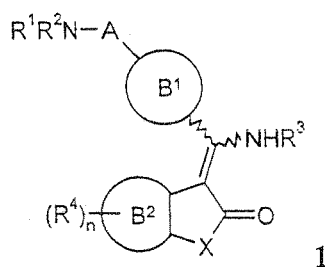


NEW COMPOUNDS FOR TREATING INFLAMMATORY DISEASES

The invention relates to new compounds of formula of formula 1 and hetero derivatives thereof, as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof,

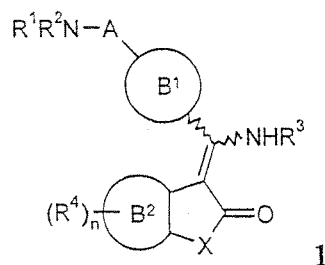


which are suitable for the treatment of respiratory or gastrointestinal complaints or diseases, inflammatory diseases of the joints, skin or eyes, diseases of the peripheral or central nervous system or cancers, as well as pharmaceutical compositions which contain these compounds.

DESCRIPTION OF THE INVENTION

Surprisingly it has now been found that the compounds of formula 1 are suitable for the treatment of inflammatory diseases.

In a first aspect, there is provided compounds of formula 1,



wherein

A denotes CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene

B¹ denotes phenyl or an aromatic or non-aromatic ring which may optionally contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and which may optionally be mono- or polysubstituted by one or more groups selected from among OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

B² denotes phenyl or a heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen;

X denotes O or CR⁶R⁷;

n denotes 0, 1, 2 or 3;

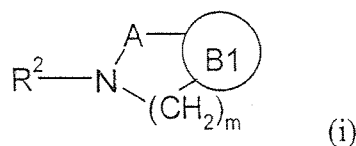
R¹ denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, COR^{1.1}, COOR^{1.1} CH₂COOR^{1.1};

R^{1.1} denotes H or C₁₋₆-alkyl;

R² denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

or **R¹** and **R²** together with the nitrogen form a non-aromatic heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen;

or **R²**, N, A and B¹ together form a bicyclic group of formula (i)



wherein

A denotes CO, C=NH or C₁₋₃-alkyl

m denotes 1, 2 or 3,

and

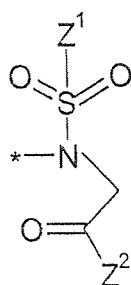
R^3 denotes H or a group selected from among OH, C_{1-6} -haloalkyl, a C_{6-10} -aryl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, while the C_{3-10} -heterocycle and the C_{5-10} -heteroaryl may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, which may optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{6-10} -aryl, optionally bridged C_{3-8} -cycloalkyl and C_{1-6} -haloalkyl, which may optionally be substituted by a group selected from C_{1-6} -alkyl, C_{1-6} -haloalkyl, OH, halogen and C_{6-10} -aryl ;

or R^3 denotes C_{1-6} -alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkanol; SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and $N(C_{1-6}-alkyl)_2$,

or R^3 denotes a group selected from among C_{3-8} -cycloalkyl, C_{5-8} -cycloalkenyl, C_{1-6} -alkyl and C_{1-6} -alkanol, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{3-8} -cycloalkyl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, COaryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, while the C_{5-10} -heteroaryl and the C_{3-10} -heterocycle may optionally be substituted by a group selected from oxo, hydroxyl, halogen, C_{1-6} -alkyl and C_{1-6} -haloalkyl;

or R^3 denotes a group selected from among C_{6-10} -aryl, a C_{6-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among aryl, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH , $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$ and $N-(SO_2-C_{1-4}-alkyl)(R^{3,4})$;

or R^3 denotes a group selected from among C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{3-7} -cycloalkyl, C_{6-10} -aryl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among B, halogen, OH , C_{1-6} -alkyl and oxo, while B is a compound of formula 2



2,

wherein Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}-alkyl)$, C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}-alkyl)$, $N(C_{1-6}-alkyl)_2$, or C_{3-7} -cycloalkyl; and Z^2 denotes OH, NH_2 , $NH(C_{1-6}-alkyl)$, $N(C_{1-6}-alkyl)_2$, $O(C_{1-6}-alkyl)$, mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic C_{3-10} -heterocycle, mono- or bicyclic C_{5-10} -heteroaryl or C_{6-10} -aryl;

or R^3 denotes a group selected from among C_{6-10} -aryl and a C_{5-10} -heteroaryl, which may optionally be substituted by C_{1-6} -alkyl, which may optionally be substituted by a group selected from among $COOR^{3,3}$, $NR^{3,3}R^{3,4}$, $NHCOR^{3,3}$, $NHCOOR^{3,3}$, phenyl, while phenyl may optionally be substituted by a group selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, CN , C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$,

COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂, a C₃₋₁₀-heterocycle and a C₅₋₁₀-heteroaryl, while the C₃₋₁₀-heterocycle and the C₅₋₁₀-heteroaryl may optionally be substituted by an oxo group or a methyl group;

while

R^{3.3} denotes H or C₁₋₆-alkyl;

R^{3.4} denotes H, C₁₋₆-alkyl or C₇₋₁₁-aralkyl, -C₁₋₆-alkylene or C₅₋₁₀-heteroaryl-C₁₋₆-alkylene,

or R³ denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heteroaryl, which may optionally be substituted by NR^{3.1}R^{3.2};

wherein

R^{3.1} denotes H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-haloalkyl, COR^{3.1.1}, COOR^{3.1.1}, CONR^{3.1.1}R^{3.1.2} or SO₂-R^{3.1.1};

and

R^{3.1.1} denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₃₋₆-cycloalkyl or C₆₋₁₀-aryl; and

R^{3.1.2} denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₃₋₆-cycloalkyl or C₆₋₁₀-aryl;

and

R^{3.2} denotes H or a group selected from among C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₁₋₆-haloalkyl, which may optionally be substituted by one or more groups selected from among NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, oxo and a non-aromatic C₃₋₁₀-heterocycle, which may contain one or two heteroatoms selected from among nitrogen, oxygen and sulphur, while the non-aromatic C₃₋₁₀-heterocycle may optionally be substituted by C₁₋₄-alkyl;

or R³ denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heteroaryl, which may optionally be substituted by a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, CN,

C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, oxo, OH, O-C₁₋₆-alkyl, halogen, SH, S-C₁₋₆-alkyl, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

or **R**³ denotes benzimidazolyl, which may optionally be substituted by a group selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl and C₃₋₆-cycloalkyl;

and

R⁴ denotes C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₁₋₆-haloalkyl, OR^{4.1}, NR^{4.1}R^{4.2}, CN or halogen; wherein

R^{4.1} denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

R^{4.2} denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

and

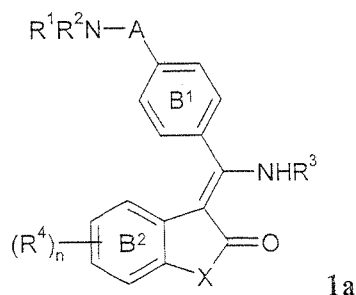
R⁶ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

R⁷ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

or **R**⁶ and **R**⁷ together form a 3-6 membered carbocycle;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

In a second aspect, there is provided compounds of formula **1a**,



wherein A, X, n, **R**¹, **R**², **R**³ and **R**⁴ have the meanings given as disclosed above, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

In a third aspect, there is provided the use of compounds as disclosed above for preparing a medicament for the treatment of inflammatory and obstructive diseases such as COPD, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis.

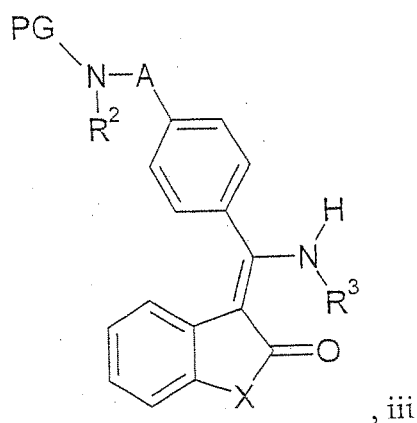
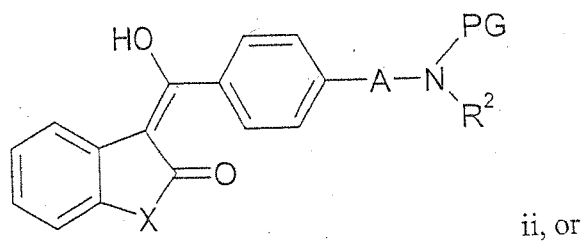
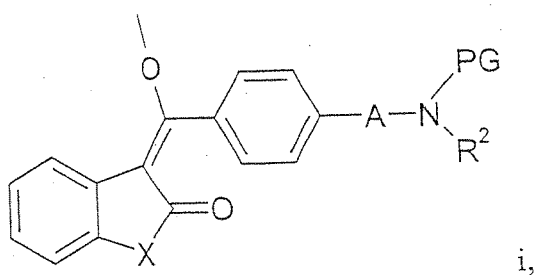
In a fourth aspect, there is provided the use of compounds as disclosed above for preparing a medicament for the prevention and treatment of diseases of the peripheral or central nervous system such as depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

In a fifth aspect, there is provided pharmaceutical formulations, characterised in that they contain one or more compounds of formula **1** or **1a** as disclosed above.

In a sixth aspect, there is provided pharmaceutical formulation suitable for administration by inhalation, characterised in that it contains a compound of formula **1** or **1a** as disclosed above.

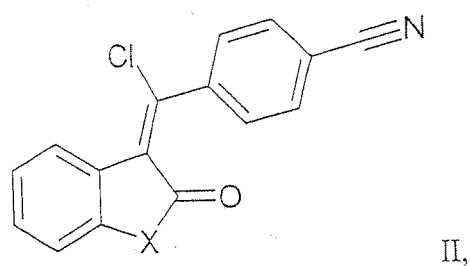
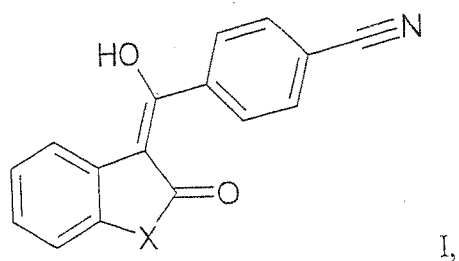
In a seventh aspect, there is provided pharmaceutical combinations which contain as an additional active substance, in addition to one or more compounds of formula **1** or **1a** as disclosed above, one or more compounds selected from the categories of the betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof.

In an eighth aspect, there is provided intermediate products of the process according to Scheme 1 of the formulae i, ii or iii

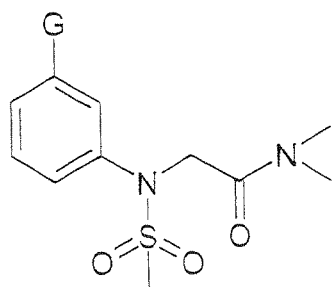


wherein X, A, R² and R³ have the meanings disclosed above and PG is hydrogen or a suitable protecting group.

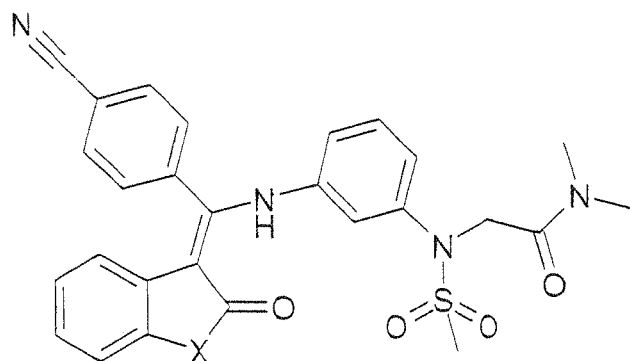
In a ninth aspect, there is provided intermediate products of the process according to Scheme 2 of the formulae I, II, III, IV or V



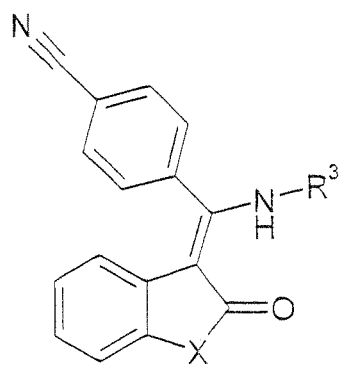
1h



III,



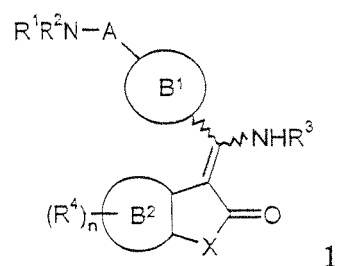
IV, or



V

wherein G denotes NO₂ or NH₂ and wherein X and R³ have the meanings as disclosed above.

The present disclosure therefore relates to compounds of formula 1



1

wherein

A denotes CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene

B¹ denotes phenyl or an aromatic or non-aromatic ring which may optionally contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and which may optionally be mono- or polysubstituted by one or more groups selected from among OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

B² denotes phenyl or a heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen;

X denotes O, S, NR⁵ or CR⁶R⁷;

n denotes 0, 1, 2 or 3;

R¹ denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, COR^{1.1}, COOR^{1.1} CH₂COOR^{1.1}; preferably H, C₁₋₆-alkyl, C₁₋₆-haloalkyl,

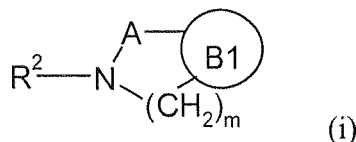
R^{1.1} denotes H or C₁₋₆-alkyl;

R² denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

20

or **R¹** and **R²** together with the nitrogen form a non-aromatic heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen;

or **R²**, N, A and B¹ together form a bicyclic group of formula (i)



25

wherein

A denotes CO, C=NH or C₁₋₃-alkyl

m denotes 1, 2 or 3,

and

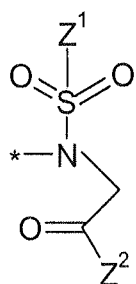
R³ denotes H or a group selected from among OH, C₁₋₆-haloalkyl, a C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, while the C₃₋₁₀-heterocycle and the C₅₋₁₀-heteroaryl may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl, optionally bridged C₃₋₈-cycloalkyl and C₁₋₆-haloalkyl, which may optionally be substituted by a group selected from C₁₋₆-alkyl, C₁₋₆-haloalkyl, OH, halogen and C₆₋₁₀-aryl ;

or **R³** denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂,

or **R³** denotes a group selected from among C₃₋₈-cycloalkyl, C₅₋₈-cycloalkenyl, C₁₋₆-alkyl and C₁₋₆-alkanol, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₃₋₈-cycloalkyl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-haloalkyl, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, while the C₅₋₁₀-heteroaryl and the C₃₋₁₀-heterocycle may optionally be substituted by a group selected from oxo, hydroxyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

or R^3 denotes a group selected from among C_{6-10} -aryl, a C_{6-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-$
 5 C_{6-10} -aryl, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH , $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$ and $N-(SO_2-C_{1-4}-alkyl)(R^{3,4})$;

or R^3 denotes a group selected from among C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -
 10 heteroaryl- C_{1-6} -alkylene, C_{3-7} -cycloalkyl, C_{6-10} -aryl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among B, halogen, OH , C_{1-6} -alkyl and oxo, while B is a compound of formula 2



2,

15 wherein Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}-alkyl)$, C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}-alkyl)$, $N(C_{1-6}-alkyl)_2$, or C_{3-7} -cycloalkyl;
 and Z^2 denotes OH, NH_2 , $NH(C_{1-6}-alkyl)$, $N(C_{1-6}-alkyl)_2$, $O(C_{1-6}-alkyl)$, mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic C_{3-10} -heterocycle, mono- or bicyclic C_{5-10} -heteroaryl or C_{6-10} -aryl;

20 or R^3 denotes a group selected from among C_{6-10} -aryl and a C_{5-10} -heteroaryl, which may optionally be substituted by C_{1-6} -alkyl, which may optionally be substituted by a group selected from among $COOR^{3,3}$, $NR^{3,3}R^{3,4}$, $NHCOR^{3,3}$, $NHCOOR^{3,3}$, phenyl, while phenyl
 25 may optionally be substituted by a group selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, CN, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$,

COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂, a C₃₋₁₀-heterocycle and a C₅₋₁₀-heteroaryl, while the C₃₋₁₀-heterocycle and the C₅₋₁₀-heteroaryl may optionally be substituted by an oxo group or a methyl group;

while

R^{3.3} denotes H or C₁₋₆-alkyl;

R^{3.4} denotes H, C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene or C₅₋₁₀-heteroaryl-C₁₋₆-alkylene,

or R³ denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heteroaryl, which may optionally be substituted by NR^{3.1}R^{3.2};

wherein

R^{3.1} denotes H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-haloalkyl, COR^{3.1.1}, COOR^{3.1.1}, CONR^{3.1.1}R^{3.1.2} or SO₂-R^{3.1.1};

and

R^{3.1.1} denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₃₋₆-cycloalkyl or C₆₋₁₀-aryl; and

