converted into the corresponding amino compound by reduction reaction, e.g. with the aid of a suitable reduction agent, such as tin dichloride or hydrogen gas and a palladium on carbon catalyst;
- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) carbonylamino-, e.g. –NH-C(O)-R^{B46}, –NH-C(O)-R^{B56}, –NH-C(O)-R^{B66}, –NH-C(O)-R^{B76} or –NH-C(O)-R^{B86}, can be prepared e.g. from a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represents an amino group by reaction with an appropriate carboxylic acid chloride or carboxylic anhydride, in the presence of a base, e.g.

triethylamine, pyridine or potassium carbonate, or with an appropriate carboxylic acid in the presence of a dehydrating agent, e.g. dicyclohexylcarbodiimide;

- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represents -NH-C(O)-NH_2 can be obtained e.g. from a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represents an amino group by reaction with potassium cyanate in the presence of a mineral acid, such as hydrochloric acid, or by condensation with urea;
- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} is hydroxy can be synthesized e.g. from a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} is 1-3C-alkoxy by dealkylation with a Lewis acid, such as boron tribromide.
- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) substituted amino, e.g. $-NR^{B44}R^{B45}$, $-NR^{B54}R^{B55}$, $-NR^{B64}R^{B65}$, $-NR^{B74}R^{B75}$ or $-NR^{B84}R^{B85}$, can be prepared e.g. from a compound of formula (I), wherein the corresponding R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) a halogen, preferably bromine or chlorine, by reaction with an appropriate amine, e.g. $HNR^{B44}R^{B45}$, $HNR^{B54}R^{B55}$, $HNR^{B64}R^{B65}$, $HNR^{B74}R^{B75}$ or $HNR^{B84}R^{B85}$, respectively, in the presence of a catalytic amount of a transition metal complex, preferably incorporating palladium or copper, e.g. tris(dibenzylideneacetone)-dipalladium(0) or palladium(II) acetate, a catalytic amount of an appropriate ligand, preferably phosphines or diamines, e.g. dicyclohexyl-(2',4',6'-trisisopropyl-biphenyl-2-yl)-phosphane and a stoichiometric amount of base, e.g. cesium carbonate or sodium carbonate, in an appropriate solvent, e.g. toluene or tert-butanol, at elevated temperature, preferably 80-110°C, and under nitrogen or argon atmosphere [see e.g. J. Am. Chem. Soc. 125, 6653-6655 (2003)];
- a compound of formula (I), wherein R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) C_{6-14}-aryl or C_{1-13}-heteroaryl can be prepared e.g. from a compound of formula (I), wherein the corresponding R^{B41} and/or R^{B51} and/or R^{B61} and/or R^{B71} and/or R^{B81} represent(s) a halogen, preferably bromine or chlorine, by reaction with an appropriate boronic acid, e.g. C_{6-14}-aryl-$B(OH)_2$ or C_{1-13}-heteroaryl-$B(OH)_2$, respectively, in the presence of a catalytic amount of a transition metal complex, preferably incorporating palladium, e.g. dichlorobis (tricyclohexyl-phosphine) palladium (II), optionally a catalytic amount of an appropriate ligand, preferably phosphines, and a stoichiometric amount of base, e.g. cesium carbonate or sodium carbonate, in an appropriate solvent, e.g. dimethoxyethane and/or tetrahydrofuran and/or ethanol, at elevated temperature, preferably 80-110°C, or using microwave radiation at 120-140°C, and under nitrogen or argon atmosphere;

It is known to the person skilled in the art that, if there are a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center.

Starting materials or building blocks, that are necessary for the synthesis of compounds according to the invention are either commercially available, or are prior art, or can be synthesized by a person skilled in the art, or are described within this document as an example or as a general methodology.

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material, e.g. silica gel, reversed phase silica gel, amino modified silica gel, aluminium oxide.

Salts of the compounds of formula (I), the N-oxides thereof and the stereoisomers of the compounds and the N-oxides thereof according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxan, a chlorinated hydrocarbon such as methylene chloride or chloroform, a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol, a low molecular weight aliphatic ester such as ethyl acetate or isopropyl acetate, or water) which contains the desired acid or base, or to which the desired acid or base is then added. Examples for acids include hydrochloric acid, hydrobromic acid, p-tolylsulfonic acid, methylsulfonic acid, trifluoromethylsulfonic acid, succinic acid, malic acid, citric acid, maleic acid, formic acid, acetic acid or pyroglutamic acid. Examples for bases include metal hydrides, such as sodium hydride or calcium hydride, metal hydroxides, such as sodium hydroxide, lithium hydroxide, potassium hydroxide, magnesium hydroxide or calcium hydroxide, or amines, e.g. ammonia, trimethylamine or methylamine. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art.

The compounds of formula (I), the salts thereof and the stereoisomers of the compounds and the salts according to the invention can be converted into their N-oxides, for example, by reaction with peracids, such as m-chloroperbenzoic acid or peracetic acid. The person skilled in the art is familiar with the reaction conditions for carrying out the N-oxidation.

Pure diastereomers and pure enantiomers of the compounds of formula (I), the salts thereof, the N-oxides of the compounds and the N-oxides of the salts according to the invention can be obtained

e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and/or by splitting up enantiomeric and diasteriomeric mixtures obtained in synthesis. Preferably, the pure diastereomeric and pure enantiomeric compounds of the invention are obtainable by asymmetric synthesis and/or by using chiral starting compounds in synthesis.

In particular, for example the (1S)-enantiomers of the compounds of formula (Ib), the salts thereof, the N-oxides of the compounds and the salts thereof according to the invention can be obtained by reduction of the corresponding ketone precursors (wherein R^{A01} and R^{A02} combine to form an oxo group) with sodium borohydride in the presence of (4S,5S)-2-(3-nitro-phenyl)-[1,3,2]dioxaborolane-4,5-dicarboxylic acid in a suitable aprotic solvent, preferably tetrahydrofuran or dioxan, preferably at room temperature. (4S,5S)-2-(3-Nitro-phenyl)-[1,3,2]dioxaborolane-4,5-dicarboxylic acid can be prepared by esterification of 3-nitrophenyl boronic acid and D-tartaric acid in the presence of a dehydrating agent such as calcium hydride, preferably at temperatures of 60-80°C. Likewise, for example the (1R)-enantiomers of the compounds of formula (Ib), the salts thereof, the N-oxides of the compounds and the salts thereof according to the invention can be obtained using (4R,5R)-2-(3-nitro-phenyl)-[1,3,2]dioxaborolane-4,5-dicarboxylic acid in a suitable aprotic solvent, preferably tetrahydrofuran or dioxan, preferably at room temperature. (4R,5R)-2-(3-Nitro-phenyl)-[1,3,2]dioxaborolane-4,5-dicarboxylic acid can be prepared by esterification of 3-nitrophenyl boronic acid and L-tartaric acid in the presence of a dehydrating agent such as calcium hydride, preferably at temperatures of 60-80°C.

Enantiomeric and diastereomeric mixtures can be split up into the pure enantiomers and pure diastereomers by methods known to a person skilled in the art. Preferably, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxiliary agent, resolving the diastereomers obtained and removing the chiral auxiliary agent. As chiral auxiliary agents, for example, chiral acids, such as (+)- or (-)-tartaric acid, (+)- or (-)-malic acid, (+)- or (-)-mandelic acid, (+)- or (-)-lactic acid or (+)- or (-)-camphersulfonic acid, can be used to separate enantiomeric bases and chiral bases, such as (+)- or (-)-brucine, (+)- or (-)-quinidine or (+)- or (-)-quinine, can be used to separate enantiomeric acids via formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids, such as (+)- or (-)-lactic acid or (+)- or (-)-mandelic acid, or chiral alcohols, such as (+)- or (-)-1-phenylethanol, respectively, as chiral auxiliary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up using chiral separating columns in chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

All patents, patent applications, publications, test methods and other materials cited herein are incorporated by reference in their entireties.

The following examples illustrate the invention in greater detail, without restricting it. Further compounds according to the invention, of which the preparation is not explicitly described, can be prepared in an analogous way.

The compounds which are mentioned in the examples, the salts thereof, N-oxides of the compounds and the salts thereof and stereoisomers of the compounds, salts, N-oxides of the compounds and N-oxides of the salts thereof represent preferred embodiments of the invention.

Examples

^{1}H NMR spectra are recorded on a Bruker DPX200 (^{1}H 200 MHz), a Bruker Avance (^{1}H 300 MHz) or a Bruker AV400 (^{1}H 400 MHz) spectrometer. Spectra are calibrated on tetramethylsilane (TMS) as internal standard (0.00 ppm for ^{1}H). Chemical shifts are given in ppm (δ) relative to TMS, multiplicities are indicated by s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), q (quartet), m (multiplet) and b (broadened). Coupling constants, *J*, are reported in Hz. Data are reported in the form δ = chemical shift (multiplicity, (coupling constant(s) if appropriate), integral in fold of 1H).
Mass spectra are recorded on a LCQ classic or an LCQ advantage ion trap mass spectrometer from Thermofinnigan, using combined liquid chromatography / mass spectroscopy methodology. Samples are dissolved in acetonitrile and chromatographed on a Survey HPLC from Thermofinnigan, using a reversed phase column (Merck LiChroCART 75-4, 60 RP-B) as stationary phase and a gradient of aqueous buffer (20 mM ammoniumacetate / formic acid, pH 4) and methanol as mobile phase at a flow of 0.8 ml/min, and ionized by electrospray ionization (ESI), positive mode. Data are reported in the form MS (ionized particle found) = *m/z*. In that context, the molecule is abbreviated by M. For compounds containing bromine, both isotopic forms are reported, for compounds containing chlorine and all other elements, only the major isotopes are reported.
Melting points, mp., are measured on a Büchi B-540 or a Büchi B-541 instrument and are uncorrected.
The following abbreviations are used: min: minutes, h: hour(s), DCM: dichloromethane, DCE: dichloroethane, THF: tetrahydrofuran, mp.: melting point, RT: room temperature (20 to 25°C), tlc: thin layer chromatography, MS: mass spectrometry, ^{1}H-NMR: ^{1}H nuclear magnetic resonance spectroscopy.

Reactions are performed in dry (water free) solvents and under air atmosphere unless otherwise noted. Glassware is heated to 150°C in a vacuum of 10^{-1} mbar for 5 min prior to use, unless otherwise noted. Furthermore, reactions and single processes, such as dissolutions, additions, filtering, extractions or chromatography, are performed at room temperature and under air atmosphere unless otherwise noted.

Reactions using microwave radiation are performed using Biotage Initiator Sixty (0 – 300 W) and Biotage Emry's Optimizer (0 – 300 W) instruments. The temperatures and times indicated for these reactions refer to the input data using the user interface of these instruments. The reaction mixtures are stirred in closed (sealed) reaction vials for the indicated time at the indicated internal temperature, the microwave radiation power is controlled by the internal temperature. Heating and cooling phase are not considered.

Purchased chemicals and solvents are used without further purification.

Column chromatography is performed using silica gel 60 (0.040 – 0.063 mm), pH 6.5 – 7.5, from Merck KGaA or amino modified silica gel Bulk Isolute® Sorbent Flash NH2 60 (0.040 – 0.070 mm) from International Sorbent Technology Ltd. If pressure (max. 0.3 bar) is applied to increase the flow of the mobile phase the chromatography is referred to as flash chromatography.

Preparative HPLC purification is performed on a customary instrument from Gilson using a reversed phase column (C18, Phenomenex, Gemini, 75x30 mm, 5µm) as stationary phase and an acetonitrile / water gradient as mobile phase at a flow of 40 ml/min.

Starting Compounds

A1. 3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethyl-cyclohex-2-enone

Step 1: 2-(1-Acetyl-1H-indol-1-yl)-3-hydroxy-5,5-dimethyl-cyclohex-2-enone. 1-Acetyl-1,2-dihydro-indol-3-one (10.5 g) is suspended in acetic acid (50 ml) and a suspension of 5,5-dimethyl-cyclohexane-1,3-dione (8.4 g) in acetic acid (50 ml) is added. The reaction mixture is stirred for 20 min and triethylamine (8.3 ml) is added slowly. The mixture is refluxed for 24 h, evaporated to dryness, treated with 2N methanolic hydrogen chloride solution (30 ml) and evaporated to dryness again. The residue is purified by flash chromatography and crystallized from diethyl ether to give 11.5 g of 2-(1-acetyl-1H-indol-1-yl)-3-hydroxy-5,5-dimethyl-cyclohex-2-enone.

^{1}H-NMR (200 MHz, d_6-DMSO): δ = 1.13 (s, 6H), 2.42 (br, 4H), 2.61 (s, 3H), 7.17-7.19 (m, 2H), 7.23-7.31 (m, 1H), 8.31 (d, J = 7.8 Hz, 1H).

mp.: 230°C

Step 2: 3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethyl-cyclohex-2-enone. 2-(1-Acetyl-1H-indol-1-yl)-3-hydroxy-5,5-dimethyl-cyclohex-2-enone (5.95 g) is dissolved in aqueous 1N sodium hydroxide solution (65 ml) and stirred for 2 h. The reaction mixture is diluted with dichloromethane and acidified with aqueous 6N hydrogen chloride solution (pH 5). The organic layer is separated and the aqueous layer is extracted again with dichloromethane. The combined organic layers are dried ($MgSO_4$) and concentrated in vacuo to give 5.09 g of the title compound.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.22 (s, 6H), 2.50 (s, 4H), 7.00 (d, *J* = 2.5 Hz, 1H), 7.06-7.21 (m, 2H), 7.25-7.32 (m, 2H), 8.73 (br, 1H).
mp.: 178°C

A2. 6-(4-Bromobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one hydrochloride

3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (1.0 g) is suspended in dichloromethane (30 ml) and the suspension is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 34 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. A solution of (4-bromophenyl)acetyl chloride (5.0 g) in dichloromethane (75 ml) is added drop by drop within 15 min. The mixture is stirred 2 h at room temperature. After that, it is poured into ice water (50 ml), the organic phase is washed with 1M aqueous hydrochloric acid (50 ml) and 1M aqueous sodium carbonate solution (50 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is dissolved in glacial acetic acid (30 ml), ammonium acetate (1.5 g) is added and the mixture is stirred for 2 h at 60°C. After that it is concentrated in vacuo. The residue is dissolved in ethyl acetate (50 ml), water (50 ml) is added, the organic phase is washed with 1M sodium carbonate solution (50 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue is dissolved in tetrahydrofuran (10 ml), hydrogen chloride (4M in diethyl ether, 5 ml) is added, the precipitate is filtered and dried in vacuo to give rise to 0.70 g (39%) of the title compound.
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.16 (s, 6H), 2.71 (s, 2H), 3.51 (s, 2H), 5.16 (s, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.36 (dd, *J* = 7.6 Hz, 7.7 Hz, 1H), 7.52-7.80 (m, 3H), 7.99 (d, *J* = 8.3 Hz, 1H), 9.26 (d, *J* = 8.5 Hz, 1H), 13.27 (s, 1H), 15.33 (s, 1H).
MS (MH+ found) = 433.3, 435.3
mp.: 244 °C (dec.)

A3. 6-(4-Aminobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

Step 1: 3,3-Dimethyl-6-(4-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one. (4-Nitrophenyl)acetyl chloride (22.7 g) is dissolved in dichloromethane (500 ml) and the solution is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 118 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. A suspension of 3-hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (10.0 g) in dichloromethane (40 ml) and ether (40 ml) is added drop by drop within 30 min. The mixture is stirred for 2 h at room temperature. After that, it is poured into cold 1M aqueous hydrochloric acid (250 ml), the organic phase is washed with 1M aqueous hydrochloric acid (1 x 200 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is dissolved in glacial acetic acid (500 ml), ammonium acetate (125 g) is added and the mixture is stirred for 18 h at 80°C. After that the volume is reduced in vacuo to 200 ml, solid sodium carbonate is added until pH 7 and ethyl acetate (300 ml) and water (200 ml) are added. The aqueous phase is extracted with ethyl acetate (1 x 200 ml), the combined organic extracts are washed with 1M sodium carbonate solution (1 x 200 ml) and water (1 x 200 ml), dried ($MgSO_4$) and concentrated in vacuo.

The crude product is purified by column chromatography (silica gel, eluting with ethyl acetate / petroleum ether 3:5 (v/v)), followed by crystallization from ethyl acetate / petroleum ether to obtain 3.05 g (20%) of 3,3-dimethyl-6-(4-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one.

Step 2: 6-(4-Aminobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one. 3,3-Dimethyl-6-(4-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (3.0 g) is dissolved in ethanol (100 ml), tin(II)dichloride dihydrate (8.8 g) is added and the mixture is stirred for 2 h at 70°C. After that, it is poured into ice water (100 ml) and basified by addition of 1M aqueous sodium hydroxide solution. The product is extracted with ethyl acetate (2 x 200 ml), the combined organic extracts are dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by crystallization from diethyl ether to yield 2.1 g (76%) of the title compound.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.09 (s, 6H), 2.61 (s, 2H), 3.14 (s, 2H), 3,66 (bs, 2H), 4.37 (bs, 2H), 6.48-6.52 (m, 2H), 6.98-7.02 (m, 2H), 7.12-7.20 (m, 1H), 7.33-7.47 (m, 2H), 9.25 (d, *J* = 8.3 Hz, 1H), 9.59 (bs, 1H).

mp.: 123-124°C

Final Compounds

1. 6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (1.2 g) is dissolved in dichloroethane (10 ml) and the solution is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 7 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. In parallel, cyclohexylacetic acid (1.00 ml) is dissolved in trifluoroacetic acid anhydride (1.0 ml) and the mixture is stirred for 15 min at room temperature. The formed mixed anhydride is diluted with dichloroethane (2 ml) and added to the zinc chloride mixture, prepared above, within 5 min. The mixture is stirred for 2 h at room temperature. After that, ammonia (7M in methanol, 7 ml) is added and the mixture is refluxed for 18 h. After cooling, 2M ammonia solution (25 ml) is added and the aqueous phase is extracted with dichloromethane (2 x 25 ml). The combined organic extracts are washed with 2M ammonia solution (3 x 40 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by crystallization from methanol to yield 0.82 g (48%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.01-1.27 (m, 11H), 1.54-1.71 (m, 5H), 1.90-2.05 (m, 1H), 2.66 (s, 2H), 3.14 (d, *J* = 7.2 Hz, 2H), 3.13 (s, 2H), 7.21 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.52-7.68 (m, 2H), 9.22 (d, *J* = 8.3 Hz, 1H), 11.76 (s, 1H).

mp.: 235-237 °C

The following compound is obtained by using the procedure of example 1 analogously.

2. 3,3-Dimethyl-6-(3-methylbenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

Starting compounds: 3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) and (3-methylphenyl)acetic acid; yield 13%;

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.08 (s, 6H), 2.24 (s, 3H), 2.67 (s, 2H), 3.13 (s, 2H), 4.48 (s, 2H), 6.92-7.02 (m, 1H), 7.10-7.26 (m, 4H), 7.52-7.68 (m, 2H), 9.23 (d, *J* = 8.3 Hz, 1H), 11.97 (s, 1H).

MS (MH^+ found) = 369.3

mp.: 181-183 °C

3. 6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (2.9 g) is suspended in dichloromethane (100 ml) and the suspension is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 34 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. A solution of cyclopentylacetic acid chloride (5.0 g) in dichloromethane (75 ml) is added drop by drop within 15 min. The mixture is stirred for 30 min at 0°C, then 2 h at room temperature. After that, it is poured into 1M aqueous hydrochloric acid (125 ml), the organic phase is washed with 1M aqueous hydrochloric acid (3 x 100 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is dissolved in glacial acetic acid (75 ml), ammonium acetate (17.5 g) is added and the mixture is stirred for 3 h at 60°C. After that it is concentrated in vacuo. The residue is dissolved in ethyl acetate (150 ml), poured into 1M sodium carbonate solution (150 ml) and the aqueous phase is extracted with ethyl acetate (2 x 150 ml). The combined organic extracts are washed with 1M sodium carbonate solution (2 x 200 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue is crystallized from ethyl acetate / petroleum (1st crop) and diethyl ether (2nd crop) to yield 2.16 g (55%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.09 (s, 6H), 1.24-1.40 (m, 2H), 1.41-1.59 (m, 2H), 1.59-1.76 (m, 4H), 2.66 (s, 2H), 3.10-3.21 (m, 4H), 7.14-7.28 (m, 1H), 7.51-7.68 (m, 2H), 9.22 (d, *J* = 8.3 Hz, 1H), 11.80 (s, 1H).

MS (MH^+ found) = 347.3

The following compound is obtained by using the procedure of example 3 analogously, with adaptation of the purification step.

4. 3,3-Dimethyl-6-(2-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

Starting compounds: 3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) and (2-nitrophenyl)acetic acid chloride; purification by column chromatography (silica gel, eluting with gradient petroleum ether / ethyl acetate 8:2 to 7:3 (v/v)); yield 15%;

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.03 (s, 6H), 2.64 (s, 2H), 2.93 (s, 2H), 4.94 (s, 2H), 7.24 (dd, *J* = 6.8 Hz, 6.9 Hz, 1H), 7.50 (d, *J* = 6.6 Hz, 1H), 7.52-7.73 (m, 4H), 8.06 (d, *J* = 8.1 Hz, 1H), 9.23 (d, *J* = 8.3 Hz, 1H), 12.06 (s, 1H).

5. 3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (1.0 g) is dissolved in dry dichloroethane (15 ml) and the solution is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 8.2 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. In parallel, 3-thiopheneacetic acid (1.17 g) is dissolved in trifluoroacetic acid anhydride (1.17 ml) and the mixture is stirred for 20 min at room temperature. The formed mixed anhydride is diluted with dichloroethane (5 ml) and added to the zinc chloride mixture, prepared above, within 5 min at 0°C. The mixture is stirred for 5 h at room temperature. After that, ammonia (7M in methanol, 5.6 ml) and ammonium acetate (3.02 g) are added and the mixture is refluxed for 18 h. After cooling, 2M ammonia solution (30 ml) is added and the aqueous phase is extracted with dichloromethane (2 x 30 ml). The combined organic extracts are washed with 2M ammonia solution (2 x 50 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with gradient dichloromethane / ethyl acetate 98:2 to 90:10 (v/v)) to yield 57 mg (4%) of the title compound.