R^{3.1.2} denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₃₋₆-cycloalkyl or C₆₋₁₀-aryl;

and

R^{3.2} denotes H or a group selected from among C₁₋₆-alkyl, C₃₋₇-cycloalkyl and C₁₋₆-haloalkyl, which may optionally be substituted by one or more groups selected from among NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, oxo and a non-aromatic C₃₋₁₀-heterocycle, which may contain one or two heteroatoms selected from among nitrogen, oxygen and sulphur, while the non-aromatic C₃₋₁₀-heterocycle may optionally be substituted by C₁₋₄-alkyl;

or R³ denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heteroaryl, which may optionally be substituted by a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, CN,

C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, oxo, OH, O-C₁₋₆-alkyl, halogen, SH, S-C₁₋₆-alkyl, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

5 or **R**³ denotes benzimidazolyl, which may optionally be substituted by a group selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl and C₃₋₆-cycloalkyl;

and

R⁴ denotes C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₁₋₆-haloalkyl, OR^{4.1}, NR^{4.1}R^{4.2}, CN or halogen; wherein

10 **R**^{4.1} denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

R^{4.2} denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

and

R⁵ denotes C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₁₋₆-haloalkyl, COR^{5.1}, CONHR^{5.1}, CON(R^{5.1})₂, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-C₆₋₁₀-aryl or a group selected from among
15 **R**^{5.2}, SO₂-C₁₋₆-alkyl-**R**^{5.2} and C₁₋₆-alkyl-**R**^{5.2}, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, CN, C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, O-C₃₋₆-cycloalkyl, O-C₁₋₆-haloalkyl, O-C₁₋₆-alkyl, halogen, SO₂-C₁₋₆-alkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl,
20 SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

wherein

R^{5.1} denotes C₁₋₆-alkyl, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene or C₆₋₁₀-aryl-C₁₋₆-alkylene
and

R^{5.2} denotes C₆₋₁₀-aryl or a C₅₋₁₀-heteroaryl;

25 and

R⁶ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

R⁷ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

30 or **R**⁶ and **R**⁷ together form a 3-6 membered carbocycle;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

5 Preferred compounds of formula **1** above are those wherein

A denotes CO, C=NH, C₁₋₄-alkylene or C₃₋₆-cycloalkylene;

10 **B**¹ denotes phenyl or a C₅₋₁₀-heteroaryl, which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen;

B² denotes phenyl or pyridinyl;

15 **X** denotes O, S, NR⁵ or CR⁶R⁷;

n denotes 0, 1, 2 or 3;

R¹ denotes H, C₁₋₄-alkyl, C₁₋₄-haloalkyl;

20 **R**² denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;

or **R**¹ and **R**² together with the nitrogen form a non-aromatic heterocycle, which may contain one or two nitrogen atoms ;

25 **R**³ denotes H, OH, C₁₋₄-haloalkyl, C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C₆₋₁₀-aryl and the C₅₋₁₀-heteroaryl may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl, C₃₋₆-cycloalkyl and C₁₋₄-haloalkyl;

30 or **R**³ denotes a group selected from among C₃₋₈-cycloalkyl, C₅₋₈-cycloalkenyl and C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from

among C₆₋₁₀-aryl or a C₅₋₁₀-heteroaryl, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl, CN, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

5

a group selected from among C₆₋₁₀-aryl and a heterocyclic, aromatic ring, substituted by one or more groups selected from among C₆₋₁₀-aryl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₁₋₄-haloalkyl, CONH₂, CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂, COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₄-alkyl, O-C₁₋₄-haloalkyl, halogen, SH, S-C₁₋₄-alkyl, S-C₁₋₄-haloalkyl, SO₂-C₁₋₄-alkyl, SO₂-C₁₋₄-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₄-alkyl, SO₂-N(C₁₋₄-alkyl)₂, NO₂, NH₂, NH-C₁₋₄-alkyl and N(C₁₋₄-alkyl)₂;

10

a group selected from among C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl, C₆₋₁₀-aryl-C₁₋₄-alkylene and C₅₋₁₀-heteroaryl-C₁₋₄-alkylene, which may optionally be substituted by one or more groups selected from among COOR^{3.3}, NR^{3.3}R^{3.4}, NHCOR^{3.3}, NHCOOR^{3.3} and phenyl, which may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, CN, C₁₋₄-haloalkyl, CONH₂, CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂, COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, OH, O-C₁₋₄-alkyl, O-C₁₋₄-haloalkyl, halogen, SH, S-C₁₋₄-alkyl, S-C₁₋₄-haloalkyl, SO₂-C₁₋₄-alkyl, SO₂-C₁₋₄-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₄-alkyl, SO₂-N(C₁₋₄-alkyl)₂, NO₂, NH₂, NH-C₁₋₄-alkyl and N(C₁₋₄-alkyl)₂, and a C₅₋₁₀-heterocycle, which may contain one, two or three heteroatoms selected from among oxygen, nitrogen and sulphur and which may optionally be substituted by an oxo group,

20

25

wherein

R^{3.3} denotes H or C₁₋₄-alkyl;

R^{3.4} denotes H, C₁₋₄-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene or C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;

or R³ denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heterocycle, which may be substituted by NR^{3.1}R^{3.2}

30

wherein

$R^{3.1}$ denotes H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl, C_{1-4} -haloalkyl, $COR^{3.1.1}$, $COOR^{3.1.1}$, $CONR^{3.1.1}R^{3.1.2}$ or $SO_2-R^{3.1.1}$;

and

5 $R^{3.1.1}$ denotes H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

$R^{3.1.2}$ denotes H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

and

10 $R^{3.2}$ denotes H or a group selected from among C_{1-4} -alkyl, C_{3-6} -cycloalkyl and C_{1-4} -haloalkyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NH(C_{1-4}\text{-alkyl})$, $N(C_{1-4}\text{-alkyl})_2$, oxo and a C_{3-10} -heterocycle, which may contain one or two heteroatoms selected from among nitrogen, oxygen and
15 sulphur and which may optionally be substituted by C_{1-4} -alkyl;

or R^3 denotes C_{6-10} -aryl, which may be substituted by a C_{5-10} -heteroaryl which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen and which may optionally be substituted by one or more groups selected from among
20 C_{6-10} -aryl, C_{1-4} -alkyl, C_{3-6} -cycloalkyl, CN, C_{1-4} -haloalkyl, $CONH_2$, $CONH-C_{1-4}\text{-alkyl}$, $CON(C_{1-4}\text{-alkyl})_2$, $COOH$, $COO-C_{1-4}\text{-alkyl}$, COH , $CO-C_{1-4}\text{-alkyl}$, OH , $O-C_{1-4}\text{-alkyl}$, halogen, SH, $S-C_{1-4}\text{-alkyl}$, NH_2 , $NH-C_{1-4}\text{-alkyl}$ and $N(C_{1-4}\text{-alkyl})_2$;

or R^3 denotes C_{6-10} -aryl, which may be substituted by a C_{3-10} -heterocycle which may
25 contain one or two heteroatoms, selected from among oxygen, sulphur and nitrogen and which may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo;

or R^3 denotes benzimidazolyl, which may optionally be substituted by a group selected
30 from among C_{1-4} -alkyl, C_{1-4} -haloalkyl and C_{3-6} -cycloalkyl;

and wherein

R⁴ denotes C₁₋₄-alkyl, C₃₋₆-cycloalkyl, C₁₋₄-haloalkyl, OR^{4.1}, NR^{4.1}R^{4.2}, CN or halogen;
and

R^{4.1} denotes H, C₁₋₄-alkyl, C₃₋₆-cycloalkyl or C₁₋₄-haloalkyl;

5 **R^{4.2}** denotes H, C₁₋₄-alkyl, C₃₋₆-cycloalkyl or C₁₋₄-haloalkyl;

and

R⁵ denotes C₁₋₄-alkyl, C₃₋₈-cycloalkyl, C₁₋₄-haloalkyl, COR^{5.1}, CONHR^{5.1}, CON(R^{5.1})₂,
SO₂-C₁₋₄-alkyl, SO₂-C₁₋₄-haloalkyl, SO₂-C₆₋₁₀-aryl or a group selected from among
R^{5.2}, SO₂-C₁₋₄-alkyl-R^{5.2} and C₁₋₄-alkyl-R^{5.2}, while this group may optionally be
10 substituted by one or more groups selected from among C₁₋₄-alkyl, C₂₋₄-alkenyl,
C₂₋₄-alkynyl, CN, C₁₋₄-haloalkyl, CONH₂, CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂,
COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, O-C₁₋₄-cycloalkyl, O-C₁₋₄-haloalkyl,
O-C₁₋₄-alkyl, halogen, SO₂-C₁₋₄-alkyl, SO₂-NH₂, SO₂-NH-C₁₋₄-alkyl,
SO₂-N(C₁₋₄-alkyl)₂, NO₂, NH₂, NH-C₁₋₄-alkyl and N(C₁₋₄-alkyl)₂;

15 wherein

R^{5.1} denotes C₁₋₄-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene or C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;

R^{5.2} denotes C₆₋₁₀-aryl or a C₅₋₁₀-heteroaryl;

and wherein

20 **R⁶** denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;

R⁷ denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;

or **R⁶** and **R⁷** together form a 3-6 membered carbocycle;

25

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally
in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates
thereof, as well as deuterated forms thereof.

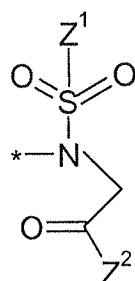
Preferred compounds of formula **1** above are those wherein

- A** denotes CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene,
- 5 **B¹** denotes phenyl or an aromatic or non-aromatic ring, which may optionally contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen and which may optionally be mono- or polysubstituted by one or more groups selected from among OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;
- 10 **B²** denotes phenyl or pyridinyl;
- X** denotes O, S, NR⁵ or CR⁶R⁷;
- n** denotes 0, 1, 2 or 3;
- 15 **R¹** denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;
- R²** denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;
- 20 or **R¹** and **R²** together with the nitrogen form a non-aromatic heterocycle, which may contain one or two nitrogen atoms;
- R³** denotes H, OH, C₁₋₆-haloalkyl or a group selected from among C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by a methyl group, oxo or OH;
- 25 or **R³** denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, COaryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂,
- 30

SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

5 or R³ denotes a group selected from among C₃₋₈-cycloalkyl, a C₃₋₈-cycloalkyl bridged with C₁₋₃-alkylene, a C₅₋₈-cycloalkenyl, C₁₋₆-alkyl and C₁₋₆-alkanol, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₃₋₈-cycloalkyl, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl, CN, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, 10 NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, while the C₅₋₁₀-heteroaryl and the C₃₋₁₀-heterocycle may optionally be substituted by a group selected from oxo, hydroxyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

or R³ denotes a group selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl- C₁₋₆-alkylene, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, C₆₋₁₀-aryl, C₅₋₁₀-heteroaryl and a 15 C₃₋₁₀-heterocycle, which is substituted by one or more groups selected from among B, halogen, OH, C₁₋₆-alkyl, oxo, where B is a compound of formula 2



2,

wherein

20 Z¹ denotes H, OH, halogen, C₁₋₆-alkyl, C₁₋₆-alkanol, O(C₁₋₆-alkyl), C₆₋₁₀-aryl, O-C₆₋₁₀-aryl, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ or C₃₋₇-cycloalkyl; and Z² denotes OH, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, O(C₁₋₆-alkyl), mono- or bicyclic C₃₋₇-cycloalkyl, a mono- or bicyclic C₃₋₁₀-heterocycle, a mono- or bicyclic C₅₋₁₀-heteroaryl or C₆₋₁₀-aryl;

or R^3 denotes phenyl, which is substituted by one or more groups selected from among C_{6-10} -aryl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $COaryl$, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-4}$ -haloalkyl, halogen, SH , $S-C_{1-6}$ -alkyl, $S-C_{1-4}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-4} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and $N(C_{1-6}-alkyl)_2$;

or R^3 denotes phenyl, which is substituted by C_{1-4} -alkyl, which may optionally be substituted by a group selected from among $COOR^{3.3}$, $NR^{3.3}R^{3.4}$, $NHCOR^{3.3}$, $NHCOOR^{3.3}$ and phenyl, which may optionally be substituted by one or more groups selected from among methyl, *t*-butyl, F , Cl , Br , CN , OH , and a heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen, while the heterocycle may optionally be substituted by an oxo group or a methyl group;

wherein

$R^{3.3}$ denotes H or C_{1-6} -alkyl;

$R^{3.4}$ denotes H , C_{1-6} -alkyl or C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene;

or R^3 denotes phenyl, substituted by $NR^{3.1}R^{3.2}$;

while

$R^{3.1}$ denotes H , C_{1-4} -alkyl, C_{1-4} -haloalkyl, $COR^{3.1.1}$, $COOR^{3.1.1}$, $CONR^{3.1.1}R^{3.1.2}$ or $SO_2-R^{3.1.1}$;

and

$R^{3.1.1}$ denotes H , C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

$R^{3.1.2}$ denotes H , C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

and

$R^{3.2}$ denotes H , C_{1-4} -alkyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NH(C_{1-4}-alkyl)$,

$N(C_{1-4}\text{-alkyl})_2$, oxo or a non-aromatic C_{3-10} -heterocycle, which may contain one or two nitrogen atoms and may optionally be substituted by a methyl group;

5 or R^3 denotes C_{6-10} -aryl, which may be substituted by a C_{5-10} -heteroaryl containing one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-4} -alkyl, C_{3-6} -cycloalkyl, CN, C_{1-4} -haloalkyl, $CONH_2$, $CONH-C_{1-4}$ -alkyl, $CON(C_{1-4}\text{-alkyl})_2$, $COOH$, $COO-C_{1-4}$ -alkyl, COH ,
10 $CO-C_{1-4}$ -alkyl, OH , $O-C_{1-4}$ -alkyl, halogen, SH , $S-C_{1-4}$ -alkyl, NH_2 , $NH-C_{1-4}$ -alkyl and $N(C_{1-4}\text{-alkyl})_2$;

or R^3 denotes C_{6-10} -aryl, which may be substituted by a non-aromatic C_{3-10} -heterocycle, which may contain one or two heteroatoms, selected from among oxygen, sulphur and
15 nitrogen, while the C_{3-10} -heterocycle may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo;

or R^3 denotes benzimidazolyl, which may optionally be substituted by one group or several groups selected from among C_{1-4} -alkyl, C_{1-4} -haloalkyl and C_{3-6} -cycloalkyl;
20 and

R^4 denotes C_{1-4} -alkyl, C_{3-6} -cycloalkyl, C_{1-4} -haloalkyl, $OR^{4.1}$, $NR^{4.1}R^{4.2}$, CN or halogen;

$R^{4.1}$ denotes H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl or C_{1-4} -haloalkyl;

$R^{4.2}$ denotes H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl or C_{1-4} -haloalkyl;

25 and

R^5 denotes C_{1-4} -alkyl, C_{3-8} -cycloalkyl, C_{1-4} -haloalkyl, $COR^{5.1}$, $CONHR^{5.1}$, $CON(R^{5.1})_2$, SO_2-C_{1-4} -alkyl, SO_2-C_{1-4} -haloalkyl, SO_2 -aryl or a group selected from among $R^{5.2}$, SO_2-C_{1-4} -alkyl- $R^{5.2}$ and C_{1-4} -alkyl- $R^{5.2}$, which may optionally be substituted by C_{1-4} -alkyl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, CN, C_{1-4} -haloalkyl, $CONH_2$,
30 $CONH-C_{1-4}$ -alkyl, $CON(C_{1-4}\text{-alkyl})_2$, $COOH$, $COO-C_{1-4}$ -alkyl, COH , $CO-C_{1-4}$ -alkyl, $O-C_{1-4}$ -cycloalkyl, $O-C_{1-4}$ -haloalkyl, $O-C_{1-4}$ -alkyl, halogen,

SO₂-C₁₋₄-alkyl, SO₂-NH₂, SO₂-NH-C₁₋₄-alkyl, SO₂-N(C₁₋₄-alkyl)₂, NO₂, NH₂,
NH-C₁₋₄-alkyl and N(C₁₋₄-alkyl)₂;

while

5 R^{5.1} denotes C₁₋₆-alkyl, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene or C₆₋₁₀-aryl-C₁₋₆-alkylene
 and

 R^{5.2} denotes C₆₋₁₀-aryl or a C₅₋₁₀-heteroaryl;

and

R⁶ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

10 R⁷ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

or R⁶ and R⁷ together form 3-6 membered carbocycle;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the
15 form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
as well as deuterated forms thereof. .