^{1}H-NMR (300 MHz, d6-DMSO + CD_3OD); δ = 1.10 (s, 6H), 2.68 (s, 2H), 3.16 (s, 2H), 4.52 (s, 2H), 7.10 (dd, *J* = 1.5 Hz, 4.9 Hz, 1H), 7.23 (ddd, *J* = 1.5 Hz, 6.4 Hz, 8.1 Hz, 1H), 7.26-7.29 (m, 1H), 7.39-7.44 (m, 1H), 7.55-7.66 (m, 1H), 9.24 (d, *J* = 8.1 Hz, 1H).

MS (MH^+ found) = 361.3

6. 3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

3-Hydroxy-2-(1H-indol-3-yl)-5,5-dimethylcyclohex-2-en-1-one (example A1) (520 mg) is dissolved in dichloroethane (10 ml) and the solution is cooled to 0°C (ice bath). Zinc chloride (1M in diethyl ether, 6 ml) is added drop by drop and the mixture is stirred at 0°C for 30 min. 2-Thienylacetyl chloride (0.30 ml) is added drop by drop and the mixture is stirred for 3 h at room temperature. After that, ammonia (7M in methanol, 20 ml) is added and the mixture is refluxed for 18 h. After cooling, it is filtered and the precipitate is washed with dichloromethane. The combined filtrate is washed with 1M aqueous sodium carbonate solution (20 ml), the organic phase is dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with gradient dichloromethane to dichloromethane / ethyl acetate 95:5 (v/v)) to obtain 220 mg (31%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.09 (s, 6H), 2.68 (s, 2H), 3.15 (s, 2H), 4.72 (s, 2H), 6.89-6.98 (m, 1H), 7.00-7.06 (m, 1H), 7.23 (dd, *J* = 6.9 Hz, 7.0 Hz, 1H), 7.29-7.35 (m, 1H), 7.53-7.69 (m, 2H), 9.23 (d, *J* = 8.4 Hz, 1H), 12.02 (s, 1H).

MS (MH^+ found) = 361.3

7. 3,3-Dimethyl-6-[4-(2-thienyl)benzyl]-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one

A Schlenk tube is charged with tris(dibenzylideneacetone)dipalladium(0) (4.9 mg), 2-thiopheneboronic acid (150 mg) and potassium fluoride (0.20 g), the mixture is degased and set under nitrogen atmosphere. 6-(4-Bromobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-

c]quinolin-1-one hydrochloride (example A2) (0.5 g), dioxane (3 ml) and a solution of di-t-butylmethylphosphonium tetrafluoroborate (3.2 mg) in dioxane (1 ml) are added, the mixture is again degased, set under nitrogen atmosphere and stirred for 18 h at 70°C. After cooling, it is concentrated in vacuo, ethyl acetate (10 ml) and water (10 ml) are added, the organic phase is washed with 1M aqueous sodium carbonate solution (10 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with ethyl acetate / petroleum ether 1:3 (v/v)), followed by crystallization from diethyl ether to yield 150 mg (33%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.09 (s, 6H), 2.67 (s, 2H), 3.14 (s, 2H), 4.54 (s, 2H), 7.04-7.14 (m, 1H), 7.19-7.29 (m, 1H), 7.38-7.47 (m, 3H), 7.48-7.52 (m, 1H), 7.51-7.69 (m, 4H), 9.23 (d, *J* = 8.4 Hz, 1H), 12.01 (s, 1H).

mp.: 178-179°C

8. 1-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}pyrrolidine-2,5-dione

Step 1: 4-({4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}-amino)-4-oxobutanoic acid. 6-(4-Aminobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example A3) (0.5 g) is suspended in toluene (50 ml) and dioxane (1 ml) and succinic anhydride (0.15 g) is added. The mixture is refluxed for 4 h. After cooling, the precipitate is filtered, washed with toluene, stirred in refluxing diethyl ether, filtered again and dried in vacuo to give rise to 500 mg (82%) of 4-({4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}amino)-4-oxobutanoic acid.

Step 2: 1-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}-pyrrolidine-2,5-dione. 4-({4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}amino)-4-oxobutanoic acid (400 mg) is suspended in dioxane (20 ml), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.37 g) and triethylamine (712 µl) are added and the mixture is refluxed for 18 h. After cooling, it is concentrated in vacuo, dichloromethane (20 ml) and 1M aqueous sodium carbonate solution (20 ml) are added and the aqueous phase is extracted with dichloromethane (2 x 20 ml). The combined organic extracts are washed with 1M aqueous sodium carbonate solution (1 x 30 ml) and water (1 x 30 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with gradient ethyl acetate / petroleum ether 1:1 to 3:1 (v/v)), followed by crystallization from ethyl acetate to yield 100 mg (21%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 1.08 (s, 6H), 2.66 (s, 2H), 2.75 (s, 4H), 3.15 (s, 2H), 4.57 (s, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.23 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.55-7.69 (m, 2H), 9.24 (d, *J* = 8.4 Hz, 1H), 12.04 (s, 1H).

MS (MH^+ found) = 452.4

9. N-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide

6-(4-Aminobenzyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example A3) (0.5 g) is suspended in dichloromethane (10 ml), cyclopropanecarbonyl chloride (0.14 g) and triethylamine (174 µl) are added and the mixture is stirred for 1 h at room temperature. After that, water (10 ml) is added, the volume is reduced in vacuo, the precipitate is filtered, washed with water and diethyl ether to yield 0.51 g (96%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.69-0.81 (m, 4H), 1.08 (s, 6H), 1.67-1.79 (m, 1H), 2.66 (s, 2H), 3.13 (s, 2H), 4.46 (s, 2H), 7.17-7.31 (m, 3H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.51-7.69 (m, 2H), 9.22 (d, *J* = 8.4 Hz, 1H), 10.06 (s, 1H), 11.95 (s, 1H).

MS (MH^+ found) = 438.4

10. 6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-amine

Step 1: N-[6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-yl]formamide. 6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example 3) (1.5 g) is suspended in formamide (13 ml) and ammoniumformiate (20.5 g), formic acid (85%, 12 ml) are added. The mixture is stirred for 40 h at 180°C. After cooling, ethanol (10 ml) is added, the mixture is stirred for 15 min and concentrated ammonia (25%, 20 ml) is added (pH > 10). It is extracted with dichloromethane (3 x 50 ml), the combined organic extracts are washed with water (1 x 100 ml), dried ($MgSO_4$), the solvents are removed in vacuo. The residue, crude N-[6-(cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-yl]formamide (2.0 g) is used in the next step without further purification.

Step 2: 6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-amine. N-[6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-yl]formamide (crude from preceeding step, 2.0 g) is dissolved in a 2M solution of HCl in methanol (250 ml, prepared before by dropping acetyl chloride (35 ml) in methanol (250 ml)). The mixture is refluxed for 3 h, after that it is concentrated in vacuo. The residue is dissolved in ethyl acetate (100 ml), washed with 1M sodium carbonate solution (3 x 100 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with gradient ethyl acetate to ethyl acetate / methanol 8:1 (v/v)), followed by crystallization from diethyl ether to yield 230 mg (15%, 2 steps) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.88 (s, 3H), 1.14 (s, 3H), 1.24-1.40 (m, 2H), 1.40-1.57 (m, 2H), 1.57-1.74 (m, 5H), 1.88 (s, 2H), 2.02-2.12 (m, 1H), 2.48-2.56 (m, 1H), 2.62 (d, AB, *J* = 16.0 Hz, 1H), 2.86 (d, AB, *J* = 16.0 Hz, 1H), 2.96-3.12 (m, 2H), 4.61 (dd, *J* = 7.0 Hz, 7.0 Hz, 1H), 7.18 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.47 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 11.35 (s, 1H).

MS (MH^+ found) = 348.5

11. 6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol

6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example 3) (350 mg) is dissolved in methanol (25 ml) and sodium borohydride (110 mg) is added in portions. The reaction mixture is stirred for 1 h at room temperature. After that, water (20 ml) is added, the formed precipitate is filtered, washed with water and dried in vacuo to give rise to 270 mg (77%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.93 (s, 3H), 1.13 (s, 3H), 1.26-1.40 (m, 2H), 1.41-1.58 (m, 2H), 1.58-1.72 (m, 4H), 1.72-1.84 (m, 1H), 1.99-2.10 (m, 1H), 2.38-2.55 (m, 1H), 2.65 (d, AB, *J* = 16.2 Hz, 1H), 2.85 (d, AB, *J* = 16.1 Hz, 1H), 2.95-3.12 (m, 2H), 4.94-5.08 (m, 1H), 5.24 (m, 1H), 7.15 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.46 (dd, *J* = 7.1 Hz, 7.2 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 11.31 (s, 1H).

MS (MH^+ found) = 349.4

12. 3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol

3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example 6) (120 mg) is dissolved in methanol (10 ml) and sodium borohydride (28 mg) is added in portions. The reaction mixture is stirred for 1 h at room temperature. After that, water (50 ml) and ethyl acetate (25 ml) are added and the aqueous phase is extracted with ethyl acetate (2 x 25 ml). The combined organic extracts are washed with concentrated sodium chloride solution (1 x 50 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with ethyl acetate / dichloromethane 1:9 (v/v)), followed by crystallization from diethyl ether / petroleum ether to yield 90 mg (30%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.94 (s, 3H), 1.13 (s, 3H), 1.72-1.84 (m, 1H), 2.00-2.11 (m, 1H), 2.67 (d, AB, *J* = 16.2 Hz, 1H), 2.87 (d, AB, *J* = 16.3 Hz, 1H), 4.55 (d, AB, *J* = 15.1 Hz, 1H), 4.64 (d, AB, *J* = 15.0 Hz, 1H), 5.05 (d, *J* = 6.8 Hz, 1H), 5.28-5.39 (m, 1H), 6.87-6.95 (m, 1H), 6.97-7.02 (m, 1H), 7.15 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H),7.35 (d, *J* = 5.0 Hz, 1H), 7.48 (dd, *J* = 8.2 Hz, 8.3 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 8.47 (d, *J* = 8.1 Hz, 1H), 11.50 (s, 1H).

MS (MH^+ found) = 363.3

13. N-{4-[(1-Hydroxy-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide

N-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide (example 9) (400 mg) is suspended in methanol (50 ml) and ethanol (10 ml) and sodium borohydride (107 mg) is added in portions. The reaction mixture is stirred for 1 h at room temperature. After that, the formed precipitate is filtered and washed with methanol. The combined filtrate is treated with water (50 ml), the precipitate is filtered and dried in vacuo to yield 150 mg (38%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.69-0.81 (m, 4H), 0.93 (s, 3H), 1.12 (s, 3H), 1.68-1.72 (m, 2H), 1.98-2.10 (m, 1H), 2.65 (d, AB, *J* = 16.0 Hz, 1H), 2.85 (d, AB, *J* = 16.1 Hz, 1H), 4.29 (d, AB, *J* =

14.2 Hz, 1H), 4.39 (d, AB, *J* = 14.3 Hz, 1H), 4.97-5.09 (m, 1H), 5.25-5.49 (m, 1H), 7.16 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.39-7.51 (m, 3H), 7.56 (d, *J* = 8.1 Hz, 1H), 8.46 (d, *J* = 8.1 Hz, 1H), 10.03 (s, 1H), 11.44 (s, 1H).

MS (MH^+ found) = 440.4

14. (1S)-6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol

3-Nitrophenylboronic acid (0.50 g), D-tartaric acid (0.45 g) and calcium hydride (0.25 g) are suspended in dry tetrahydrofuran (10 ml) and the mixture is refluxed for 1 h. The suspension is cooled, filtered under nitrogen atmosphere and washed with dry tetrahydrofuran (10 ml). 6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example 1) (360 mg) is suspended in the combined filtrate, the suspension is cooled to 0°C (ice bath) and sodium borohydride (110 mg) is added in portions. The mixture is stirred for 30 min at 0°C, then 2 h at room temperature. After that, methanol (5 ml) is added slowly (hydrogen evolution) and the mixture is stirred for 30 min. Next, 1M hydrochloric acid (5 ml) is added and stirring is continued for 1 h. The mixture is basified with 1M aqueous sodium carbonate solution (10 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts are washed with 1M aqueous sodium carbonate solution (2 x 40 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with gradient dichloromethane to ethyl acetate / dichloromethane 1:4 (v/v)), followed by crystallization from diethyl ether to yield 140 mg (39%) of the title compound.

^{1}H-NMR (400 MHz, d6-DMSO); δ = 0.93 (s, 3H), 1.00-1.27 (m, 8H), 1.53-1.71 (m, 5H), 1.74-1.81 (m, 1H), 1.81-1.98 (m, 1H), 1.99-2.10 (m, 1H), 2.58-2.70 (m, 1H), 2.78-2.91 (m, 2H), 2.91-3.02 (m, 1H), 4.99 (d, *J* = 6.8 Hz, 1H), 5.28 (d, AB, *J* = 6.6 Hz, 1H), 5.32 (d, AB, *J* = 6.6 Hz, 1H), 7.15 (dd, *J* = 7.0 Hz, 7.1 Hz, 1H), 7.46 (dd, *J* = 6.9 Hz, 7.0 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 11.26 (s, 1H).

mp.: 210-211 °C

ee > 95% (S) (absolute configuration by analogy)

15. (1S)-3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol

3-Nitrophenylboronic acid (208 mg), D-tartaric acid (187 mg) and calcium hydride (105 mg) are suspended in dry tetrahydrofuran (5 ml) and the mixture is refluxed for 3 h. The suspension is cooled, filtered under nitrogen atmosphere and washed with dry tetrahydrofuran (5 ml). 3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one (example 5) (150 mg) is suspended in the combined filtrate, the suspension is cooled to 0°C (ice bath) and sodium borohydride (31 mg) is added in portions. The mixture is stirred for 1 h at room temperature. After that, methanol (3 ml) is added slowly (hydrogen evolution) and the mixture is stirred for 30 min. Next, 1M hydrochloric acid (5 ml) is added and stirring is continued for 1 h. The mixture is basified with 2M aqueous sodium hydroxide solution (5 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic extracts are washed with 1M aqueous sodium carbonate solu-

tion (2 x 40 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product is purified by column chromatography (silica gel, eluting with ethyl acetate / dichloromethane 1:4 (v/v)), followed by crystallization from diethyl ether to yield 54 mg (36%) of the title compound.

^{1}H-NMR (300 MHz, d6-DMSO); δ = 0.93 (s, 3H), 1.13 (s, 3H), 1.77 (dd, *J* = 6.7 Hz, 13.3 Hz, 1H), 2.04 (dd, *J* = 6.1 Hz, 13.3 Hz, 1H), 2.66 (d, AB, *J* = 16.3 Hz, 1H), 2.85 (d, AB, *J* = 16.2 Hz, 1H), 4.34 (d, AB, *J* = 14.4 Hz, 1H), 4.44 (d, AB, *J* = 14.5 Hz, 1H), 5.06 (d, *J* = 6.8 Hz, 1H), 5.26-5.37 (m, 1H), 7.06 (dd, *J* = 1.2 Hz, 4.9 Hz, 1H), 7.17 (ddd, *J* = 1.2 Hz, 8.1 Hz, 8.1 Hz, 1H), 7.21-7.28 (m, 1H), 7.40 (dd, *J* = 2.9 Hz, 4.9 Hz, 1H), 7.43-7.52 (m, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 11.51 (s, 1H).

MS (MH^+ found) = 363.3

ee > 95% (S) (determined by chiral HPLC using Diacel Chiralcel OD-RH, 250x4.6 mm, 5µ as stationary phase and acetonitrile / water / triethylamine 49:49:2 (v/v/v), isocratic, as mobile phase, UV detection, flow 1 ml/min, T = 35°C, t_R (R-isomer) = 8.2 min, t_R (S-isomer) = 9.1 min, absolute configuration by analogy)

Commercial utility

The compounds, salts thereof, N-oxides of the compounds and the salts thereof, and the stereoisomers of the compounds, the salts, the N-oxides of the compounds and the N-oxides of the salts thereof according to the invention are hereinafter referred to as the compounds of the invention. In particular, the compounds of the invention are pharmaceutically acceptable.

The compounds of the invention have valuable pharmaceutical properties which make them commercially utilizable. In particular, as type 5 phosphodiesterase (PDE5) inhibitors, they are able to influence the physiological and pathophysiological function of various cells, e.g., but not limited to, smooth muscle cells, fibroblasts, myofibroblasts and platelets, which are involved in a great variety of physiological and pathophysiological mechanisms. In particular, the PDE5 inhibiting compounds of the invention can effect relaxation of the vasculature, thus increasing blood flow, improve the spatial balance between blood perfusion and ventilation within the lung ("re-matching" effect) thereby reducing the amount of so-called low V/Q-areas [areas within the lung with high perfusion (Q) but no or reduced ventilation (V)] and high V/Q-areas (areas within the lung with low perfusion but high ventilation), induce neurogenesis, inhibit platelet function, such as aggregation, adhesion and mediator release and, thus, have an anti-inflammatory effect. The compounds of the invention are distinguished by valuable and desirable properties, such as, for example, high efficacy, high selectivity, low toxicity, superior bioavailability in general (e.g. good enteral absorption), superior

therapeutic window, superior pharmacokinetics (e.g. half-life), absence of significant side effects, and further beneficial effects related with their therapeutic and pharmaceutical suitability.

Accordingly, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of diseases, especially diseases alleviated by inhibition of the type 5 phosphodiesterase. In particular, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of the following diseases:
male and female sexual dysfunction, such as, but not limited to, male erectile dysfunction, premature ejaculation, Peyronie´s disease;
acute and chronic airway diseases, such as, but not limited to, COPD (chronic obstructive pulmonary disease), bronchitis, emphysema, pulmonary vascular remodeling, pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, connective tissue diseases, sarcoidosis, kyphoscoliosis, pneumoconiosis, amyotrophic lateral sclerosis, thoracoplasty, extrinsic allergic alveolitis;
inflammatory diseases, such as, but not limited to, vasculature inflammation, acute respiratory distress syndrome, mesangial glomerulonephritis, chronic inflammatory bowel disease, disseminated intravascular inflammation, allergic vasculitis, dermatoses (e.g., but not limited to, psoriasis, toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea), disorders of the arthritis type (e.g., but not limited to, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis), disorders of the immune system [e.g., but not limited to, AIDS (acquired immunodeficiency syndrome), multiple sclerosis], graft versus host reaction, allograft rejections, shock [e.g., but not limited to, septic shock, endotoxin shock, gram-negative sepsis shock, toxic shock syndrome and ARDS (adult respiratory distress syndrome)], gastrointestinal inflammations (e.g., but not limited to, Crohn´s disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions (e.g., but not limited to, allergic rhinitis, allergic sinusitis, chronic rhinitis, chronic sinusitis, allergic conjunctivitis, nasal polyps);
pain, such as, but not limited to, inflammatory pain;
right-heart failure, right heart hypertrophy (cor pulmonale), hypertension, hypercholesterolemia, hypertriglyceridemia;
ischaemic diseases, such as, but not limited to, diabetes mellitus, stroke, coronary artery disease, angina (including, but not limited to, vasospastic angina), myocardial infarction, peripheral artery disease, cerebrovascular obstruction, sleep apnea, macular ischaemia, arterial and venous occlusion, congestive heart failure;
diabetic gastroparesis and diseases with symptoms of gastroparesis;
diseases or conditions in which it is desirable to suppress platelet function, for example, but not limited to, after stent implantations (e.g., but not limited to, coronary stenting), after bypass operations, in pulmonary hypertension, thrombotic diseases, post-angioplasty stenosis, coronary artery

disease, infarction (e.g., but not limited to, myocardial infarction), instable angina pectoris, stroke, and arterial and venous occlusion diseases (e.g., but not limited to, claudicatio intermittens); diseases or conditions with an impairment or dysfunction of cerebral vascular reactivity and/or neurovascular coupling, such as, but not limited to, arteriosclerotic dementia, multi-infarct dementia, cerebral senility;
diseases which are based on neuronal damage or degradation, such as but not limited to, stroke, spinal cord injury, brain injury, morbus parkinson, amyotrophic lateral sclerosis, morbus alzheimer, amyloidosis, prion diseases and neuropathy;
peripheral arterial diseases, chronic renal failure, chronic heart failure, sepsis, senile dementia (Alzheimer's disease), Creutzfeld-Jacob disease, septic encephalopathy, arteriosclerotic encephalopathy, diabetes associated encephalopathy, toxic encephalopathy, vascular and neuronal dementia, Huntington´s disease, Parkinson's disease, multiple sclerosis and preeclampsia;
portal hypertension, liver cirrhosis, toxic liver damage (e.g., but not limited to, alcohol-induced liver damage), hepatitis, thrombosis of the portal vein, Budd-Chiari syndrome, malformation of liver veins, compression of liver veins (e.g., but without limitation, due to tumors), arteriovenous fistula, diseases associated with an enlarged spleen, schistosomiasis (bilharziosis), sarcoidosis and other granulomatous diseases, primary biliary cirrhosis, myeloproliferative disorders (e.g., but not limited to, chronic myeloid leukemia, osteomyelofibrosis), lymphatic systemic diseases, collagenosis (e.g., but not limited to, systemic lupus erythematodes, sclerodermia), morbus Osler (congenital arteriovenous malformations, inter alia in the liver), nodular regenerative hyperplasia, tricuspid insufficiency, pericarditis constrictiva, veno-occlusive disease (VOD), non-alcoholic steatohepatitis (NASH), liver fibrosis;
benign prostatic hyperplasia; overactive bladder, lower urinary tract disease, Raynaud´s syndrome, insufficient uteroplacental blood flow in pregnancies with fetal growth restriction;
insufficient brain skills, such as but not limited to, verbal attainment, attention, concentration, deductive thinking, central auditory processing, cognition, learning, vigilance, apprehension and reagibility.