Preferred compounds of formula 1 above are those wherein R¹, R², R⁴, R⁵, R⁶, R⁷ and A,
B¹, B², X and n have the meanings given above and wherein

20

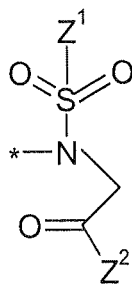
R³ denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups
 selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl,
 CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl,
 OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl,
25 SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂,
 SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and
 N(C₁₋₆-alkyl)₂,

or R³ denotes a group selected from among C₃₋₈-cycloalkyl, a C₃₋₈-cycloalkyl bridged with
30 C₁₋₃-alkylene, a C₅₋₈-cycloalkenyl, C₁₋₆-alkyl, and C₁₋₆-alkanol, which may
 optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl,

C₃₋₈-cycloalkyl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which in turn may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-haloalkyl, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from oxo, hydroxyl, halogen or C₁₋₆-alkyl and C₁₋₆-haloalkyl;

or R³ denotes a group selected from among C₆₋₁₀-aryl, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂ and N-(SO₂-C₁₋₄-alkyl)(R^{3,4});

or R³ denotes a group selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, C₆₋₁₀-aryl, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among B, halogen, OH, C₁₋₆-alkyl and oxo, while B is a compound of formula 2



25

2

wherein

Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}$ -alkyl), C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$ or C_{3-7} -cycloalkyl and
 Z^2 denotes OH, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$, $O(C_{1-6}$ -alkyl), mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic C_{5-10} -heteroaryl, mono- or bicyclic C_{3-10} -heterocycle or C_{6-10} -aryl;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Preferred compounds of formula **1** above are those wherein R^3 and R^4 have the above-mentioned meanings and wherein

A denotes CH_2 , CD_2 , $C=NH$, $CHMe$, CMe_2 , 1,1'-cyclopropylene or 1,1'-cyclobutylidene;

B¹ denotes phenyl;

B² denotes phenyl;

X denotes O or NR^5 ; wherein

R⁵ denotes methyl, ethyl, cyclopropyl, cyclobutyl, $CONHCH_2$ -phenyl, CH_2CF_3 or benzyl, which may optionally be substituted by F;

and wherein

n denotes 0 or 1;

R¹ denotes H;

R² denotes H,

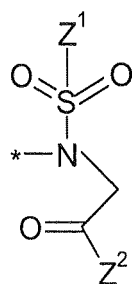
optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

- 5 Preferred are the above compounds of formula **1**, wherein R^1 , R^2 , R^5 , R^6 , R^7 and A , B^1 , B^2 , X and n have the meanings given above and wherein

- R^3 denotes C_{1-6} -alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl,
 10 $CON(C_{1-6}$ -alkyl) $_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH, $O-C_{1-6}$ -alkyl, SO_2-C_{1-6} -alkanol; SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}$ -alkyl) $_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and $N(C_{1-6}$ -alkyl) $_2$,
- 15 or R^3 denotes a group selected from among C_{3-8} -cycloalkyl, a C_{3-8} -cycloalkyl bridged by C_{1-3} -alkylene and C_{1-6} -alkyl, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{3-8} -cycloalkyl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may in turn optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl,
 20 CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}$ -alkyl) $_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}$ -alkyl) $_2$, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may
 25 optionally be substituted by one or more groups selected from oxo, hydroxyl, halogen or C_{1-6} -alkyl and C_{1-6} -haloalkyl;
- or R^3 denotes a group selected from among C_{6-10} -aryl, a C_{3-8} -heterocycle with 1 to 4 heteroatoms selected from N, O, S and a C_{5-10} -heteroaryl with 1 to 2 heteroatoms
 30 selected from N, O, S, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-6} -alkyl, C_{1-6} -haloalkyl, $CONH_2$,

CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH,
 CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen,
 SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂,
 SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂
 5 and N-(SO₂-C₁₋₄-alkyl)(R^{3,4}), wherein R^{3,4} is a C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;

or R³ denotes a group selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene, C₅₋₁₀-
 heteroaryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, C₆₋₁₀-aryl, C₃₋₈-heterocycle with 1 to 4
 heteroatoms selected from N, O, S, and a C₅₋₁₀-heteroaryl with 1 to 2 heteroatoms
 10 selected from N, O, S, which may optionally be substituted in each case by one or
 more groups selected from among B, halogen, OH, C₁₋₆-alkyl, oxo, wherein B is a
 compound of formula 2



2

wherein
 15 Z¹ is H, OH, halogen, C₁₋₆-alkyl, C₁₋₆-alkanol or O(C₁₋₆-alkyl) and
 Z² is OH, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, O(C₁₋₆-alkyl), mono- or bicyclic C₃₋₇-
 cycloalkyl, mono- or bicyclic C₅₋₁₀-heteroaryl, mono- or bicyclic C₃₋₁₀-
 heterocycle or C₆₋₁₀-aryl;

20 and wherein R⁴ denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the
 form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
 as well as deuterated forms thereof.

Preferred are the above compounds of formula **1**, wherein

A denotes CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene,

5 **B**¹ denotes phenyl or pyridinyl;

B² denotes phenyl or pyridinyl;

X denotes O or NR⁵;

10

n denotes 0, 1, 2 or 3;

R¹ denotes H, methyl, ethyl or propyl;

15 **R**² denotes H, methyl, ethyl or propyl;

R³ denotes H, OH, C₁₋₆-haloalkyl or C₆₋₁₀-aryl or a group selected from among a C₅₋₁₀-heteroaryl and a C₃₋₁₀-cycloalkyl, which may contain one, two or three nitrogen atoms and which may optionally be substituted by a methyl group;

20

or **R**³ denotes a group selected from among cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methyl, ethyl, propyl and butyl, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heterocycle, which may in turn optionally be substituted by one or more groups selected from
25 among C₁₋₆-alkyl, C₁₋₆-haloalkyl, CN, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

25

or **R**³ denotes phenyl, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₁₋₄-haloalkyl, CONH₂,
30 CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂, COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₄-alkyl, O-C₁₋₄-haloalkyl, halogen, SH,

30

S-C₁₋₄-alkyl, S-C₁₋₄-haloalkyl, SO₂-C₁₋₄-alkyl, SO₂-C₁₋₄-haloalkyl, SO₂-NH₂,
 SO₂-NH-C₁₋₄-alkyl, SO₂-N(C₁₋₄-alkyl)₂, NO₂, NO₂, NH₂, NH-C₁₋₄-alkyl and
 N(C₁₋₄-alkyl)₂;

5 or **R**³ denotes phenyl, which may optionally be substituted by C₁₋₄-alkyl, which may in
 turn optionally be substituted by a group selected from among COOR^{3.3}, NR^{3.3}R^{3.4},
 NHCOR^{3.3}, NHCOOR^{3.3}, *p*-fluorophenyl and a heterocycle, which may contain one, two or
 three heteroatoms selected from among oxygen and nitrogen and which may optionally be
 substituted by an oxo group;

10 wherein

R^{3.3} denotes H or C₁₋₄-alkyl;

R^{3.4} denotes H, C₁₋₄-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene or C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;

15 or **R**³ denotes phenyl, which may be substituted by NR^{3.1}R^{3.2};

wherein

R^{3.1} denotes H, C₁₋₄-alkyl, COR^{3.1.1}, COOR^{3.1.1}, CONR^{3.1.1}R^{3.1.2} or
 SO₂-R^{3.1.1};

and

20 R^{3.1.1} denotes H, C₁₋₄-alkyl or C₆₋₁₀-aryl;

R^{3.1.2} denotes H, C₁₋₄-alkyl or C₆₋₁₀-aryl;

25 R^{3.2} denotes H, C₁₋₄-alkyl, which may optionally be substituted by one or
 more groups selected from among NH₂, NH(C₁₋₄-alkyl),
 N(C₁₋₄-alkyl)₂, oxo or a C₃₋₁₀-heterocycle, which may contain one or
 two nitrogen atoms and which may optionally be substituted by a
 methyl group;

30 or **R**³ denotes phenyl, which may be substituted by a C₅₋₁₀-heteroaryl, which may contain
 one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while
 the C₅₋₁₀-heteroaryl may optionally be substituted by one or more groups selected from

among C₆₋₁₀-aryl, C₁₋₄-alkyl, C₁₋₄-haloalkyl, C₃₋₆-cycloalkyl, CN, CONH₂, CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂, COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, OH, O-C₁₋₄-alkyl, halogen, NH₂ and N(C₁₋₄-alkyl)₂ ;

5 or **R**³ denotes phenyl, which may be substituted by a C₅₋₁₀-heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C₅₋₁₀-heteroaryl may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl and oxo;

10 or **R**³ denotes benzimidazolyl, which may optionally be substituted by one or more groups selected from among methyl, ethyl, propyl, CF₃, CH₂CF₃, cyclopropyl, cyclopentyl and cyclohexyl;

and

R⁴ denotes C₁₋₄-alkyl, C₁₋₄-haloalkyl or halogen;

15 and

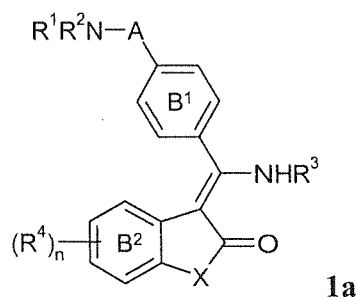
R⁵ denotes a group selected from among C₁₋₄-alkyl, C₃₋₆-cycloalkyl, COR^{5.1}, CONHR^{5.1}, C₆₋₁₀-aryl, SO₂-C₆₋₁₀-aryl-C₁₋₆-alkylene, SO₂-C₆₋₁₀-aryl or C₆₋₁₀-aryl-C₁₋₆-alkylene and C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, which may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, 20 CN, C₁₋₄-haloalkyl, CONH₂, CONH-C₁₋₄-alkyl, CON(C₁₋₄-alkyl)₂, COOH, COO-C₁₋₄-alkyl, COH, CO-C₁₋₄-alkyl, OH, O-C₁₋₄-alkyl, halogen, SO₂-C₁₋₄-alkyl, SO₂-NH₂, SO₂-NH-C₁₋₄-alkyl, SO₂-N(C₁₋₄-alkyl)₂, NO₂, NH₂, NH-C₁₋₄-alkyl and N(C₁₋₄-alkyl)₂ ;

and

25 **R**^{5.1} denotes C₁₋₄-alkyl or C₆₋₁₀-aryl-C₁₋₆-alkylene;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Particularly preferred are the compounds of formula **1a**,



5 wherein A, X, n, R¹, R², R³ and R⁴ are as hereinbefore defined, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

10 Particularly preferred are the above compounds of formula **1** or **1a**, wherein R¹, R², R³, R⁴ and A, B¹, B² and n have the meanings given above and wherein

X denotes O;

15 optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Particularly preferred are the above compounds of formula **1** or **1a**, wherein R¹, R², R³, R⁴,
20 R⁵ and A, B¹, B² and n have the meanings given above and wherein

X denotes NR⁵;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the
25 form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Particularly preferred are the above compounds of formula **1** or **1a**, wherein R^1 , R^2 , R^3 , R^4 , R^6 and R^7 as well as A , B^1 , B^2 and n have the meanings given above and wherein

X denotes CR^6R^7 ;

5

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

10

Particularly preferred are the above compounds of formula **1** or **1a**, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 as well as A , B^1 , B^2 and X have the meanings given above and wherein

n denotes 0, 1, or 2, preferably 0 or 1, particularly preferably 0,

15

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

20

Particularly preferred are the above compounds of formula **1** or **1a**, wherein

A denotes CH_2 , $CHMe$, CMe_2 , $C=NH$, 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

25

B¹ denotes phenyl;

B² denotes phenyl;

X denotes O or NR^5 ;

30

n denotes 0, 1 or 2;

R^1 denotes H, methyl or ethyl;

R^2 denotes H, methyl or ethyl;

5

R^3 denotes H, cyclopropyl, cyclobutyl, N-methyl-piperidinyl, pyridinyl, phenyl or 4-phenyl-cyclohexanyl or

R^3 denotes phenyl, which may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, CF_3 , $CONH_2$, $CONHMe$, $CONMe_2$, $COOH$, $COOMe$, $COOEt$, COH , $COMe$, OH , OMe , OEt , F , Cl , Br , SH , SO_2Me , $SONH_2$, $SONMe_2$, NO_2 , NH_2 , $NHMe$ and NMe_2 ;

10

or

R^3 denotes phenyl, which is optionally substituted by a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among $COOH$, $COOMe$, NH_2 , NMe_2 , $NHCOMe$, $NHCOO$ -*tert*-butyl, NMe (benzyl), *p*-fluorophenyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolidin-2-onyl, imidazolyl and triazolyl;

15

or

R^3 denotes phenyl, which is substituted by $NR^{3.1}R^{3.2}$, wherein

20

$R^{3.1}$ denotes H, methyl, COH , $COMe$, $COOMe$, $CONH_2$, $CONMe_2$, SO_2Me , SO_2CF_3 or SO_2 -phenyl,

25

and wherein

$R^{3.2}$ denotes H or a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NHMe$, NMe_2 , N-piperidinyl, N-morpholinyl and N-methyl-piperazinyl, wherein the N-piperidinyl, N-morpholinyl and the N-methyl-piperazinyl may optionally be substituted by a further oxo;

30

or

R³ denotes phenyl, which may be substituted by a C₅₋₁₀-heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C₅₋₁₀-heteroaryl may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF₃, CN, CONH₂, CONMe₂, CONEt₂, COOH, COOMe, COOEt, COH, COMe, OH, OMe, OEt, F, Cl, Br, NH₂, NMe₂, NEt₂ and NPr₂;

or

R³ denotes phenyl, which is substituted by a C₃₋₁₀-heterocycle, which may contain one or two heteroatoms selected from among oxygen and nitrogen, while the C₃₋₁₀-heterocycle may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl and oxo;

or **R³** denotes benzimidazolyl, which may optionally be substituted by one or more groups selected from among methyl, propyl, CF₃, CH₂CF₃, cyclopropyl and cyclohexyl;

and wherein

R⁴ denotes methyl, ethyl, propyl, butyl, CF₃, CH₂CF₃, F, Cl, or Br;

R⁵ denotes a group selected from among methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF₃, CH₂CF₃, COR^{5.1}, CONHR^{5.1}, phenyl, phenylsulphonyl and benzyl, while benzyl may optionally be substituted by one or more groups selected from among methyl, ethyl, propyl, butyl, CF₃, CN, CONH₂, CONMe₂, CONEt₂, COOH, COOMe, COOEt, COH, COMe, OH, OMe, OEt, F, Cl, Br, SO₂Me, SONH₂, SONMe₂, NO₂, NH₂, NMe₂, NEt₂ and NPr₂;

R^{5.1} denotes methyl, ethyl, propyl, butyl or benzyl;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

5 Particularly preferred are the above compounds of formula **1** or **1a**, wherein

A denotes CH₂, CHMe, CMe₂, CO, C=NH, 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

B¹ denotes phenyl;

10

B² denotes phenyl;

X denotes O or NR⁵;

15

n denotes 0 or 1;

R¹ denotes H, methyl or ethyl, preferably H;

R² denotes H, methyl or ethyl, preferably H;

20

R³ denotes H, OH, cyclopropyl, cyclobutyl, N-methyl-piperidinyl, pyridinyl, phenyl or 4-phenyl-cyclohexanyl

or

R³ denotes phenyl, which may be substituted by a group selected from among phenyl, OH, F and CONH₂;

25

or

R³ denotes phenyl, which is substituted by a group selected from among methyl and ethyl, which may optionally be substituted by a group selected from among COOH, COOMe, NH₂, NMe₂, NHCOMe, NHCOO-*tert*-butyl, NMe(benzyl), *p*-

30

fluorophenyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolidin-2-onyl, imidazolyl and triazolyl;

or

5 **R³** denotes phenyl, which is substituted by NR^{3.1}R^{3.2};

wherein

R^{3.1} denotes H, methyl, SO₂Me, SO₂CF₃ or SO₂-phenyl;

R^{3.2} denotes H or a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among NH₂, NHMe, NMe₂, oxo, N-piperidinyl, N-morpholinyl and N-methyl-piperazinyl;

or

15 **R³** denotes phenyl, which may be substituted by a C₅₋₁₀-heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen and which may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF₃, CN, CONH₂, CONMe₂, CONEt₂, COOH, COOMe, COOEt, COH, COMe, OH, OMe, OEt, F, Cl, Br, SO₂Me, SONH₂, SONMe₂, NO₂, NH₂, NMe₂, NEt₂ and NPr₂,

or

20 **R³** denotes phenyl, which is substituted by a C₃₋₁₀-heterocycle which may contain one or two heteroatoms selected from among oxygen and nitrogen and may optionally be substituted by one or more groups selected from among C₁₋₄-alkyl and oxo,

25 or

R³ denotes benzimidazolyl, which may optionally be substituted by methyl;

and wherein

30 **R⁴** denotes F or Cl;

and

R⁵ denotes a group selected from among methyl, ethyl, cyclopropyl, COMe, CONHR^{5.1}, phenyl, phenylsulphonyl and benzyl, which may optionally be substituted by F;

5 wherein

R^{5.1} denotes butyl or benzyl,

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
10 as well as deuterated forms thereof.

Particularly preferred are the above compounds of formula **1** or **1a**, wherein

A denotes CH₂, CHMe, CMe₂, 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

15

B¹ denotes phenyl;

B² denotes phenyl;

20 **X** denotes O or NR⁵;

n denotes 0 or 1;

R¹ denotes H;

25

R² denotes H;

R³ denotes H, 4-phenyl-cyclohexanyl or

30 **R³** denotes phenyl, which may optionally be substituted by NR^{3.1}R^{3.2};
wherein

$R^{3.1}$ denotes H, methyl, SO_2Me , SO_2CF_3 , or SO_2 -phenyl;

and

$R^{3.2}$ denotes H or a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NHMe$, NMe_2 , oxo, N-piperidinyl, N-morpholinyl and N-methyl-piperazinyl,

or

R^3 denotes phenyl, which is substituted by a C_{5-10} -heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C_{5-10} -heteroaryl may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF_3 , CN, $CONH_2$, $CONMe_2$, $CONEt_2$, $COOH$, $COOMe$, $COOEt$, COH , $COMe$, OH , OMe , OEt , F, Cl, Br, SO_2Me , $SONH_2$, $SONMe_2$, NO_2 , NH_2 , NMe_2 , NEt_2 and NPr_2 ,
or

R^3 denotes phenyl, which is substituted by a C_{3-10} -heterocycle, which may contain one or two heteroatoms selected from among oxygen and nitrogen, while the C_{3-10} -heterocycle may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo,

and wherein

R^4 denotes H, F or Cl;

R^5 denotes methyl, ethyl, cyclopropyl, cyclobutyl CH_2CF_3 or benzyl, while the benzyl may optionally be substituted by F;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Also particularly preferred are the above compounds of formula **1** or **1a**, wherein

A denotes a group selected from among CH_2 , CHMe , CMe_2 , CO , C=NH and



5

B¹ denotes phenyl;

B² denotes phenyl;

10

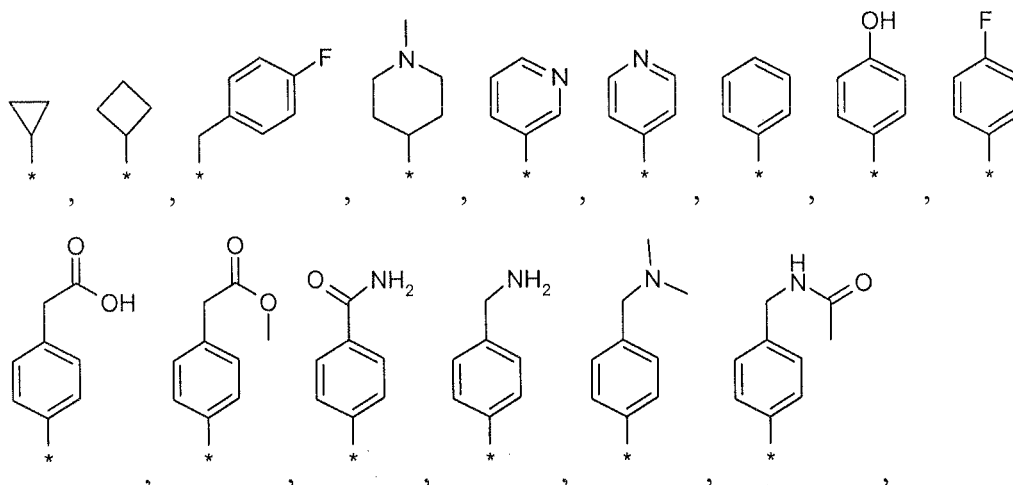
X denotes O or NR^5 ;

n denotes 0 or 1;

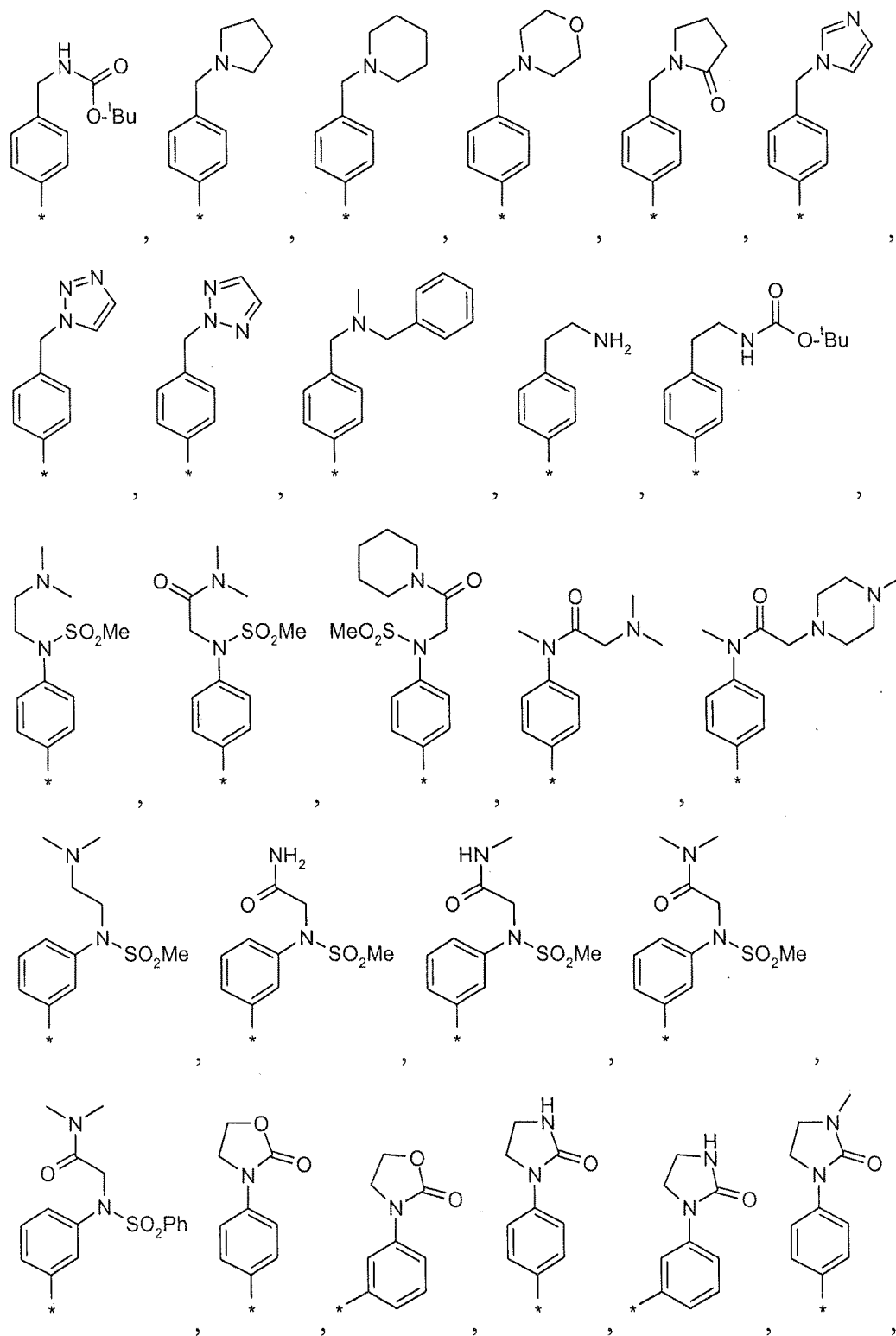
15 **R¹** denotes H;

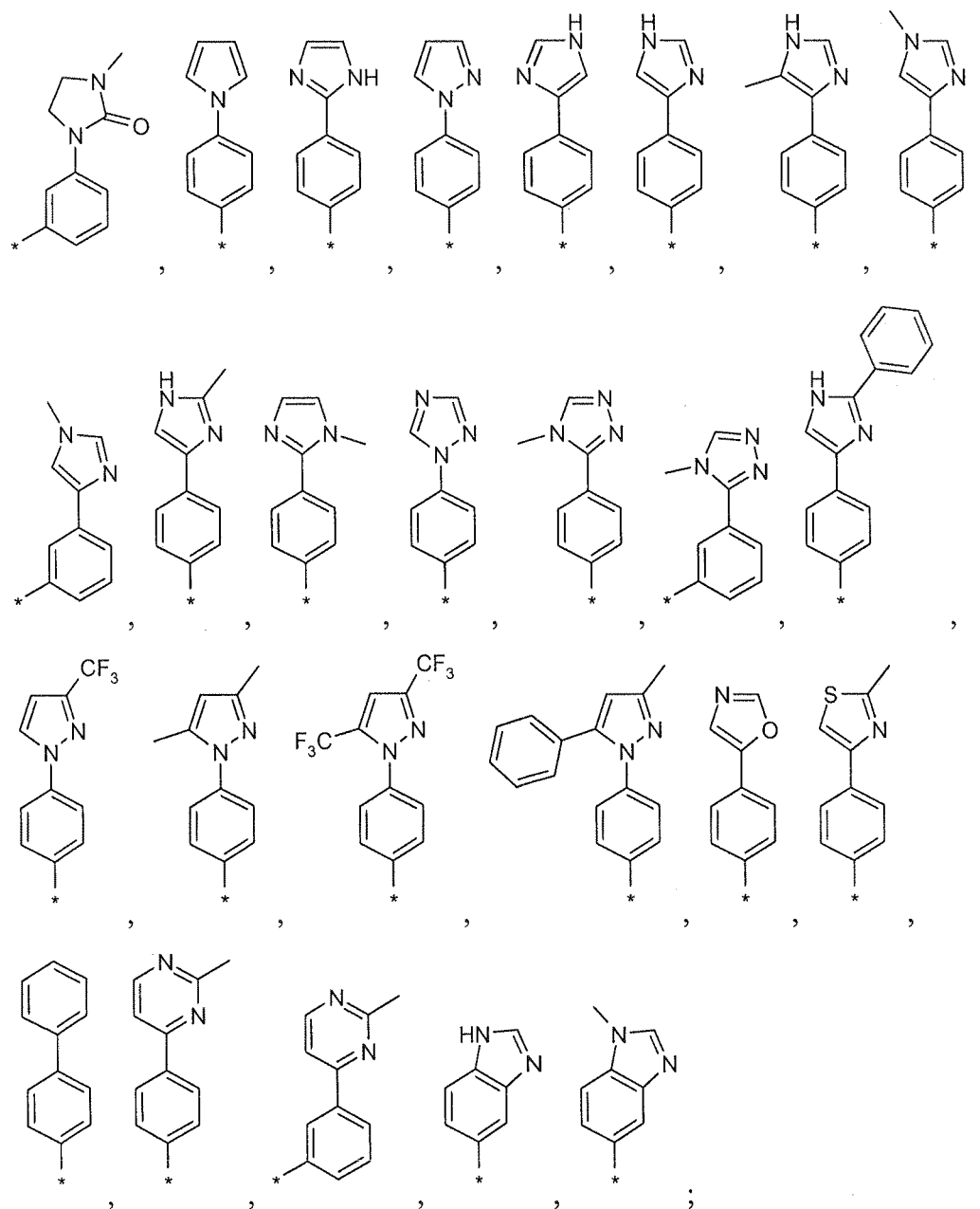
R² denotes H;

R³ denotes H, OH, 4-phenyl-cyclohexyl or a group selected from among



20



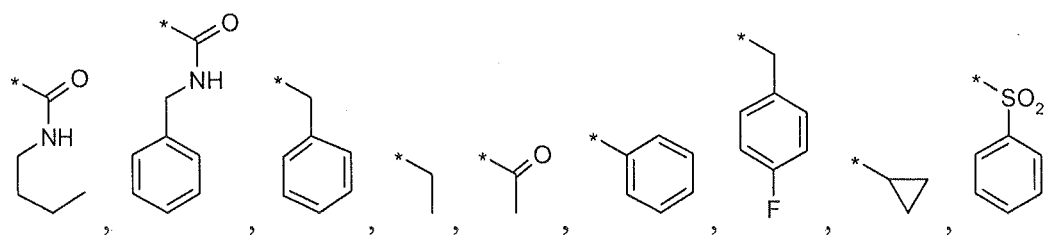


5 and

R⁴ denotes H, F or Cl;

and

R⁵ denotes methyl or a group selected from among



optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally
 5 in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates
 thereof, as well as deuterated forms thereof.

Also particularly preferred are the above compounds of formula **1** or **1a**, wherein

10 **A** denotes CH₂, CD₂, C=NH, CHMe, CMe₂, 1,1'-cyclopropylene, 1,1'-
 cyclobutylidene;

B¹ denotes phenyl;

15 **B**² denotes phenyl;

X denotes O or NR⁵; wherein

R⁵ denotes methyl, ethyl, cyclopropyl, cyclobutyl, CONHCH₂-phenyl, CH₂CF₃ or
 20 benzyl, optionally substituted by F;

n denotes 0 or 1;

R¹ denotes H;

25

R² denotes H;

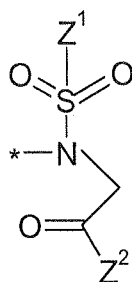
wherein R^3 denotes C_{1-6} -alkyl, optionally substituted by one or more groups selected from among halogen, OH, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, COOH, COO- C_{1-6} -alkyl, COH, CO- C_{1-6} -alkyl, COaryl, OH, O- C_{1-6} -alkyl, O- C_{1-6} -haloalkyl, halogen, SH, S- C_{1-6} -alkyl, S- C_{1-6} -haloalkyl, SO_2 - C_{1-6} -alkanol; SO_2 - C_{1-6} -alkyl, SO_2 - C_{1-6} -haloalkyl, SO_2 - NH_2 , SO_2 -NH- C_{1-6} -alkyl, SO_2 -N(C_{1-6} -alkyl) $_2$, NO_2 , NH_2 , NH- C_{1-6} -alkyl and N(C_{1-6} -alkyl) $_2$,

or R^3 denotes a group selected from among C_{3-8} -cycloalkyl, a C_{3-8} -cycloalkyl bridged by C_{1-3} -alkylene, or C_{5-8} -cycloalkenyl and C_{1-6} -alkyl, C_{1-6} -alkanol, which may optionally be substituted in each case by one or more groups selected from among C_{6-10} -aryl, C_{3-8} -cycloalkyl, C_{5-10} -heteroaryl and C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, COOH, COO- C_{1-6} -alkyl, COH, CO- C_{1-6} -alkyl, CO- C_{6-10} -aryl, OH, O- C_{1-6} -alkyl, O- C_{1-6} -haloalkyl, halogen, SH, S- C_{1-6} -alkyl, S- C_{1-6} -haloalkyl, SO_2 - C_{1-6} -alkanol, SO_2 - C_{1-6} -alkyl, SO_2 - C_{1-6} -haloalkyl, SO_2 - NH_2 , SO_2 -NH- C_{1-6} -alkyl, SO_2 -N(C_{1-6} -alkyl) $_2$, NO_2 , NH_2 , NH- C_{1-6} -alkyl, N(C_{1-6} -alkyl) $_2$, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by a group selected from oxo, hydroxyl, halogen or C_{1-6} -alkyl and C_{1-6} -haloalkyl;

or R^3 denotes a group selected from among C_{6-10} -aryl, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may be substituted in each case by one or more groups selected from among C_{6-10} -aryl, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, COOH, COO- C_{1-6} -alkyl, COH, CO- C_{1-6} -alkyl, CO- C_{6-10} -aryl, OH, O- C_{1-6} -alkyl, O- C_{1-6} -haloalkyl, halogen, SH, S- C_{1-6} -alkyl, S- C_{1-6} -haloalkyl, SO_2 - C_{1-6} -alkyl, SO_2 - C_{1-6} -alkanol, SO_2 - C_{1-6} -haloalkyl, SO_2 - NH_2 , SO_2 -NH- C_{1-6} -alkyl, SO_2 -N(C_{1-6} -alkyl) $_2$, NO_2 , NH_2 , NH- C_{1-6} -alkyl, N(C_{1-6} -alkyl) $_2$ and N-(SO_2 - C_{1-4} -alkyl)($R^{3,4}$),

wherein $R^{3,4}$ is a C_{6-10} -aryl, C_{6-10} -aryl- C_{1-6} -alkylene or a C_{5-10} -heteroaryl- C_{1-6} -alkylene;

or R^3 denotes a group selected from among C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{3-7} -cycloalkyl, C_{6-10} -aryl, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted in each case by one or more groups selected from among B, halogen, OH, C_{1-6} -alkyl, oxo, where B is a compound of formula 2



2

wherein Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}$ -alkyl), C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl)₂ or C_{3-7} -cycloalkyl; and Z^2 OH, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl)₂, $O(C_{1-6}$ -alkyl), C_{6-10} -aryl; mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic aromatic or non-aromatic C_{3-10} -heterocycle,

and wherein

R^4 denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

Also particularly preferred are compounds of formula 1 or 1a, wherein

A denotes CH_2 , CD_2 , $C=NH$, $CHMe$, CMe_2 , 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