In a further embodiment, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of diseases, especially diseases alleviated by inhibition of the type 5 phosphodiesterase. In particular, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of the following diseases: male and female sexual dysfunction, acute and chronic airway diseases, inflammatory diseases, disorders which are based on allergic and/or chronic, immunological false reactions, pain, right-heart failure, right heart hypertrophy (cor pulmonale), hypertension, hypercholesterolemia, hypertriglyceridemia, ischaemic diseases, diabetic gastroparesis and diseases with symptoms of gastroparesis, diseases or conditions in which it is desirable to suppress platelet function, diseases or conditions with an impairment or dysfunction of cerebral vascular reactivity and/or neurovascular coupling, diseases which are based on neuronal damage or degradation, peripheral arterial diseases, chronic renal failure, chronic heart failure, sepsis, senile dementia, Creutzfeld-Jacob disease, septic encephalopathy, arteriosclerotic en-

cephalopathy, diabetes associated encephalopathy, toxic encephalopathy, vascular and neuronal dementia, Huntington´s disease, Parkinson's disease, multiple sclerosis and preeclampsia, portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, thrombosis of the portal vein, Budd-Chiari syndrome, malformation of liver veins, compression of liver veins, arteriovenous fistula, diseases associated with an enlarged spleen, schistosomiasis, sarcoidosis and other granulomatous diseases, primary biliary cirrhosis, myeloproliferative disorders, lymphatic systemic diseases, collagenosis, morbus Osler, nodular regenerative hyperplasia, tricuspid insufficiency, pericarditis constrictiva, veno-occlusive disease (VOD), non-alcoholic steatohepatitis (NASH), liver fibrosis, benign prostatic hyperplasia, overactive bladder, lower urinary tract disease, Raynaud's syndrome, insufficient uteroplacental blood flow in pregnancies with fetal growth restriction and insufficient brain skills.

In this respect, the term "pulmonary hypertension" in particular embraces

- pulmonary arterial hypertension including primary pulmonary hypertension (e.g. sporadic or familial) and pulmonary arterial hypertension related, for example, but without limitation, to collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus infection, drugs or toxins (e.g., but not limited to, anorexigens), persistent pulmonary hypertension of the newborn;
- pulmonary venous hypertension due to, for example, but without limitation, left-sided atrial or ventricular heart disease, left-sided valvular heart disease, extrinsic compression of central pulmonary veins (e.g. fibrosing mediastinitis, adenopathy in relation to tumors), pulmonary veno-occlusive disease;
- pulmonary hypertension associated with disorders of the respiratory system or hypoxemia including, for example, but without limitation, chronic obstructive pulmonary disease (COPD), interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia;
- pulmonary hypertension caused by chronic thrombotic or embolic diseases including thromboembolic obstruction of proximal pulmonary arteries and obstruction of distal pulmonary arteries, such as pulmonary embolism (due to thrombus, tumor, ova, parasites, or foreign material), in situ thrombosis and sickle-cell disease, in particular chronic thromboembolic pulmonary hypertension (CTEPH);
- pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature including inflammatory disorders (e.g., but not limited to, schistosomiasis, sarcoidosis) and pulmonary capillary hemangiomatosis.

Preferably, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of the following diseases: acute and chronic airway diseases, such as pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease; portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis and liver fibrosis.

Furthermore, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of the following diseases: acute and chronic airway diseases, such as pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, bronchitis, emphysema and chronic obstructive pulmonary disease; portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis and liver fibrosis.

The invention also relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition inhibiting the type 5 phosphodiesterase, in particular a pharmaceutical composition for the treatment or prophylaxis of diseases alleviated by inhibition of the type 5 phosphodiesterase, preferably, a pharmaceutical composition for the treatment or prophylaxis of the diseases exemplified above.

In particular, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of an acute or chronic airway disease, such as, but not limited to, pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.

Furthermore, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of an acute or chronic airway disease, such as, but not limited to, pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.Furthermore, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis or liver fibrosis.

The invention further relates to a method of treating or preventing a disease comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

In particular, the invention relates to a method of treating or preventing one of the above mentioned diseases comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

Especially, the invention relates to a method of treating or preventing a disease which is alleviated by inhibition of the type 5 phosphodiesterase comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

The invention relates to a method of treating or preventing male and female sexual dysfunction, acute and chronic airway diseases, inflammatory diseases, disorders which are based on allergic and/or chronic, immunological false reactions, pain, right-heart failure, right heart hypertrophy (cor pulmonale), hypertension, hypercholesterolemia, hypertriglyceridemia, ischaemic diseases, diabetic gastroparesis and diseases with symptoms of gastroparesis, diseases or conditions in which it is desirable to suppress platelet function, diseases or conditions with an impairment or dysfunction of cerebral vascular reactivity and/or neurovascular coupling, diseases which are based on neuronal damage or degradation, peripheral arterial diseases, chronic renal failure, chronic heart failure, sepsis, senile dementia, Creutzfeld-Jacob disease, septic encephalopathy, arteriosclerotic encephalopathy, diabetes associated encephalopathy, toxic encephalopathy, vascular and neuronal dementia, Huntington´s disease, Parkinson's disease, multiple sclerosis and preeclampsia, portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, thrombosis of the portal vein, Budd-Chiari syndrome, malformation of liver veins, compression of liver veins, arteriovenous fistula, diseases associated with an enlarged spleen, schistosomiasis, sarcoidosis and other granulomatous diseases, primary biliary cirrhosis, myeloproliferative disorders, lymphatic systemic diseases, collagenosis, morbus Osler, nodular regenerative hyperplasia, tricuspid insufficiency, pericarditis constrictiva, veno-occlusive disease (VOD), non-alcoholic steatohepatitis (NASH), liver fibrosis, benign prostatic hyperplasia, overactive bladder, lower urinary tract disease, Raynaud's syndrome, insufficient uteroplacental blood flow in pregnancies with fetal growth restriction and insufficient brain skills.

Preferably, the invention relates to a method of treating or preventing an acute or chronic airway disease, for example, but not limited to, pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

Furthermore, the invention preferably relates to a method of treating or preventing an acute or chronic airway disease, for example, but not limited to, pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, bronchitis, emphysema and chronic obstructive pulmonary disease, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

Furthermore, the invention preferably relates to a method of treating or preventing portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis or liver fibrosis comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

In the above methods, the patient is preferably a mammal, more preferably a human. Furthermore, in the above methods, at least one of the compounds of the invention can be used. Preferably, one

or two of the compounds of the invention are used, more preferably, one of the compounds of the invention is used.

In a particularly preferred embodiment of the invention, the above methods of treating or preventing one of the above mentioned diseases comprise administering to a patient in need thereof a therapeutically effective amount of one compound of the examples according to the present invention.

The invention furthermore relates to a pharmaceutical composition which comprises at least one of the compounds of the invention together with at least one pharmaceutically acceptable auxiliary.

The invention additionally relates to a pharmaceutical composition for the treatment or prophylaxis of an acute or chronic airway disease, in particular for the treatment or prophylaxis of pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.

The invention further relates to a pharmaceutical composition for the treatment or prophylaxis of an acute or chronic airway disease, in particular for the treatment or prophylaxis of pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.

Preferably, the pharmaceutical composition comprises one or two of the compounds of the invention. More preferably, the pharmaceutical composition comprises one of the compounds of the invention.

In a particularly preferred embodiment of the invention, the pharmaceutical composition comprises a compound of the examples according to the present invention together with at least one pharmaceutically acceptable auxiliary.

The invention additionally relates to a pharmaceutical composition comprising at least one of the compounds of the invention, at least one pharmaceutically acceptable auxiliary and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants, antibiotics, anticoagulants, diuretics and digitalis glycosides.

In this respect, the therapeutic agent includes the corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics in form of the free compounds, the pharmaceutically acceptable salts thereof, the pharmaceutically acceptable derivatives thereof

(e.g., but not limited to, ester derivatives), the solvates thereof and the stereoisomers of the compounds, salts, derivatives and solvates.

Examples of corticosteroids include without limitation budesonide, fluticasone such as fluticasone propionate, beclometasone such as beclometasone dipropionate, triamcinolone such as triamcinolone acetonide, and ciclesonide. Examples of anticholinergics include without limitation indacaterol, tiotropium such as tiotropium bromide, and ipratropium such as ipratropium bromide. Examples of beta-mimetics include without limitation formoterol such as formoterol fumarate, and salmeterol such as salmeterol xinafoate. Examples of lung surfactants include without limitation lusupultide, poractant alfa, sinapultide, beractant, bovactant, colfosceril auch as colfosceril palmitate, surfactant-TA, and calfactant. Examples of endothelin antagonists include without limitation bosentan, ambrisentan and sitaxsentan such as sitaxsentan sodium. Examples of prostacyclins include without limitation iloprost such as iloprost tromethamine, epoprostenol such as epoprostenol sodium and treprostinil such as treprostinil sodium. Examples of calcium channel blockers include without limitation amlodipine such as amlodipine besylate and amlodipine maleate, nifedipine, diltiazem such as diltiazem hydrochloride, verapamil such as verapamil hydrochloride, and felodipine. Examples of beta-blockers include without limitation bisoprolol such as bisoprolol fumarate, nebivolol, metoprolol such as metoprolol succinate and metoprolol tartrate, carvedilol, atenolol and nadolol. Examples of type 4 phosphodiesterase inhibitors include without limitation roflumilast, roflumilast N-oxide, cilomilast, tetomilast and oglemilast. Examples of antidepressants include without limitation bupropion such as bupropion hydrochloride. Examples of antibiotics include without limitation amoxicillin, ampicillin, levofloxacin, clarithromycin, ciprofloxacin such as ciprofloxacin hydrochloride, telithromycin and azithromycin. Examples of anticoagulants include without limitation clopidogrel, enoxaparin, cilostazol, nadroparin, warfarin and abciximab. Examples of diuretics include without limitation furosemide, bumetanide and torsemide. Examples of digitalis glycosides include without limitation digoxin and digitoxin.

In a preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a corticosteroid. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and budesonide,
a compound of the invention and fluticasone,
a compound of the invention and beclometasone,
a compound of the invention and triamcinolone, or
a compound of the invention and ciclesonide.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with an anticholinergic. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and indacaterol,
a compound of the invention and tiotropium, or

a compound of the invention and ipratropium.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a beta-mimetic. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and formoterol, or

a compound of the invention and salmeterol.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a lung surfactant. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and lusupultide,

a compound of the invention and poractant alfa,

a compound of the invention and sinapultide,

a compound of the invention and beractant,

a compound of the invention and bovactant,

a compound of the invention and colfosceril,

a compound of the invention and surfactant-TA, or

a compound of the invention and calfactant.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with an endothelin antagonist. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and bosentan,

a compound of the invention and ambrisentan, or

a compound of the invention and sitaxsentan.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a prostacyclin. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and iloprost,

a compound of the invention and epoprostenol,

a compound of the invention and triprostinil.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a calcium channel blocker. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and amlodipine,

a compound of the invention and nifedipine,

a compound of the invention and diltiazem,

a compound of the invention and verapamil, or

a compound of the invention and felodipine.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a beta-blocker. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and bisoprolol,
a compound of the invention and nebivolol,
a compound of the invention and metoprolol,
a compound of the invention and carvedilol,
a compound of the invention and atenolol, or
a compound of the invention and nadolol.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a type 4 phosphodiesterase inhibitor. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and roflumilast,
a compound of the invention and roflumilast N-oxide,
a compound of the invention and cilomilast,
a compound of the invention and tetomilast, or
a compound of the invention and oglemilast.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with an antidepressant. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and bupropion.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with an antibiotic. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and amoxicillin,
a compound of the invention and ampicillin,
a compound of the invention and levofloxacin,
a compound of the invention and clarithromycin,
a compound of the invention and ciprofloxacin,
a compound of the invention and telithromycin, or
a compound of the invention and azithromycin.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with an anticoagulant. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and clopidogrel,
a compound of the invention and enoxaparin,
a compound of the invention and cilostazol,
a compound of the invention and nadroparin,
a compound of the invention and warfarin, or
a compound of the invention and abciximab.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a diuretic. In a particularly preferred embodiment, the pharmaceutical composition comprises:

a compound of the invention and furosemide,
a compound of the invention and bumetanide, or
a compound of the invention and torsemide.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a digitalis glycoside. In a particularly preferred embodiment, the pharmaceutical composition comprises:
a compound of the invention and digoxin, or
a compound of the invention and digitoxin.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a corticosteroid and a beta-mimetic. In a particularly preferred embodiment, the pharmaceutical composition comprises:
a compound of the invention, budesonide and indacaterol,
a compound of the invention, budesonide and formoterol,
a compound of the invention, budesonide and salmeterol,
a compound of the invention, fluticasone and indacaterol,
a compound of the invention, fluticasone and formoterol,
a compound of the invention, fluticasone and salmeterol,
a compound of the invention, beclometasone and indacaterol,
a compound of the invention, beclometasone and formoterol,
a compound of the invention, beclometasone and salmeterol,
a compound of the invention, triamcinolone and indacaterol,
a compound of the invention, triamcinolone and formoterol,
a compound of the invention, triamcinolone and salmeterol,
a compound of the invention, ciclesonide and indacaterol,
a compound of the invention, ciclesonide and formoterol, or
a compound of the invention, ciclesonide and salmeterol.