B^1 denotes phenyl;

B² denotes phenyl;

X denotes O or NR⁵; wherein

5

R⁵ denotes methyl, ethyl, cyclopropyl, cyclobutyl, CONHCH₂-phenyl, CH₂CF₃ or benzyl, optionally substituted with F;

n denotes 0 or 1;

10

R¹ denotes H;

R² denotes H;

and

15 wherein R³ denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, phenyl, CO-phenyl, OH, O-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and
20 N(C₁₋₆-alkyl)₂;

or R³ denotes a group selected from among C₃₋₈-cycloalkyl, a C₃₋₈-cycloalkyl bridged by C₁₋₃-alkylene and C₁₋₆-alkyl, which may optionally be substituted in each case by one or more groups selected from among phenyl or another aromatic or non-aromatic C₃₋₈ ring, preferably a C₅₋₇ ring, more preferably a C₅₋₆ ring, which may optionally contain in each
25 case 1 to 4 heteroatoms independently of one another selected from N, O, S, while each of these groups may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, phenyl, CO-phenyl, OH, O-C₁₋₆-alkyl,
30 O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-alkyl, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂, an aromatic or non-aromatic C₃₋₈ ring,

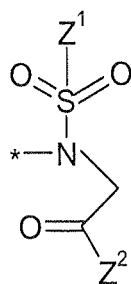
preferably a C₅₋₇ ring, more preferably a C₅₋₆ ring, which optionally contains 1 to 4 heteroatoms selected independently of one another from N, O, S, while this aromatic or non-aromatic C₃₋₈ ring may optionally be substituted by a group selected from oxo, hydroxyl, halogen or C₁₋₆-alkyl and C₁₋₆-haloalkyl;

5

or R³ denotes a group selected from among phenyl and another aromatic or non-aromatic C₃₋₈ ring, preferably a C₅₋₇ ring, more preferably a C₅₋₆ ring, which may optionally contain 1 to 4 heteroatoms selected from N, O, S and which may optionally be substituted by one or more groups selected from among phenyl, C₁₋₆-alkyl, C₁₋₆-haloalkyl, CONH₂,
 10 CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-phenyl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂ and N-(SO₂-C₁₋₄-alkyl)(R^{3,4}),

15 wherein R^{3,4} denotes a C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;

or R³ denotes or [*sic*] a group selected from among C₁₋₆-alkyl, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, C₆₋₁₀-aryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, phenyl and an aromatic or non-aromatic C₃₋₈ ring, preferably a C₅₋₇ ring, more preferably a C₅₋₆ ring, which may contain 1
 20 to 4 heteroatoms selected from N, O and S, while each of these groups may optionally be substituted by one or more groups selected from among B, halogen, OH, C₁₋₆-alkyl, oxo and B is a compound of formula 2



2

25 wherein Z¹ denotes H, OH, halogen, C₁₋₆-alkyl, C₁₋₆-alkanol or O(C₁₋₆-alkyl) and

Z^2 denotes OH, NH_2 , $NH(C_{1-6}\text{-alkyl})$, $N(C_{1-6}\text{-alkyl})_2$, $O(C_{1-6}\text{-alkyl})$, mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic aromatic or non-aromatic C_{3-10} -heterocycle or phenyl;

5 and

R^4 denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates
10 thereof, as well as deuterated forms thereof.

Also particularly preferred are compounds of the above formula **1** or **1a**, wherein

A denotes CH_2 , CD_2 , $C=NH$, $CHMe$, CMe_2 , 1,1'-cyclopropylene, 1,1'-
15 cyclobutylidene;

B¹ denotes phenyl;

B² denotes phenyl;

20

X denotes O or NR^5 ; wherein

R⁵ denotes methyl, ethyl, cyclopropyl, cyclobutyl, $CONHCH_2$ -phenyl, CH_2CF_3 or benzyl, optionally substituted by F;

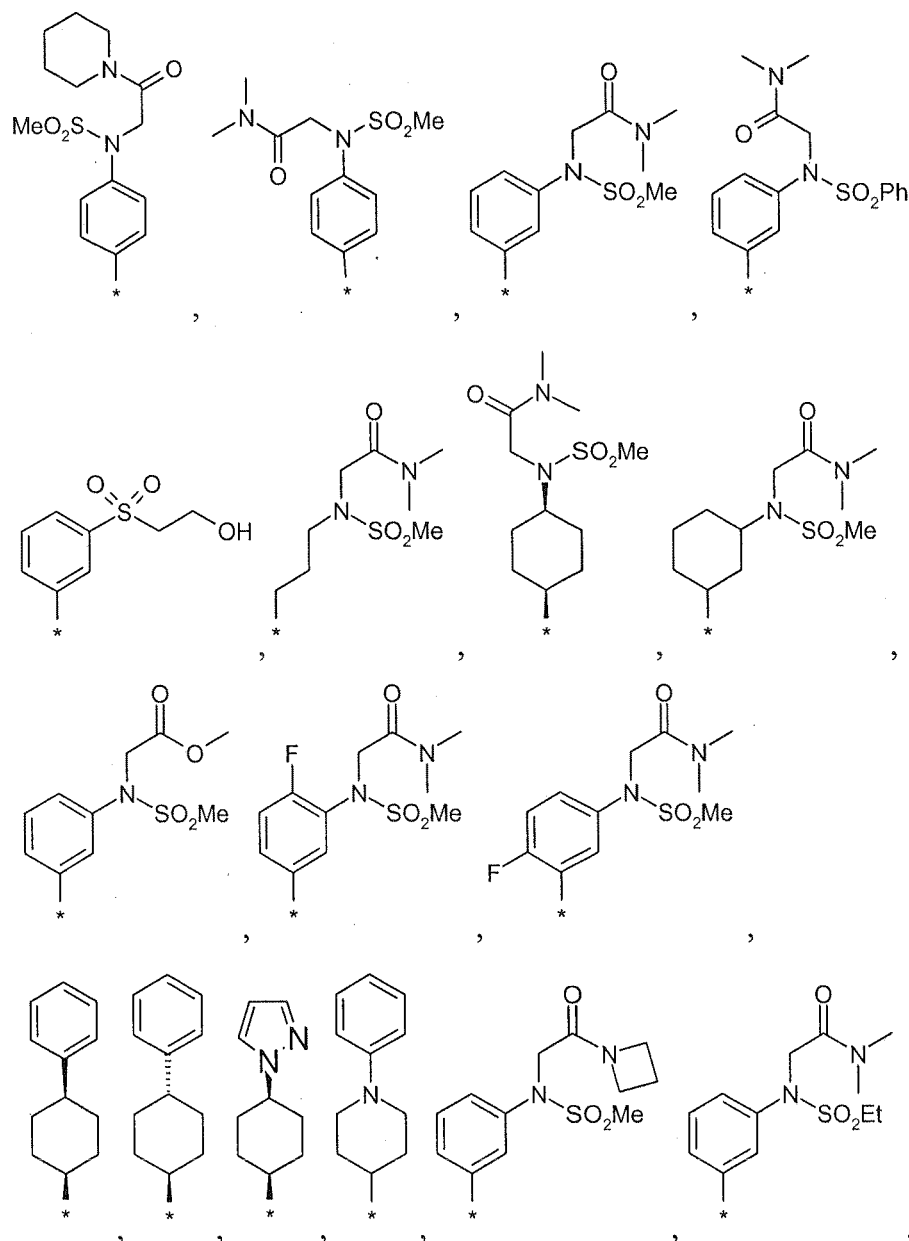
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n denotes 0 or 1;

R¹ denotes H;

30 **R²** denotes H;

wherein R^3 denotes a group selected from among



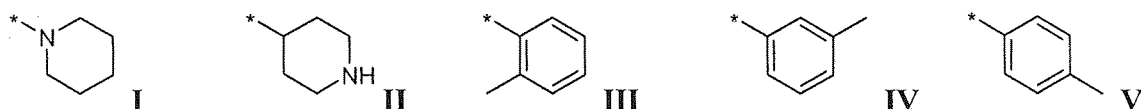
and wherein R^4 denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the
10 form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
as well as deuterated forms thereof.

TERMS AND DEFINITIONS USED

Unless otherwise stated, all the substituents are independent of one another. If for example there are a plurality of C₁₋₆-alkyl groups as substituents in one group, in the case of three substituents C₁₋₆-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule. Moreover, the atom of the substituent which follows the linking point is referred to as the atom in position number 1. Thus for example the groups N-piperidinyl (I), 4-piperidinyl (II), 2-tolyl (III), 3-tolyl (IV) and 4-tolyl (V) are shown as follows:



By the term "C₁₋₆-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C₁₋₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms.

Alkyl groups with 1 to 4 carbon atoms are preferred. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl or hexyl. The following abbreviations may optionally also be used for the above-mentioned groups: Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc.. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

By the term "C₁₋₆-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 6 carbon atoms and by the term

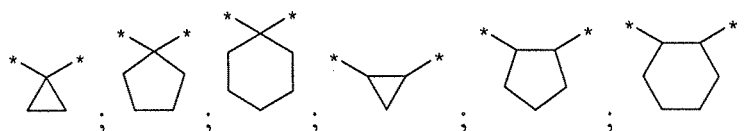
"C₁₋₄-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. Preferred are alkylene groups with 1 to 4 carbon atoms. Examples include:

methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene,

5 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene or hexylene. Unless stated otherwise, the definitions propylene, butylene, pentylene and hexylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

10

If the carbon chain is substituted by a group which together with one or two carbon atoms of the alkylene chain forms a carbocyclic ring with 3, 5 or 6 carbon atoms, the following examples of rings are also included:



15

By the term "C₂₋₆-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term "C₂₋₄-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms, provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are preferred. Examples include: ethenyl or vinyl, propenyl, butenyl, pentenyl or hexenyl. Unless stated otherwise, the definitions propenyl, butenyl, pentenyl and hexenyl include all the possible isomeric forms of the groups in question. Thus, for example, propenyl includes 1-propenyl and 2-propenyl, butenyl includes 1-, 2- and 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl etc.

25

By the term "C₂₋₆-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term "C₂₋₄-alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Alkynyl groups with 2 to 4 carbon

atoms are preferred. Examples include: ethynyl, propynyl, butynyl, pentynyl, or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1, 2- and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

By the term "C₂₋₆-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 6 carbon atoms and by the term "C₂₋₄-alkynylene" are meant branched and unbranched alkylene groups with 2 to 4 carbon atoms. Preferred are alkynylene groups with 2 to 4 carbon atoms. Examples include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene or hexynylene. Unless stated otherwise, the definitions propynylene, butynylene, pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1,1-dimethylethynylene, 1, 2-dimethylethynylene.

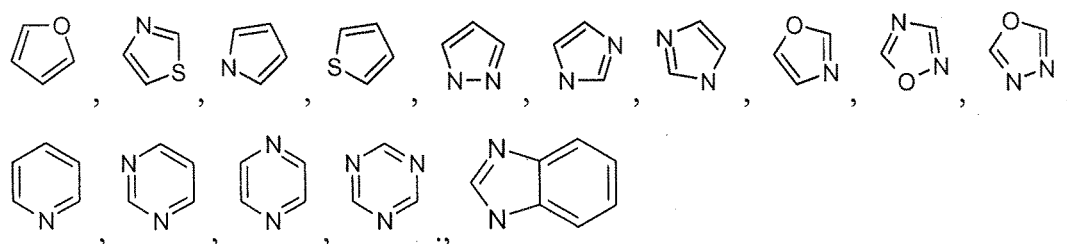
By the term "aryl" (including those which are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples include: phenyl or naphthyl, the preferred aryl group being phenyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "aryl-alkylene" or "C₆₋₁₀-aryl-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 6 carbon atoms, which are substituted by an aromatic ring system with 6 or 10 carbon atoms. Examples include: benzyl, 1- or 2-phenylethyl or 1- or 2-naphthylethyl. Unless otherwise

stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

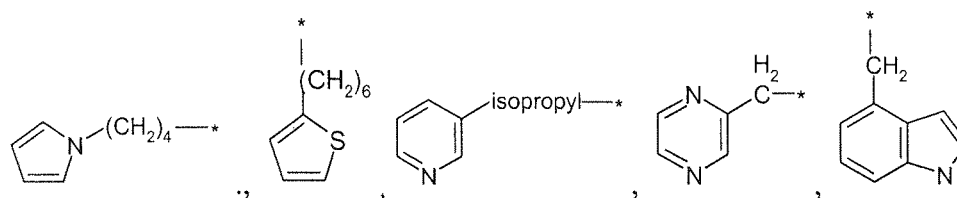
By the term "heteroaryl-alkylene" or " C_{5-10} -heteroaryl-alkylene" (including those which are part of other groups) are meant - even though they are already included under "aryl-alkylene" - branched and unbranched alkylene groups with 1 to 6 carbon atoms, which are substituted by a heteroaryl.

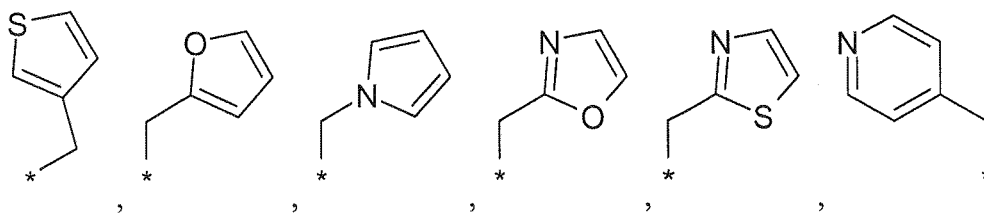
A heteroaryl of this kind includes five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. The following are examples of five- or six-membered heterocyclic aromatic groups or bicyclic heteroaryl rings:



Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

The following are examples of heteroaryl-alkylenes:





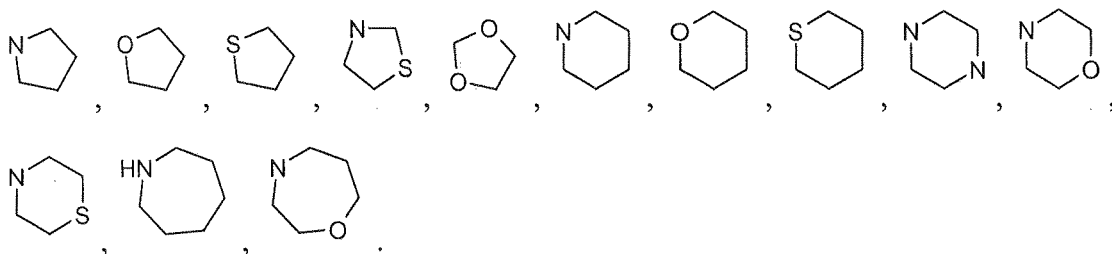
By the term "C₁₋₆-haloalkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms, which are substituted by one or more halogen atoms. By the term "C₁₋₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms, which are substituted by one or more halogen atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. Examples include: CF₃, CHF₂, CH₂F, CH₂CF₃.