In a further preferred embodiment, the pharmaceutical composition comprises a compound of the invention in combination with a corticosteroid and an anticholinergic. In a particularly preferred embodiment, the pharmaceutical composition comprises:
a compound of the invention, budesonide and tiotropium,
a compound of the invention, budesonide and ipratropium,
a compound of the invention, fluticasone and tiotropium,
a compound of the invention, fluticasone and ipratropium,
a compound of the invention, beclometasone and tiotropium,
a compound of the invention, beclometasone and ipratropium,
a compound of the invention, triamcinolone and tiotropium,
a compound of the invention, triamcinolone and ipratropium,
a compound of the invention, ciclesonide and tiotropium, or
a compound of the invention, ciclesonide and ipratropium.

The above mentioned compound of the invention is preferably a compound according to the examples.

The invention furthermore relates to pharmaceutical compositions according to the invention, as defined above, inhibiting the type 5 phosphodiesterase, especially for the treatment or prophylaxis of diseases alleviated by inhibition of type 5 phosphodiesterase, in particular for the treatment or prophylaxis of the diseases exemplified above.

The invention also encompasses pharmaceutical compositions according to the invention, as defined above, for the treatment or prophylaxis of the following diseases: acute and chronic airway diseases, such as pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease; portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis and liver fibrosis.

Futhermore, the invention also encompasses pharmaceutical compositions according to the invention, as defined above, for the treatment or prophylaxis of the following diseases: acute and chronic airway diseases, such as pulmonary hypertension, lung fibrosis, idiopathic pulmonary lung fibrosis (IPF), asthma, bronchitis, emphysema and chronic obstructive pulmonary disease; portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis and liver fibrosis.

The pharmaceutical compositions according to the invention preferably contain the compound or compounds of the invention in a total amount of from 0.1 to 99.9 wt%, more preferably 5 to 95 wt%, in particular 20 to 80 wt%. In case at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics is present in the pharmaceutical compositions of the invention, the total amount of said therapeutic agent or therapeutic agents in the pharmaceutical compositions is preferably in the range of from 0.1 to 99.9 wt%, more preferably 5 to 95 wt%, in particular 20 to 80 wt%, under the provision that the total amount of the compound or compounds of the invention and the therapeutic agent or therapeutic agents is less than 100 wt%. Preferably, the at least one compound of the invention and the at least one therapeutic agent are present in the pharmaceutical composition in a weight ratio of from 1000 : 1 to 1: 1000, more preferably 500 : 1 to 1: 500.

As pharmaceutically acceptable auxiliaries, any auxiliaries known to be suitable for preparing pharmaceutical compositions can be used. Examples thereof include, but are not limited to, solvents, excipients, dispersants, emulsifiers, solubilizers, gel formers, ointment bases, antioxidants, preservatives, stabilizers, carriers, fillers, binders, thickeners, complexing agents, disintegrating agents, buffers, permeation promoters, polymers, lubricants, coating agents, propellants, tonicity adjusting agents, surfactants, colorants, flavorings, sweeteners and dyes. In particular, auxiliaries of a type appropriate to the desired formulation and the desired mode of administration are used.

The pharmaceutical compositions can be formulated, for example, into tablets, coated tablets (dragees), pills, cachets, capsules (caplets), granules, powders, suppositories, solutions (e.g., but not limited to, sterile solutions), emulsions, suspensions, ointments, creams, lotions, pastes, oils, gels, sprays and patches (e.g., but not limited to, transdermal therapeutic systems). Additionally, the pharmaceutical compositions can be prepared as e.g. liposome delivery systems, systems in which the compound of the invention is coupled to monoclonal antibodies and systems in which the compound of the invention is coupled to polymers (e.g., but not limited to, soluble or biodegradable polymers).

In case of pharmaceutical compositions comprising at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics, the compound of the invention and the therapeutic agent may be formulated together into the same dosage form (e.g., but not limited to, tablets), separately into the same dosage form (e.g., but not limited to, tablets), or into different dosage forms (without limitation e.g. the compound of the invention may be formulated as tablet and the therapeutic agent may be formulated as powder, solution or suspension).

The pharmaceutical compositions can be manufactured in a manner known to a person skilled in the art, e.g. by dissolving, mixing, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The selected formulation depends inter alia on the route of administering the pharmaceutical composition. The pharmaceutical compositions of the invention can be administered by any suitable route, for example, by the oral, sublingual, buccal, intravenous, intraarterial, intramuscular, subcutaneous, intracutaneous, topical, transdermal, intranasal, intraocular, intraperitoneal, intrasternal, intracoronary, transurethral, rectal or vaginal route, by inhalation or by insufflation. Oral administration is preferred.

In case of pharmaceutical compositions comprising at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants, antibiotics, anticoagulants, diuretics and digitalis glycosides, the compound of the invention and the therapeutic agent may be administered by the same route, e.g., without limitation, orally, or by different routes, e.g., without limitation, the compound of the invention can be administered orally and the therapeutic agent can be administered by inhalation or instillation.

Tablets, coated tablets (dragees), pills, cachets, capsules (caplets), granules, solutions, emulsions and suspensions are e.g. suitable for oral administration. In particular, said formulations can be adapted so as to represent, for example, an enteric form, an immediate release form, a delayed release form, a repeated dose release form, a prolonged release form or a sustained release form. Said forms can be obtained, for example, by coating tablets, by dividing tablets into several compartments separated by layers disintegrating under different conditions (e.g. pH conditions) or by coupling the compound of the invention to a biodegradable polymer.

Administration by inhalation or instillation is preferably made by using an aerosol. The aerosol is a liquid-gaseous dispersion, a solid-gaseous dispersion or a mixed liquid/solid-gaseous dispersion.

The aerosol may be generated by means of aerosol-producing devices such as dry powder inhalers (DPIs), pressurized metered dose inhalers (PMDIs) and nebulizers. Depending on the kind of the compound of the invention, and optionally the therapeutic agent, to be administered, the aerosol-producing device can contain the compound and, optionally, the therapeutic agent in form of a powder, a solution or a dispersion. The powder may contain, for example, one or more of the following auxiliaries: carriers, stabilizers and fillers. The solution may contain in addition to the solvent, for example, one or more of the following auxiliaries: propellants, solubilizers (co-solvents), surfactants, stabilizers, buffers, tonicity adjusting agents, preservatives and flavorings. The dispersion may contain in addition to the dispersant, for example, one or more of the following auxiliaries: propellants, surfactants, stabilizers, buffers, preservatives and flavorings. Examples of carriers include, but are not limited to, saccharides, e.g. lactose and glucose. Examples of propellants include, but are not limited to, fluorohydrocarbons, e.g. 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane.

The particle size of the aerosol particles (solid, liquid or solid/liquid particles) is preferably less than 100 µm, more preferably it is in the range of from 0.5 to 10 µm, in particular in the range of from 2 to 6 µm (D50 value, measured by laser diffraction).

Specific aerosol-producing devices which may be used for inhaled administration include, but are not limited to, Cyclohaler®, Diskhaler®, Rotadisk®, Turbohaler®, Autohaler®, Turbohaler®, Novolizer®, Easyhaler®, Aerolizer®, Jethaler®, Diskus®, Ultrahaler® and Mystic® inhalers. The aerosol-producing devices may be combined with spacers or expanders, e.g. Aerochamber®, Nebulator®, Volumatic® and Rondo®, for improving inhalation efficiency.

In case of topical administration, suitable pharmaceutical formulations are, for example, ointments, creams, lotions, pastes, gels, powders, solutions, emulsions, suspensions, oils, sprays and patches (e.g., but not limited to, transdermal therapeutic systems).

For parenteral modes of administration such as, for example, intravenous, intraarterial, intramuscular, subcutaneous, intracutaneous, intraperitoneal and intrasternal administration, preferably solutions (e.g., but not limited to, sterile solutions, isotonic solutions) are used. They are preferably administered by injection or infusion techniques.

In case of intranasal administration, for example, sprays and solutions to be applied in drop form are preferred formulations.

For intraocular administration, solutions to be applied in drop form, gels and ointments are exemplified formulations.

Generally, the pharmaceutical compositions according to the invention can be administered such that the dose of the compound of the invention is in the range customary for type 5 phosphodiesterase inhibitors. In particular, a dose in the range of from 0.01 to 4000 mg of the compound of the invention per day is preferred. In this respect, it is to be noted that the dose is dependent, for example, on the specific compound used, the species treated, age, body weight, general health, sex and diet of the subject treated, mode and time of administration, rate of excretion, severity of the disease to be treated and drug combination. In case the pharmaceutical composition of the invention comprises at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics, anticoagulants, diuretics and digitalis glycosides,the same dose ranges apply to the therapeutic agent.

The pharmaceutical compositions according to the invention can be administered in a single dose per day or in multiple subdoses, for example, 2 to 4 doses per day. A single dose unit of the pharmaceutical composition can contain e.g. from 0.01 mg to 4000 mg, preferably 0.1 mg to 2000 mg, more preferably 0.5 to 1000 mg, most preferably 1 to 500 mg, of the compound of the invention. In case the pharmaceutical composition of the invention comprises at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics, a single dose unit of the pharmaceutical composition can contain e.g. from 0.01 mg to 4000 mg, preferably 0.1 mg to 2000 mg, more preferably 0.5 to 1000 mg, most preferably 1 to 500 mg, of the therapeutic agent. Furthermore, the pharmaceutical composition can be adapted to weekly, monthly or even more infrequent administration, for example by using an implant, e.g. a subcutaneous or intramuscular implant, by using the compound of the invention in form of a sparingly soluble salt or by using the compound of the invention coupled to a polymer. Administration of the pharmaceutical composition in a single dose per day is preferred.

In case the pharmaceutical composition of the invention comprises at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics, administration of the compound of the invention and administration of the therapeutic agent can be made simultaneously or sequentially. In case of sequential administration, the compound of the invention can be administered before or after administration of the therapeutic agent.

Biological investigations

Method for measuring inhibition of PDE5 activity:

As a source for human PDE5, platelets were used. For that purpose, 150 ml fresh blood from human donors anticoagulated with citrate [final concentration 0.3% (w/v)] was centrifuged at 200 g for 10 min to obtain the so-called platelet-rich-plasma (PRP) as a supernatant. 1/10 volume of ACD solution (85 mM Na_3-citrate, 111 mM D-glucose, 71 mM citric acid, pH 4.4) was added to 9/10 volume of PRP. After centrifugation (1,400 g, 10 min) the cell pellet was resuspended in 3 ml homogenization buffer (NaCl 140 mM, KCl 3.8 mM, EGTA 1mM, $MgCl_2$ 1mM, Tris-HCl 20 mM, beta-mercaptoethanol 1mM, pH 8.2) plus protease-inhibitor mix giving rise to the final concentrations of 0.5 mM Pefablock (Roche), 10 µM Leupeptin, 5 µM Trypsininhibitor, 2 mM Benzamidin and 10 µM Pepstatin A. The suspension was sonified and thereafter centrifuged for 15 min at 10,000 g. The resulting supernatant (platelet lysate) was used for enzymatic testings.

PDE5A1 activity is inhibited by the compounds of the invention in a modified SPA (scintillation proximity assay) test, supplied by Amersham Biosciences (see procedural instructions "phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtitre plates (MTP's). The test volume is 100 µl and contains 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM Mg^{2+}, 1 µM motapizone, 10 nM PDE2 inhibitor BAY-60-7550, 0.5 µM cGMP (including about 50,000 cpm of [3H]cGMP as a tracer), 1 µl of the respective compound dilution in dimethylsulfoxide (DMSO) and sufficient PDE5-containing platelet lysat (10,000×g supernatant, see above) to ensure that 10-20 wt% of the cGMP is converted under the said experimental conditions. The final concentration of DMSO in the assay (1% v/v) does not substantially affect the activity of the PDE investigated. After a preincubation of 5 min at 37°C, the reaction was started by adding the substrate (cGMP) and the assay was incubated for a further 15 min; after that, it was stopped by adding SPA beads (50 µl). In accordance with the manufacturer's instructions, the SPA beads had previously been resuspended in water, but were then diluted 1:3 (v/v) in water; the diluted solution also contains 3 mM 8-methoxymethyl-3-isobutyl-1-methylxanthine (IBMX) to ensure a complete PDE activity stop. After the beads have been sedimented (> 30 min), the MTP's are analyzed in commercially available luminescence detection

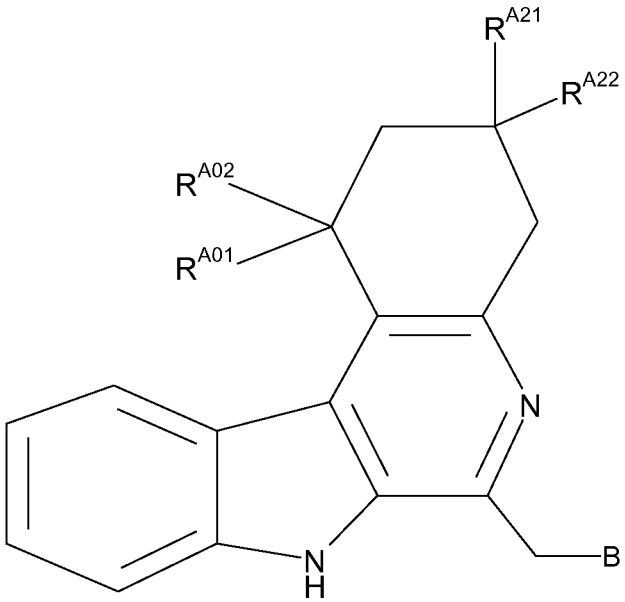
devices. The corresponding IC_{50} values of the compounds for the inhibition of PDE activity are determined from the concentration-effect curves by means of non-linear regression.

Representative inhibitory values determined for the compounds of the invention are given in the following Table:

Example	-log IC_{50} (mol/l)
1	8.17
2	7.78
3	7.20
4	6.90
5	7.36
6	7.24
7	6.39
8	6.37
9	6.91
10	6.92
11	7.13
13	7.01
15	7.61

Claims:

1. Compound of Formula (I)



(I)

wherein

R^{A01} is selected from the group consisting of hydrogen, hydroxy and $NR^{A03}R^{A04}$;

R^{A02} is hydrogen; or

R^{A01} and R^{A02} combine to form an oxo group;

R^{A03} and R^{A04} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

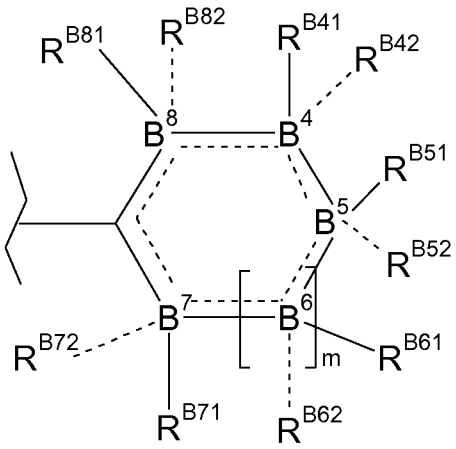
-C(O)H and –C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{A21} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

R^{A22} is selected from the group consisting of hydrogen and C_{1-3}-alkyl;

B is



wherein

m is 0 or 1;

the dotted lines signify 0, 1, 2 or 3 covalent π-bonds that may or may not be conjugated and which may each be located between any two adjacent ring atoms, with the proviso that each ring atom participates in no more than one covalent π-bond;

B^4, B^5, B^6, B^7 and B^8 are each independently selected from the group consisting of C, N, O and S;

with the proviso that the fragment B does not represent a group selected from pyridine, pyrimidine, pyrrole, pyrazine and imidazole, each of which may optionally be substituted;

wherein R^{B41} and R^{B42} are each independently selected from the members of the groups (g1) and (g2) as defined below:

(g1) hydrogen, halogen, C_{1-3}-alkoxy,

wherein the C_{1-3}-alkoxy is not substituted,

NO_2 and NH_2;

(g2) hydroxy, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-3}-alkoxy,

wherein the C_{1-3}-alkoxy is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{4-6}-alkoxy,

wherein the C_{4-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B43},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B44}R^{B45}$, and

a lone pair; or

R^{B41} and R^{B42} combine to form an oxo-group;

wherein one of the substituents R^{B41} and R^{B42} is absent in case the dotted lines signify a covalent π-bond between B^4 and one of the adjacent ring atoms;

R^{B43} is selected from the groups consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-C_{1-6}-alkyl,
wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B44} and R^{B45} are each independently selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-R^{B46}; or
R^{B44} and R^{B45} combine to form a 3- to 7-membered heterocycle,
wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,
wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B47}, O and S, and
wherein, in case the atoms adjacent to the N which binds to B^4 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B46} is selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
3- to 7-membered heterocyclyl,
wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B43},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B43},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B48}R^{B49}$;

R^{B47} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B48} and R^{B49} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B51} and R^{B52} are each independently selected from the members of the groups (h1) and (h2) as defined below:

(h1) hydrogen, halogen, hydroxy, C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is not substituted,

C_{1-3}-alkoxy,

wherein the C_{1-3}-alkoxy is not substituted,

NO_2, NH_2, -NH-C(O)-C_{1-2}-alkyl, -NH-C(O)-NH_2 and a methoxy group,

wherein the methoxy group is substituted by 2 or 3 fluorine atoms; or

one of R^{B41} and R^{B42} and one of R^{B51} and R^{B52} combine to form a group selected from -O-CH_2-O-, -O-CH_2-CH_2- and -CH_2-CH_2-O-;

(h2) C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{4-6}-alkyl,

wherein the C_{4-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{1-3}-alkoxy,

wherein the C_{1-3}-alkoxy is substituted by one or more substituents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{4-6}-alkoxy,

wherein the C_{4-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and
wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B53},

C_{6-14}-aryl,
wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,
wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and
wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,
wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,
wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B54}R^{B55}$ and

a lone pair; or

R^{B51} and R^{B52} combine to form an oxo-group;

wherein one of the substituents R^{B51} and R^{B52} is absent in case the dotted lines signify a covalent π-bond between B^5 and one of the adjacent ring atoms;

R^{B53} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,
wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B54} and R^{B55} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B56}; or

R^{B54} and R^{B55} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B57}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^5 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B56} is selected from the group consisting of

C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B53},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B53},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

$NR^{B58}R^{B59}$;

R^{B57} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B58} and R^{B59} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B61} and R^{B62} are each independently selected from the members of the groups (i1) and (i2) as defined below:

(i1) hydrogen and halogen;

(i2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B63},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B64}R^{B65}$ and

a lone pair;

wherein one of the substituents R^{B61} and R^{B62} is absent in case the dotted lines signify a covalent π-bond between B^6 and one of the adjacent ring atoms;

R^{B63} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B64} and R^{B65} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B66}; or

R^{B64} and R^{B65} combine to form a 3- to 7-membered heterocycle,

wherein the 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B67}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^6 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B66} is selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxyl, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B63},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B63},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatoms selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B68}R^{B69}$;

R^{B67} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B67} and R^{B68} are each independently selected from the group consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxyl;

wherein R^{B71} and R^{B72} are each independently selected from the members of the groups (j1) and (j2) as defined below:

(j1) hydrogen and halogen;

(j2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B73},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B74}R^{B75}$ and

a lone pair; or

R^{B71} and R^{B72} combine to form an oxo-group;

wherein one of the substituents R^{B71} and R^{B72} is absent in case the dotted lines signify a covalent π-bond between B^7 and one of the adjacent ring atoms;

R^{B73} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B74} and R^{B75} are each independently selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-R^{B76}; or

R^{B74} and R^{B75} combine to form a 3- to 7-membered heterocycle,

wherein 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,

wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B77}, O and S, and

wherein, in case the atoms adjacent to the N which binds to B^7 are carbon atoms, said carbon atoms are each independently optionally substituted by an oxo-group;

R^{B76} is selected from the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B73},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B73},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B78}R^{B79}$;

R^{B77} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B78} and R^{B79} are each independently selected from the groups consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

wherein R^{B81} and R^{B82} are each independently selected from the members of the groups (k1) and (k2) as defined below:

(k1) hydrogen and halogen;

(k2) hydroxy, NO_2, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy and C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

-O-C_{3-6}-cyclyl,

wherein the –O-C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B83},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro, hydroxy, C_{1-6}-alkoxy,

wherein the C_{1-6}-alkoxy is optionally substituted by one or more substitutents selected from fluoro and hydroxy,

$NR^{B84}R^{B85}$ and

a lone pair; or

R^{B81} and R^{B82} combine to form an oxo-group;

wherein one of the substituents R^{B81} and R^{B82} is absent in case the dotted lines signify a covalent π-bond between B^8 and one of the adjacent ring atoms;