By the term "C₃₋₈-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 8 carbon atoms. By the term "C₃₋₆-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Unless otherwise stated, the cyclic alkyl groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "C₅₋₈-cycloalkenyl" (including those which are part of other groups) are meant cyclic alkenyl groups with 5 to 8 carbon atoms. Examples include: cyclopentenyl, cyclohexenyl or cycloheptenyl. Unless otherwise stated, the cyclic alkenyl groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

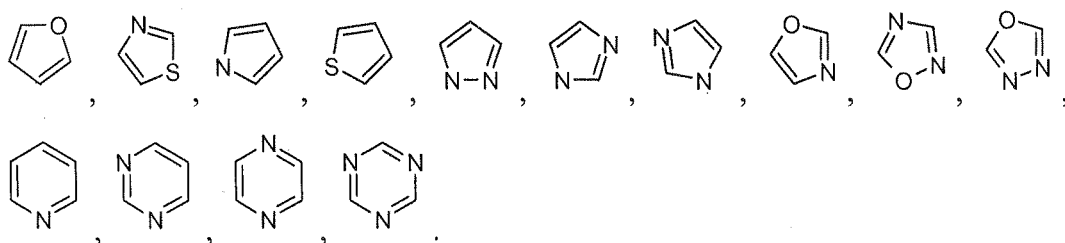
By the term "heterocycle" are meant five-, six- or seven-membered, saturated or unsaturated heterocyclic rings which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. Although included by

the term "heterocycles", the term "heterocyclic non-aromatic rings" refers to five-, six- or seven-membered unsaturated rings. Examples include:



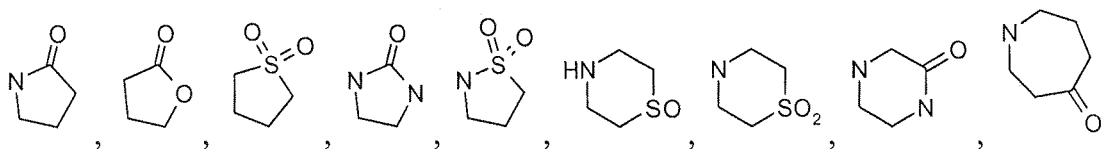
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Although included by the term "heterocycles", the term "heterocyclic aromatic rings" refers to five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. Examples of five- or six-membered heterocyclic aromatic groups include:



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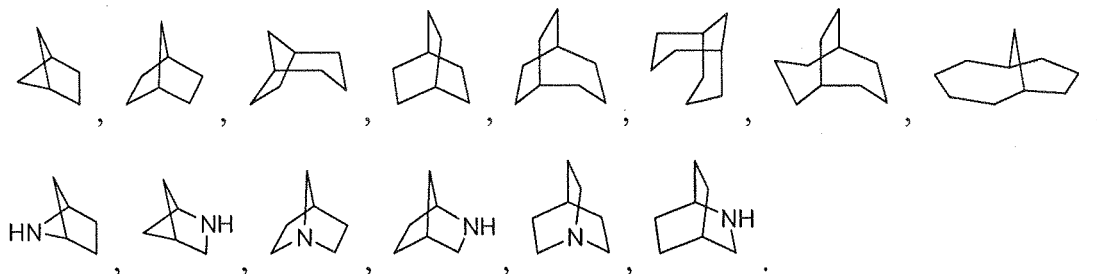
Unless otherwise mentioned, a heterocycle may be provided with a keto group. Examples include:



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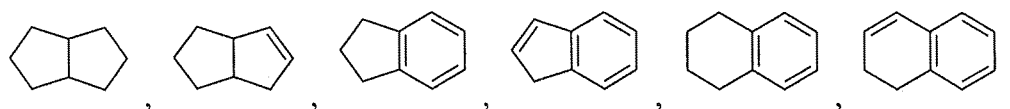
By the term "bicyclic rings" are meant eight-, nine- or ten-membered bicyclic rings which may optionally contain one or more heteroatoms, selected from among oxygen, sulphur

and nitrogen. The ring may be linked to the molecule through a carbon atom of the ring or through a nitrogen atom of the ring, if there is one. Examples include



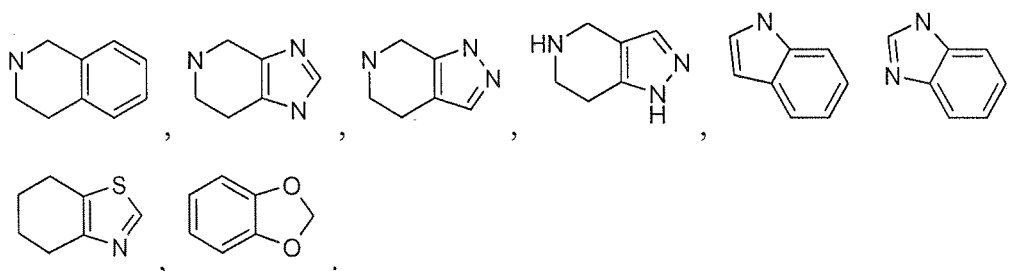
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Although included by the term "bicyclic rings", the term "fused bicyclic rings" denotes bicyclic rings wherein the bridge separating the rings denotes a direct single bond. The following are examples of a fused, bicyclic ring:



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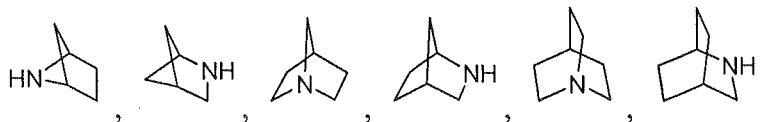
Although included by the term "bicyclic rings", the term "fused bicyclic heterorings" denotes bicyclic 5-10 membered heterorings which contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and wherein the bridge separating the rings denotes a direct single bond. Examples include pyrrolizine, indole, indolizine, isoindole, indazole, purine, quinoline, isoquinoline, benzimidazole, benzofuran, benzopyran, benzothiazole, benzothiazole, benzoisothiazole, pyridopyrimidine, pteridine, pyrimidopyrimidine,



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Although included by the term "bicyclic rings", the term "bicyclic heterocycles" denotes eight-, nine- or ten-membered bicyclic rings, which may contain one or more heteroatoms,

selected from among oxygen, sulphur and nitrogen. Examples of "bicyclic heterocycles" include:



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"Halogen" within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated to the contrary, fluorine, chlorine and bromine are regarded as preferred halogens.

- 10 Compounds of general formula **1** may have acid groups, mainly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula **1** may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as for example hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid)
- 15 or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine or triethanolamine, *inter alia*.

As mentioned hereinbefore, the compounds of formula **1** may be converted into the salts thereof, particularly for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula **1** with inorganic or organic acids. On the other hand, if R is hydrogen, the compound of formula **1** may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above-mentioned

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acids. The alkali and alkaline earth metal salts of the compound of formula I are preferably prepared using the alkali and alkaline earth metal hydroxides and hydrides thereof, of which the hydroxides and hydrides of the alkaline earth metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are particularly preferred.

5

If desired, the compounds of general formula (1) may be converted into the salts thereof, particularly, for pharmaceutical use, into the pharmacologically acceptable acid addition salts with an inorganic or organic acid. Suitable acids include for example succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic
10 acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid or citric acid. It is also possible to use mixtures of the above-mentioned acids.

Particularly preferred salts according to the invention are selected from among the chloride, bromide, iodide, hydrochloride, hydrobromide, hydriodide, hydrosulphate,
15 hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, and hydro-p-toluenesulphonate, sulphobenzoate, phosphate, isonicotinate, acetate, propionate, dihydrogen phosphate, palmitate, pivalate, furoate, preferably chloride, bromide, iodide, hydrochloride, hydrobromide, hydrosulphate, hydrophosphate,
20 hydrofumarate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate, hydro-p-toluenesulphonate and hydromethanesulphonate.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the
25 tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids - such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

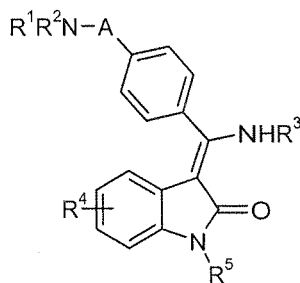
The compounds according to the invention may optionally occur as racemates, but they may also be obtained as pure enantiomers, i.e. in the (*R*) or (*S*) form. Preferred compounds are those which occur as racemates or as the (*S*) form.

- 5 The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids – such as
 10 for example oxalic, fumaric, diglycolic or methanesulphonic acid.

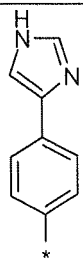
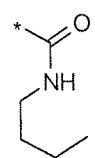
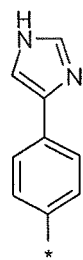
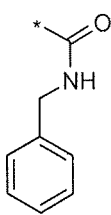
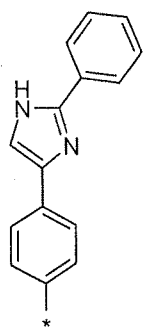
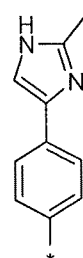
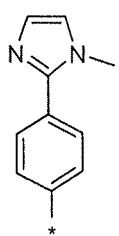
The Tables of Examples A and B that follow list compounds of formula **1** prepared according to the invention.

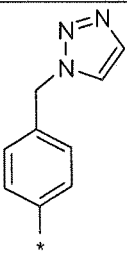
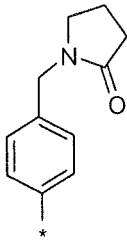
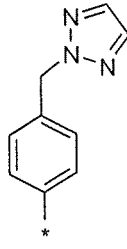
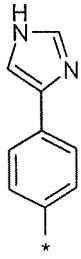
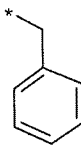
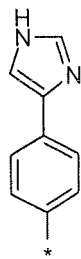
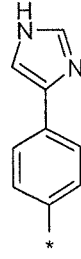
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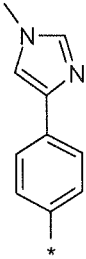
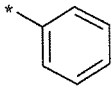
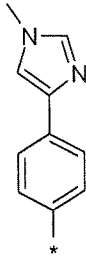
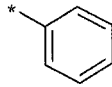
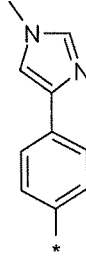
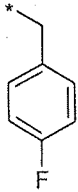
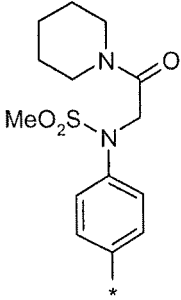
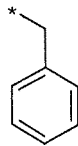
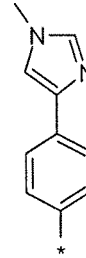
EXAMPLES A

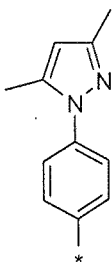
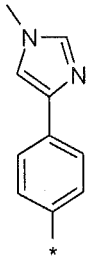
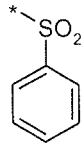
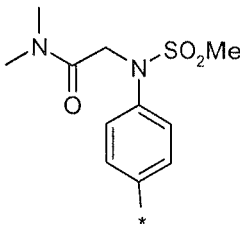
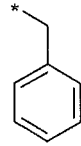
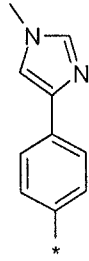
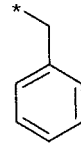
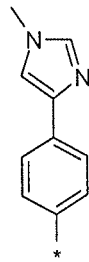
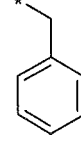


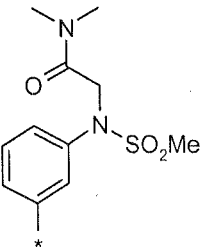
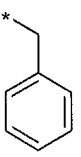
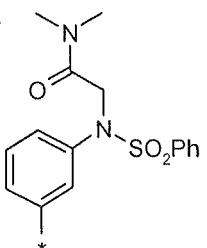
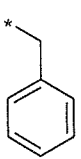
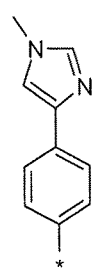
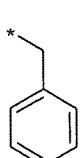
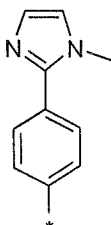
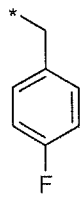
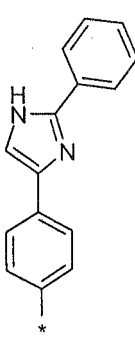
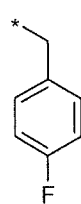
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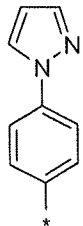
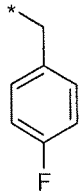
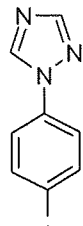
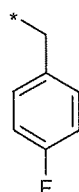
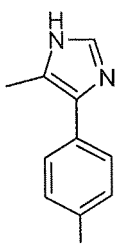
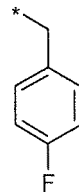
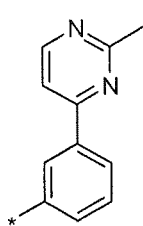
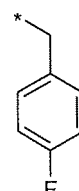
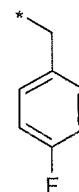
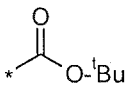
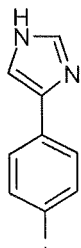
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
2.	H	H		H		CH ₂
3.	H	H		H		CH ₂
4.	H	H		H	Me	CH ₂
5.	H	H		H	Me	CH ₂
6.	H	H		H	Me	CH ₂

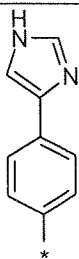
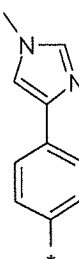
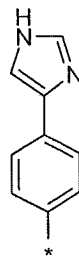
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
7.	H	H		H	Me	CH ₂
8.	H	H		H	Me	CH ₂
9.	H	H		H	Me	CH ₂
10.	H	H		H		CH ₂
11.	H	H		H		CH ₂
12.	H	H		H		CH ₂

#	R ¹	R ²	R ³	R ⁴	R ⁵	A
13.	H	H		H		CH ₂
14.	H	H		H		C=NH
15.	H	H		H		CH ₂
16.	H	H		H		CH ₂
17.	H	H		H		CH ₂

#	R ¹	R ²	R ³	R ⁴	R ⁵	A
18.	H	H		H		CH ₂
19.	H	H		H		CH ₂
20.	H	H		H		CH ₂
21.	H	H		H		CH ₂
22.	Et	Et		H		CH ₂

#	R ¹	R ²	R ³	R ⁴	R ⁵	A
23.	H	H		H		CH ₂
24.	H	H		H		CH ₂
25.	H	H		H		C=NH
26.	H	H		H		CH ₂
27.	H	H		H		CH ₂

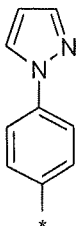
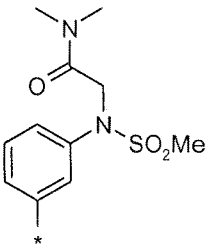
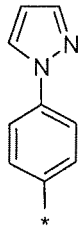
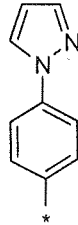
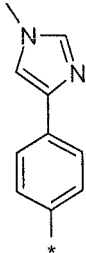
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
28.	H	H		H		CH ₂
29.	H	H		H		CH ₂
30.	H	H		H		CH ₂
31.	H	H		H		CH ₂
32.	H	H	H	H		CH ₂
33.	H	H	H	H	Me	CH ₂
34.		H		H	Me	CH ₂

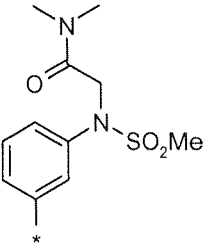
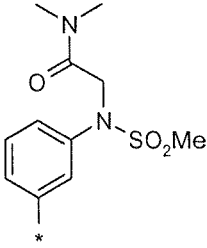
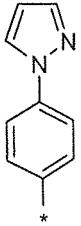
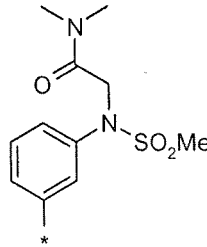
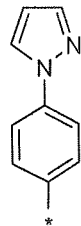
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
35.	H	H		H	Me	CH ₂
36.	H	H		H	Me	CH ₂
37.	H	H		H	Me	CH ₂

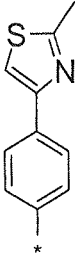
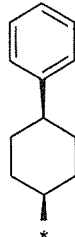
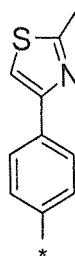
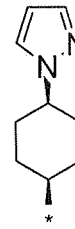
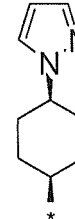
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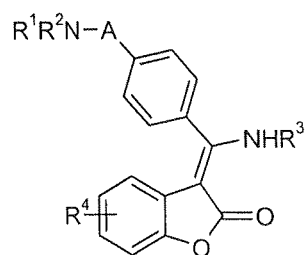
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
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#	R ¹	R ²	R ³	R ⁴	R ⁵	A
37a.	H	H		H	Me	CH ₂
37b.	H	H		H	Me	CH ₂
37c.	H	H		7-CF ₃	Me	CH ₂
37d.	H	H		H	cBu	CH ₂
37e.	H	H		H	cBu	CH ₂

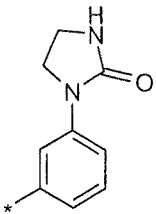
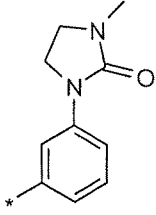
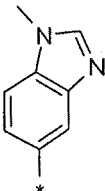
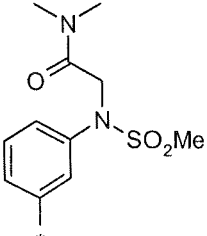
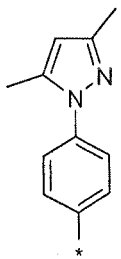
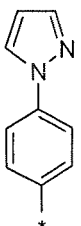
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
37f.	H	H		H	cBu	CH ₂
37g	H	H		H	CH ₂ CF ₃	CH ₂
37h	H	H		H	CH ₂ CF ₃	CH ₂
37i	H	H		H	CONHCH ₂ P _h	CH ₂
37j	H	H		H	CONHCH ₂ P _h	CH ₂

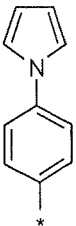
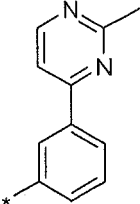
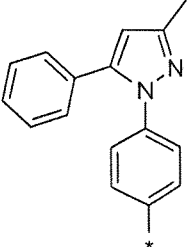
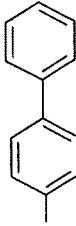
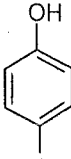
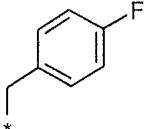
#	R ¹	R ²	R ³	R ⁴	R ⁵	A
37k	H	H		H	CH ₂ CF ₃	CH ₂
37l	H	H		H	CH ₂ CF ₃	CH ₂
37m	H	H		H	cBu	CH ₂
37n	H	H		H	CH ₂ CF ₃	CH ₂
37o	H	H		H	cBu	CH ₂

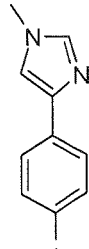
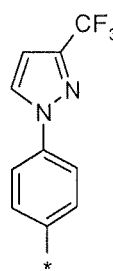
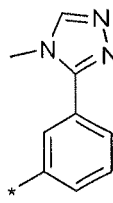
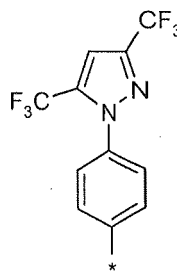
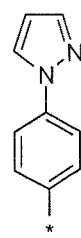
EXAMPLES B

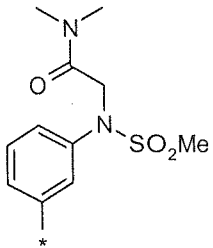
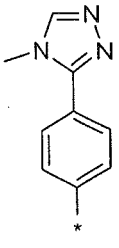
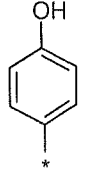
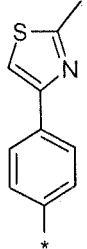
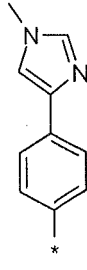


#	R ¹	R ²	R ³	R ⁴	A
38.	H	H		H	C=NH
39.	H	H		H	CH ₂
40.	H	H		H	
41.	H	H		H	CH ₂
42.	H	H		H	CH ₂

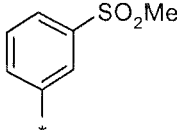
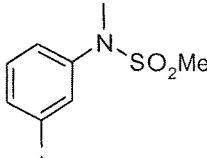
#	R ¹	R ²	R ³	R ⁴	A
43.	H	H	H	H	CH ₂
44.	H	H		H	CH ₂
45.	H	H		H	CH ₂
46.	H	H		H	CH ₂
47.	H	H		H	CH ₂
48.	H	H		H	CH ₂
49.	H	H		H	CH ₂

#	R ¹	R ²	R ³	R ⁴	A
50.	H	H		H	CH ₂
51.	H	H		H	CH ₂
52.	H	H		H	CH ₂
53.	H	H		H	CH ₂
54.	H	H		H	CH ₂
55.	H	H		H	CH ₂

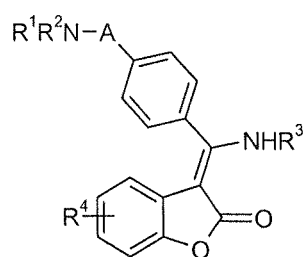
#	R ¹	R ²	R ³	R ⁴	A
56.	H	H		H	CMe ₂
57.	H	H		H	CH ₂
58.	H	H		H	CH ₂
59.	H	H		H	CH ₂
60.	H	H		H	
61.	H	H	H	H	
62.	H	H		H	CH ₂

#	R ¹	R ²	R ³	R ⁴	A
63.	H	H		H	CH ₂
64.	H	H		H	
65.	H	H	OH	H	
66.	H	H		H	CH ₂
67.	H	H		H	
68.	H	H		H	CH ₂
69.	H	H		H	CH ₂
70.	H	H	CH ₂ CF ₃	H	CH ₂

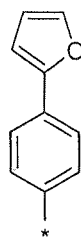
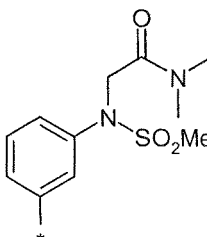
67

71.	H	H		H	CH ₂
72.	H	H		H	CH ₂

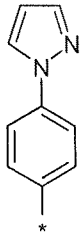
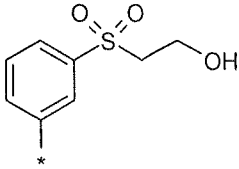
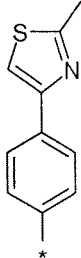
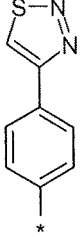
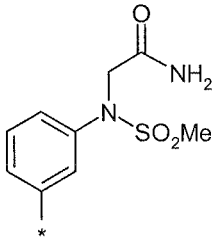
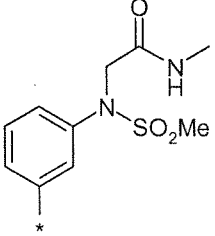
EXAMPLES C

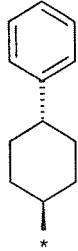
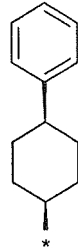
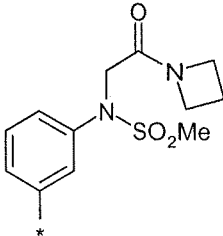
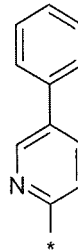
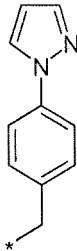


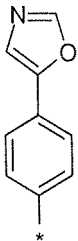
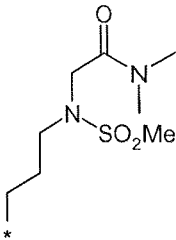
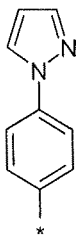
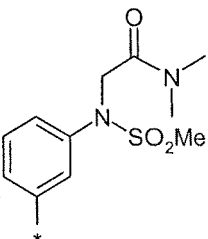
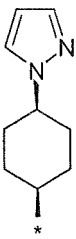
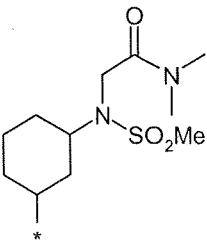
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#	R ¹	R ²	R ³	R ⁴	A
73.	H	H		H	CH ₂
74.	H	H		H	CMe ₂

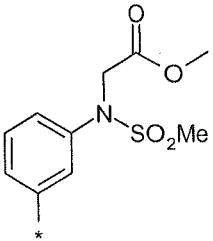
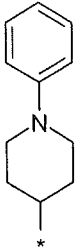
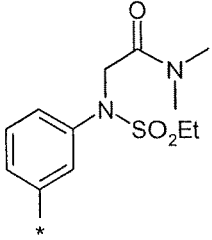
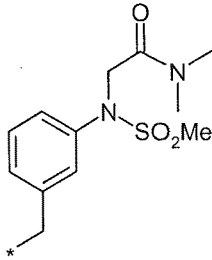
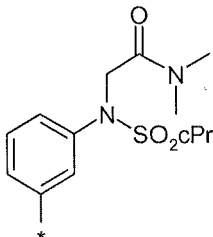
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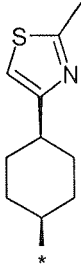
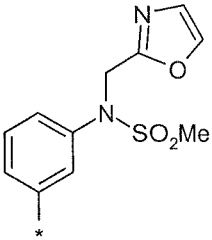
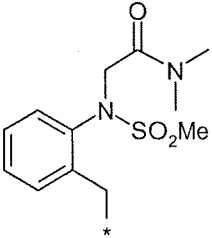
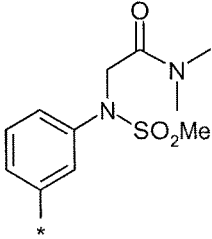
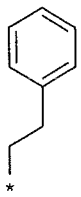
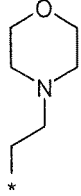
75.	H	H		H	CMe ₂
76.	H	H		H	CH ₂
77.	H	H		H	CMe ₂
78.	H	H		H	CMe ₂
79.	H	H		H	CH ₂
80.	H	H		H	CH ₂

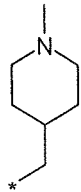
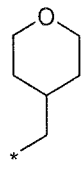
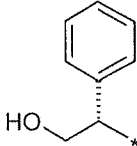
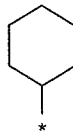
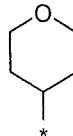
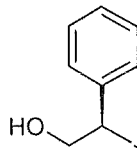
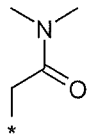
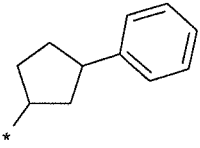
81.	H	H		H	CH ₂
82.	H	H		H	CH ₂
83.	H	H		H	CH ₂
84.	H	H		H	CH ₂
85.	H	H		H	CH ₂

86.	H	H		H	CH ₂
87.	H	H		H	CH ₂
88.	H	H		H	CD ₂
89.	H	H		H	CD ₂
90.	H	H		H	CH ₂
91.	H	H		H	CH ₂

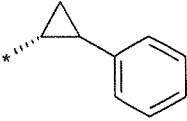
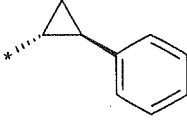
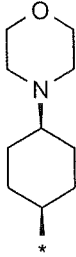
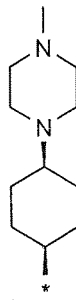
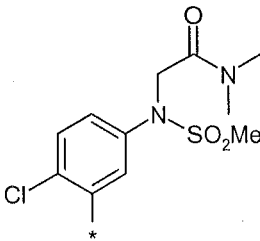
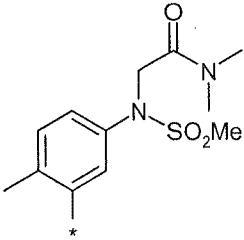
71

92.	H	H		H	CH ₂
93.	H	H		H	CH ₂
94.	H	H		H	CH ₂
95.	H	H		H	CH ₂
96.	H	H		H	CH ₂

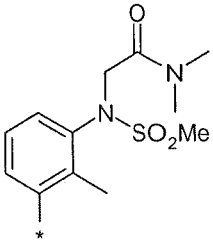
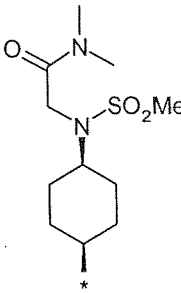
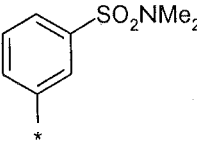
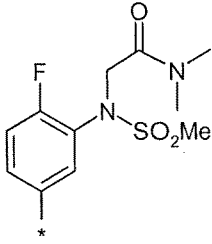
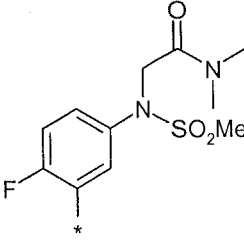
97.	H	H		H	CH ₂
98.	H	H		H	CH ₂
99.	H	H		H	CH ₂
100.	CHO	H		H	CH ₂
104.	H	H		H	CH ₂
105.	H	H		H	CH ₂

106.	H	H		H	CH ₂
107.	H	H		H	CH ₂
108.	H	H		H	CH ₂
109.	H	H		H	CH ₂
110.	H	H		H	CH ₂
111.	H	H		H	CH ₂
112.	H	H		H	CH ₂
113.	H	H		H	CH ₂
114.	H	H		H	CH ₂

74

115.	H	H		H	CH ₂
116.	H	H		H	CH ₂
117.	H	H		H	CH ₂
118.	H	H		H	CH ₂
119.	H	H		H	CH ₂
120.	H	H		H	CH ₂

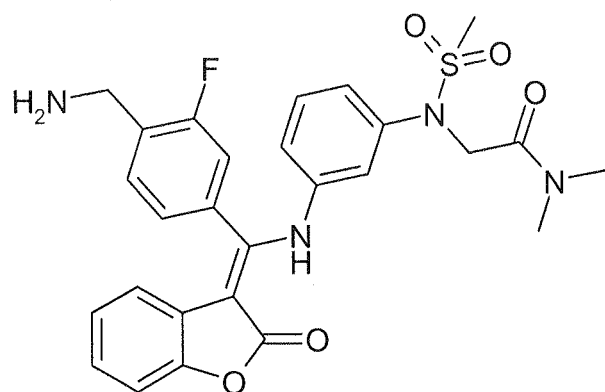
75

121.	H	H		H	CH ₂
122.	H	H		H	CH ₂
123.	H	H		H	CH ₂
124.	H	H		H	CH ₂
125.	H	H		H	CH ₂

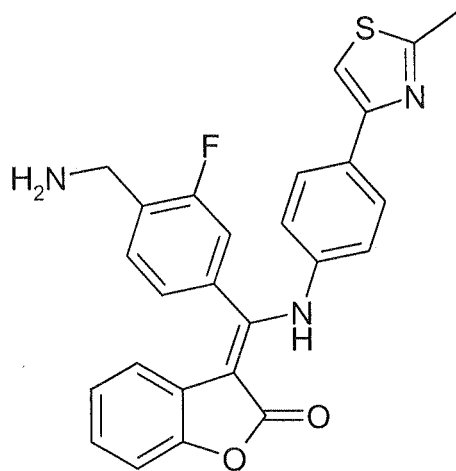
EXAMPLES D

Other Examples according to the invention are as follows:

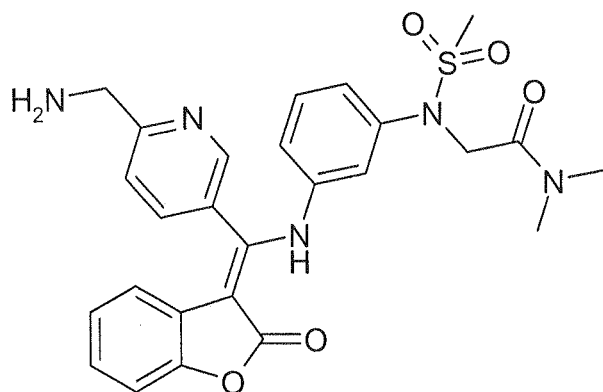
5 Example 101



Example 102



Example 103



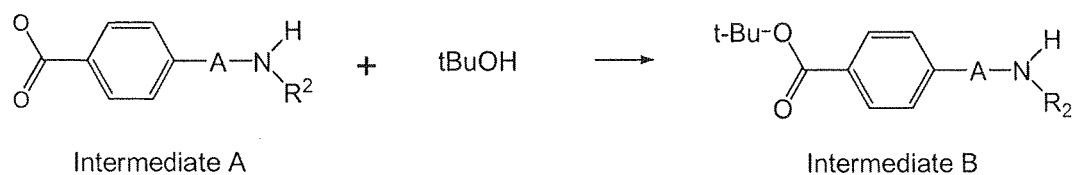
5

General synthesis scheme 1 is shown below, according to which the compounds of formula 1 according to the invention (coumaranones and indolinones) may be prepared. Instead of the allyloxycarbonyl protecting group used in Scheme 1 to protect the amino function it is also possible to use other protecting groups, preferably the tert-butyloxycarbonyl

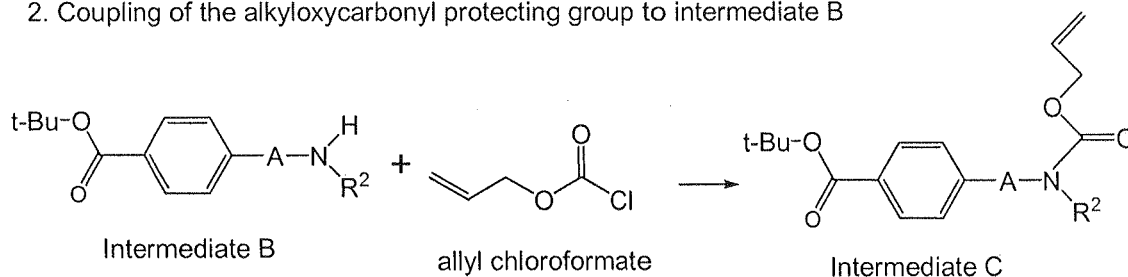
10 protecting group (BOC protecting group) .