R^{B83} is selected from the groups consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-C_{1-6}-alkyl,
wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B84} and R^{B85} are each independently selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
-C(O)-R^{B86}; or
R^{B84} and R^{B85} combine to form a 3- to 7-membered heterocycle,
wherein 3- to 7-membered heterocycle is optionally substituted by one or more substituents selected from fluoro and hydroxy,
wherein the 3- to 7-membered heterocycle optionally has one or more additional heteroatoms selected from NR^{B87}, O and S, and
wherein, in case the atoms adjacent to the N which binds to B^8 are carbon atoms, said carbon atoms independently are optionally substituted by an oxo-group;

R^{B86} is selected from the group consisting of
hydrogen, C_{1-6}-alkyl,
wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro, hydroxy, C_{3-6}-cyclyl,
wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and
3- to 7-membered heterocyclyl,
wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and
wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound to the C_{1-6}-alkyl via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound to the C_{1-6}-alkyl via C, N is substituted by R^{B83},

C_{3-6}-cyclyl,

wherein the C_{3-6}-cyclyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

3- to 7-membered heterocyclyl,

wherein the 3- to 7-membered heterocyclyl is optionally substituted by one or more substituents selected from fluoro, chloro and hydroxy, and

wherein the 3- to 7-membered heterocyclyl has at least one heteroatom selected from N, O and S, and

wherein the 3- to 7-membered heterocyclyl may be bound via C or N, with the proviso that, if the 3- to 7-membered heterocyclyl is bound via C, N is substituted by R^{B83},

C_{6-14}-aryl,

wherein the aryl is optionally substituted,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted, and

$NR^{B88}R^{B89}$;

R^{B87} is selected from the groups consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy, and

-C(O)-C_{1-6}-alkyl,

wherein the –C(O)-C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

R^{B88} and R^{B89} are each independently selected from the groups consisting of

hydrogen and C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

with the proviso that, in case m is 1, B^4, B^5, B^6, B^7 and B^8 is a carbon atom and the dotted lines signify 3 conjugated covalent π-bonds, one of each of the pairs of substituents R^{B41} and R^{B42}, R^{B51} and R^{B52}, R^{B61} and R^{B62}, R^{B71} and R^{B72}, R^{B81} and R^{B82} is absent, respectively, and at least one of the remaining substituents is selected from the members of the groups (g2), (h2), (i2), (j2) and (k2) as defined above;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

2. Compound according to claim 1, wherein R^{A01} is $NR^{A03}R^{A04}$;
a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

3. Compound according to claim 1 or 2, wherein R^{A03} and R^{A04} are each independently selected from the group consisting of

hydrogen, -C(O)H and $–C(O)-C_{1-6}$-alkyl,

wherein the $–C(O)-C_{1-6}$-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

4. Compound according to any one of claims 1 to 3, wherein

B^5 is a sulfur atom and B^4, B^7 and B^8 each are a carbon atom; or

B^7 is a sulfur atom and B^4, B^5 and B^8 each are a carbon atom; or

B^4, B^5, B^6, B^7 and B^8 each are a carbon atom;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

5. Compound according to any one of claims 1 to 4, wherein R^{B41}, R^{B42}, R^{B61} and R^{B62} are each independently selected the group consisting of

hydrogen, C_{1-6}-alkyl,

wherein the C_{1-6}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy, and

a lone pair;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

6. Compound according to any one of claims 1 to 5, wherein R^{B51} and R^{B52} are each independently selected from the group consisting of

hydrogen, C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is optionally substituted by one or more substituents selected from fluoro and hydroxy,

C_{1-13}-heteroaryl,

wherein the C_{1-13}-heteroaryl has at least one heteroatom selected from N, O and S, and

wherein the C_{1-13}-heteroaryl is optionally substituted,

$NR^{B54}R^{B55}$ and

a lone pair;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

7. Compound according to any one of claims 1 to 6, wherein R^{B71}, R^{B72}, R^{B81} and R^{B82} are each independently selected from the group consisting of

hydrogen,NO_2 and C_{1-3}-alkyl,

wherein the C_{1-3}-alkyl is optionally substituted by one or more substitutents selected from fluoro and hydroxy;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

8. Compound according to any one of claims 1 to 7, wherein

m is 0, B^7 is a sulfur atom, each of B^4, B^5 and B^8 are a carbon atom, the dotted lines signify 2 covalent π-bonds that are conjugated, each of R^{B41}, R^{B51}, R^{B81} and is hydrogen, R^{B42}, $R^{B52}$and R^{B82} are absent and R^{B71} and R^{B72} each represent a lone pair; or

m is 1, each of B^4, B^5, B^6, B^7 and B^8 is a carbon atom, the dotted lines signify 0 covalent π-bonds and each of R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B61}, R^{B62}, R^{B71}, R^{B72}, R^{B81} and R^{B82} is hydrogen; or

m is 0, each of B^4, B^5, B^7 and B^8 is a carbon atom, the dotted lines signify 0 covalent π-bonds and each of R^{B41}, R^{B42}, R^{B51}, R^{B52}, R^{B71}, R^{B72}, R^{B81} and R^{B82} is hydrogen;

a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

9. Compound according to any one of claims 1 to 9, selected from the group consisting of

6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(3-methylbenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(2-nitrobenzyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
3,3-Dimethyl-6-[4-(2-thienyl)benzyl]-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-one;
1-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}pyrrolidine-2,5-dione;
N-{4-[(3,3-Dimethyl-1-oxo-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-amine;
6-(Cyclopentylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
3,3-Dimethyl-6-(2-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
N-{4-[(1-Hydroxy-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-6-yl)methyl]phenyl}cyclopropanecarboxamide;
(1S)-6-(Cyclohexylmethyl)-3,3-dimethyl-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
(1S)-3,3-Dimethyl-6-(3-thienylmethyl)-2,3,4,7-tetrahydro-1H-indolo[2,3-c]quinolin-1-ol;
a salt thereof, an N-oxide of the compound or the salt thereof, or a stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof.

10. Compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof according to any of claims 1 to 9 for use in the treatment or prophylaxis of diseases.

11. Pharmaceutical composition comprising at least one of the compounds, pharmaceutically acceptable salts thereof, N-oxides of the compounds and the salts thereof and stereoisomers of the compounds, salts, N-oxides of the compounds and N-oxides of the salts thereof according to any of claims 1 to 9 together with at least one pharmaceutically acceptable auxiliary.

12. Pharmaceutical composition according to claim 11 further comprising at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, beta-mimetics, lung surfactants, endothelin antagonists, prostacyclins, calcium channel blockers, beta-blockers, type 4 phosphodiesterase inhibitors, antidepressants and antibiotics.

13. Use of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of diseases alleviated by inhibition of the type 5 phosphodiesterase.

14. Use of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of male and female sexual dysfunction, acute and chronic airway diseases, inflammatory diseases, disorders which are based on allergic and/or chronic, immunological false reactions, pain, right-heart failure, right heart hypertrophy (cor pulmonale), hypertension, hypercholesterolemia, hypertriglyceridemia, ischaemic diseases, diabetic gastroparesis and diseases with symptoms of gastroparesis, diseases or conditions in which it is desirable to suppress platelet function, diseases or conditions with an impairment or dysfunction of cerebral vascular reactivity and/or neurovascular coupling, diseases which are based on neuronal damage or degradation, peripheral arterial diseases, chronic renal failure, chronic heart failure, sepsis, senile dementia, Creutzfeld-Jacob disease, septic encephalopathy, arteriosclerotic encephalopathy, diabetes associated encephalopathy, toxic encephalopathy, vascular and neuronal dementia, Huntington´s disease, Parkinson's disease, multiple sclerosis and preeclampsia, portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, thrombosis of the portal vein, Budd-Chiari syndrome, malformation of liver veins, compression of liver veins, arteriovenous fistula, diseases associated with an enlarged spleen, schistosomiasis, sarcoidosis and other granulomatous diseases, primary biliary cirrhosis, myeloproliferative disorders, lymphatic systemic diseases, collagenosis, morbus Osler, nodular regenerative hyperplasia, tricuspid insufficiency, pericarditis constrictiva, veno-occlusive disease (VOD), non-alcoholic steatohepatitis (NASH), liver fibrosis, benign prostatic hyperplasia, overactive bladder, lower urinary tract disease, Raynaud's syndrome, insufficient uteroplacental blood flow in pregnancies with fetal growth restriction and insufficient brain skills.

15. Use of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof or the pharmaceutically acceptable salt thereof according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of an acute or chronic airway disease.

16. Use according to claim 15, wherein the acute or chronic airway disease is selected from pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.

17. Use of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof or the pharmaceutically acceptable salt thereof according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of portal

hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis or liver fibrosis.

18. Method of treating or preventing diseases alleviated by inhibition of the type 5 phosphodiesterase comprising administering to a patient in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof according to any of claims 1 to 9.

19. Method of treating or preventing male and female sexual dysfunction, acute and chronic airway diseases, inflammatory diseases, disorders which are based on allergic and/or chronic, immunological false reactions, pain, right-heart failure, right heart hypertrophy (cor pulmonale), hypertension, hypercholesterolemia, hypertriglyceridemia, ischaemic diseases, diabetic gastroparesis and diseases with symptoms of gastroparesis, diseases or conditions in which it is desirable to suppress platelet function, diseases or conditions with an impairment or dysfunction of cerebral vascular reactivity and/or neurovascular coupling, diseases which are based on neuronal damage or degradation, peripheral arterial diseases, chronic renal failure, chronic heart failure, sepsis, senile dementia, Creutzfeld-Jacob disease, septic encephalopathy, arteriosclerotic encephalopathy, diabetes associated encephalopathy, toxic encephalopathy, vascular and neuronal dementia, Huntington´s disease, Parkinson's disease, multiple sclerosis and preeclampsia, portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, thrombosis of the portal vein, Budd-Chiari syndrome, malformation of liver veins, compression of liver veins, arteriovenous fistula, diseases associated with an enlarged spleen, schistosomiasis, sarcoidosis and other granulomatous diseases, primary biliary cirrhosis, myeloproliferative disorders, lymphatic systemic diseases, collagenosis, morbus Osler, nodular regenerative hyperplasia, tricuspid insufficiency, pericarditis constrictiva, veno-occlusive disease (VOD), non-alcoholic steatohepatitis (NASH), liver fibrosis, benign prostatic hyperplasia, overactive bladder, lower urinary tract disease, Raynaud's syndrome, insufficient uteroplacental blood flow in pregnancies with fetal growth restriction and, insufficient brain skills comprising administering to a patient in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof according to any of claims 1 to 9.

20. Method for treating or preventing an acute or chronic airway disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof
or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof or the pharmaceutically acceptable salt thereof according to any of claims 1 to 9.

21. Method for treating or preventing an acute or chronic airway disease according to claim 20, in which the acute or chronic airway disease is selected from the group consisting of pulmonary hypertension, lung fibrosis, asthma, bronchitis, emphysema and chronic obstructive pulmonary disease.

22. Method of treating or preventing portal hypertension, liver cirrhosis, toxic liver damage, hepatitis, non-alcoholic steatohepatitis or liver fibrosis comprising administering to a patient in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt thereof, N-oxide of the compound or the salt thereof or stereoisomer of the compound, the salt, the N-oxide of the compound or the N-oxide of the salt thereof or the pharmaceutically acceptable salt thereof according to any of claims 1 to 9.