Synthesis Scheme 1

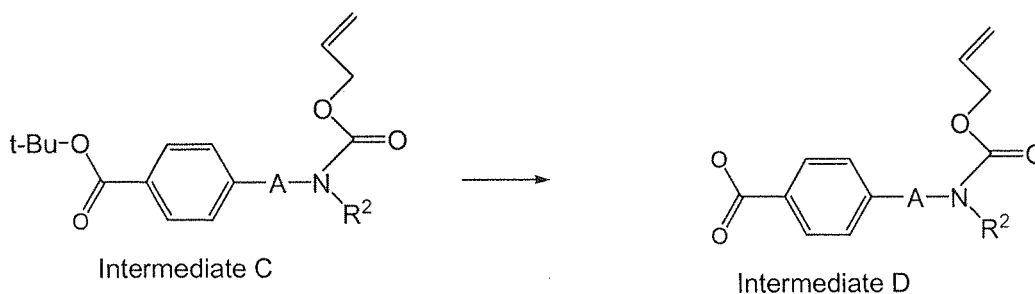
1. Coupling of the tBu-O protecting group to the substituted benzoic acid



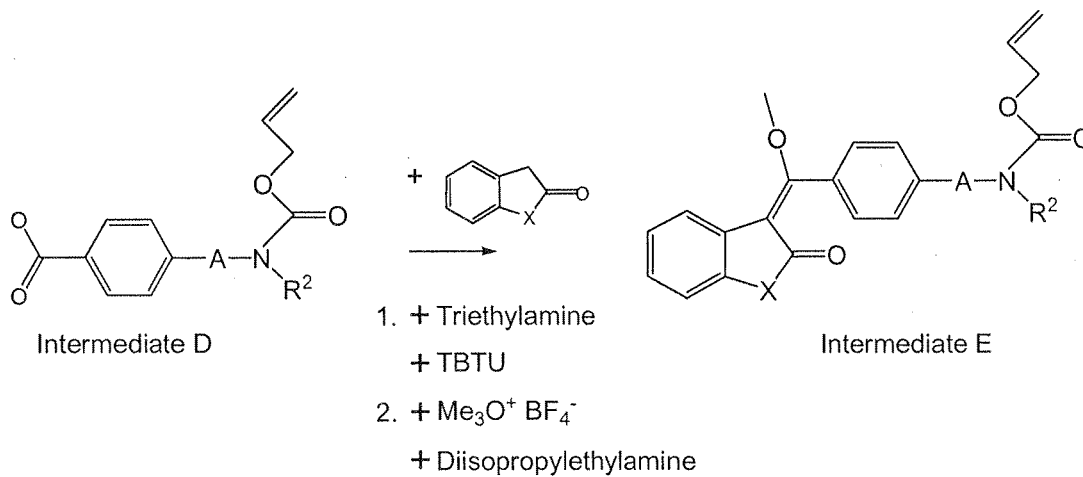
2. Coupling of the alkyloxycarbonyl protecting group to intermediate B

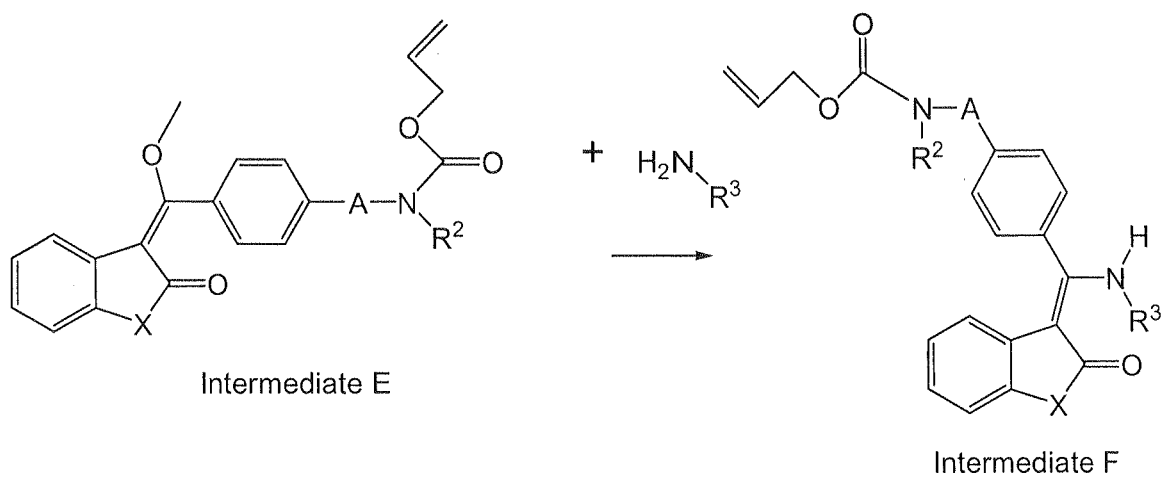


3. Cleaving of the tBu-O protecting group

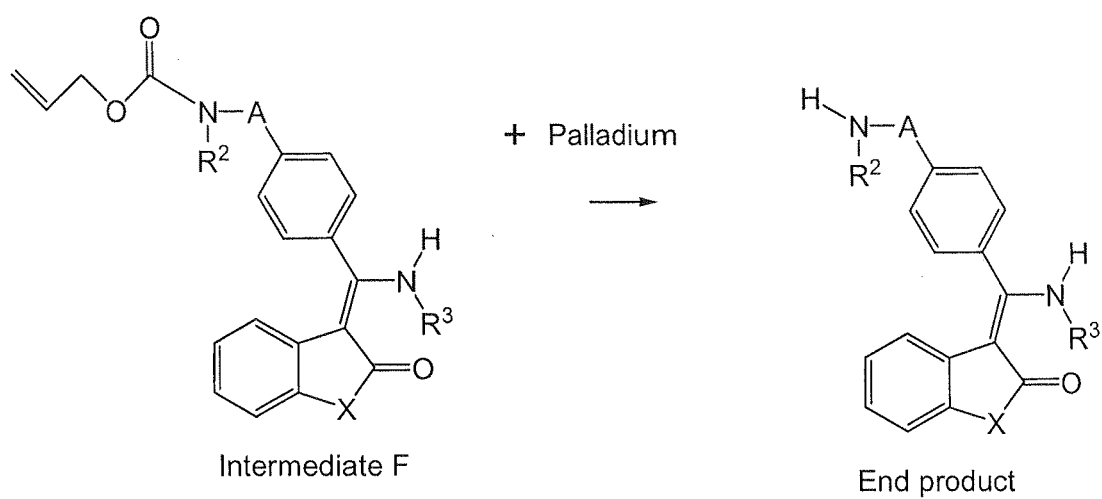


4. Coupling of the intermediate D to coumaranone or indolinone

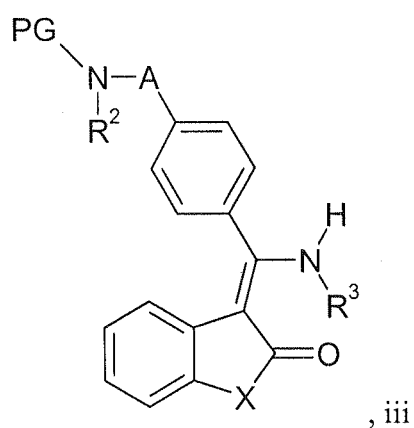
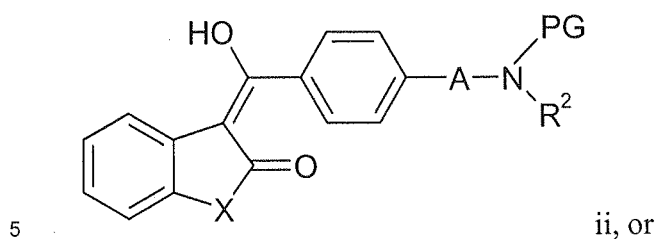
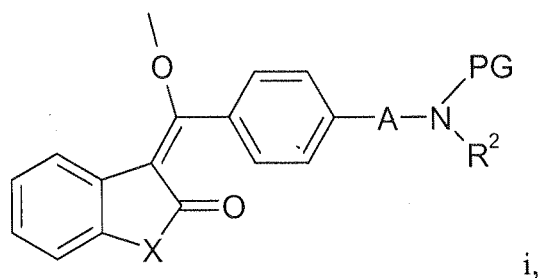


5. Coupling of the intermediate E to an R³-substituted amine

6. Cleaving of the allyloxycarbonyl protecting group from intermediate F



The present invention further relates to all intermediate products of the process according to Scheme 1, particularly the intermediate products according to formulae i, ii or iii



wherein X, A, R² and R³ have the meanings given above and PG (=protective group) is hydrogen or a suitable protecting group, preferably the allyloxycarbonyl protecting group or the tert-butyloxycarbonyl protecting group.

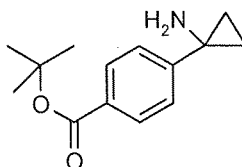
10

The following are illustrations of methods of synthesis for preparing compounds of formula 1 according to synthesis scheme 1 above.

EXAMPLE 40

1. 3-{[4-(1-AMINO-CYCLOPROPYL)-PHENYL]-[4-(1-METHYL-1H-IMIDAZOL-
5 4-YL)-PHENYLAMINO]-METHYLENE}-3H-BENZOFURAN-2-ONE (END
PRODUCT)

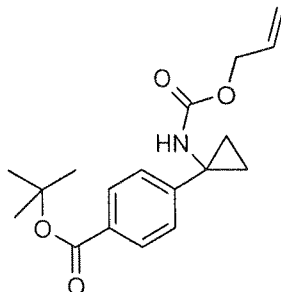
1.1 TERT-BUTYL 4-(1-AMINO-CYCLOPROPYL)-BENZOATE (INTERMEDIATE
B)



10

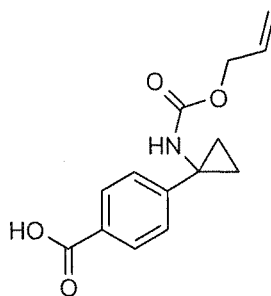
50 ml of a 2 M lithium isopropoxide solution in THF were placed under an argon
atmosphere and 13.4 g anhydrous lithium iodide were added thereto. After 15 min 45 ml of
a 1 M methyltitanium isopropoxide solution in THF was added. Then the mixture was
15 combined with 8.1 g tert.butyl 4-cyanobenzoate and stirred for 10 min. Then within 60 min
47.3 ml of a 15% diethylzinc solution in hexane was added thereto and the mixture was
stirred for 12 h at RT. After hydrolysis with 20 ml water it was stirred for a further 30 min,
filtered off and washed 3x with 100 ml ether. After extraction of the organic phase with
water the mixture was evaporated down with silica gel and the substance was
20 chromatographed with dichloromethane/methanol 98:2 at 20 ml/min on silica gel 70.
Residue: 3 g oil.

1.2 TERT-BUTYL 4-(1-ALLYLOXYCARBONYLAMINO-CYCLOPROPYL)-
BENZOATE (INTERMEDIATE C)



- 5 3 g tert.butyl 4-(1-amino-cyclopropyl)-benzoate were placed in 30 ml dichloromethane and 1.8 ml pyridine. The solution was cooled to 0°C and 1.2 ml allyl chloroformate (dissolved in 5 ml dichloromethane) were added dropwise at 0-5°C. The mixture was left to react for 30 min at 0°C and 2 h at RT. The solution was combined with silica gel and evaporated down to the residue. This was chromatographed with dichloromethane on silica gel 70.
- 10 Yield: 1.46 g oil.

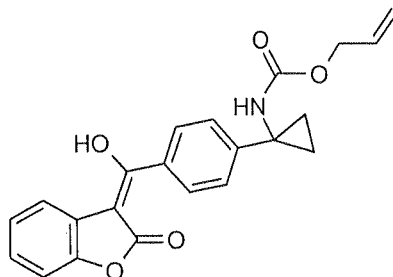
1.3 4-(1-ALLYLOXYCARBONYLAMINO-CYCLOPROPYL)-BENZOIC ACID



15

- A solution of 1.46 g tert.butyl 4-(1-allyloxycarbonylamino-cyclopropyl)-benzoate in 10 ml acetonitrile were combined with 1 g montmorillonite and refluxed for 3 h. Then more montmorillonite was added and the mixture was boiled for 4 h. The suspension was filtered hot, the inorganic material was extracted 3x with hot acetonitrile and filtered off, the
- 20 acetonitrile solutions were combined and evaporated down. Residue: 0.8 g crystals.

1.4 ALLYL (1-{4-[HYDROXY-(2-OXO-BENZOFURAN-3-YLIDENE)-METHYL]-PHENYL}-CYCLOPROPYL)-CARBAMATE (INTERMEDIATE D)

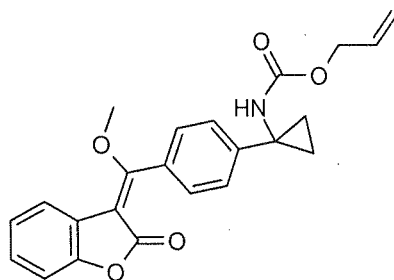


5

0.8 g 4-(1-allyloxycarbonylamino-cyclopropyl)-benzoic acid and 0.585 ml triethylamine were dissolved in 10 ml anhydrous DMF and combined with 1.16 g TBTU, stirred for 15 min at RT, then combined with 0.4 g coumaranone and stirred for a further 10 min. While cooling with the ice bath, 0.42 g NaH were added batchwise as a 60% suspension in white oil, the mixture was stirred for 2 h at RT and once the reaction had ended the mixture was diluted with water to a total volume of approx. 150 ml. The mixture was acidified with 2 N acetic acid. The crystals were suction filtered and washed with water. Yield: 1.1 g solid with a melting point 125-126°C.

15

1.5 ALLYL (1-{4-[METHOXY-(2-OXO-BENZOFURAN-3-YLIDEN)-METHYL]-PHENYL}-CYCLOPROPYL)-CARBAMATE (INTERMEDIATE E)



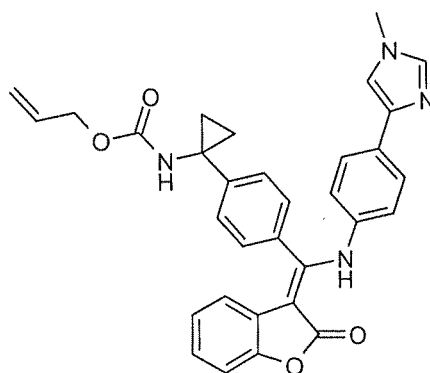
1 g of allyl (1-{4-[Hydroxy-(2-oxo-benzofuran-3-ylidene)-methyl]-phenyl}-cyclopropyl)-carbamate, 0.78 g trimethyloxonium-tetrafluoroborate (Meerwein salt) and 1 ml diisopropyl-ethylamine (Hünig base) were refluxed in 20 ml dichloromethane for 2 h,

20

another 1 ml Hünig base and 0.5 g Meerwein salt were added and the mixture was refluxed again for 2 h. After cooling the mixture was extracted 3x with water, the organic phase was dried on MgSO₄ and evaporated down to the residue. Yield: 1.05 g crude.

5

1.6 ALLYL (1-{4-[[4-(1-METHYL-1H-IMIDAZOL-4-YL)-PHENYLAMINO]-(2-OXO-BENZOFURAN-3-YLIDENE)-METHYL]-PHENYL}-CYCLOPROPYL)-CARBAMATE (INTERMEDIATE F)



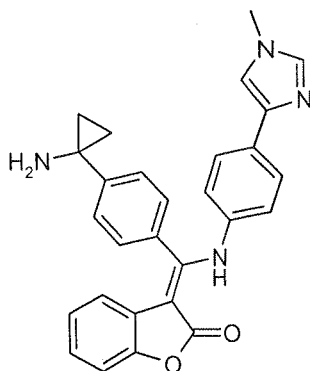
10

1.05 g allyl (1-{4-[methoxy-(2-oxo-benzofuran-3-ylidene)-methyl]-phenyl}-cyclopropyl)-carbamate and 0.47 g 4-(4-amino-phenyl)-1-methyl-imidazole in 3 ml DMPU were reacted in the microwave reactor at 180°C. After cooling the mixture was diluted to 150 ml with ethyl acetate, extracted 2x with water, the organic phase was dried on MgSO₄ and

15 evaporated down to the residue with silica gel. The substance was chromatographed with dichloromethane/methanol 97:3 on silica gel 70 at a flow rate of 30 ml/min.

Residue: 0.6 g yellow oil.

1.7 3-{[4-(1-AMINO-CYCLOPROPYL)-PHENYL]-[4-(1-METHYL-1H-IMIDAZOL-4-YL)-PHENYLAMINO]-METHYLENE}-3H-BENZOFURAN-2-ONE (END PRODUCT)



- 5 0.58 g allyl (1-{4-[[4-(1-methyl-1H-imidazol-4-yl)-phenylamino]-(2-oxo-benzofuran-3-ylidene)-methyl]-phenyl}-cyclopropyl)-carbamate were dissolved in 20 ml dichloromethane. The solution was freed from oxygen using argon. Then at RT 0.52 ml diethylamine and 0.058 g tetrakis-triphenylphosphine-palladium(0) were added. The mixture was stirred for 2 h at RT, the suspension was evaporated down with silica gel and
- 10 chromatographed with dichloromethane / methanol 97:3 on silica gel 70 at a flow rate of 30 ml/min. The clean fractions were combined, evaporated down to the residue, dissolved in dichloromethane, filtered and combined with diisopropylether. The dichloromethane was distilled off, the crystals formed were suction filtered and washed with diisopropylether. Yield: 0.26 g yellow crystals, melting point 190-191°C, as base.
- 15 R_f value: 0.51 (dichloromethane/methanol 9:1).

The following compounds were prepared analogously to synthesis scheme 1 or to Ex. 40:

Example	salt form	melting point (°C)
20 60	x HCl	> 250
61	x HCl	185-187
64	x HCl	261-262
65	x HCl	210-211

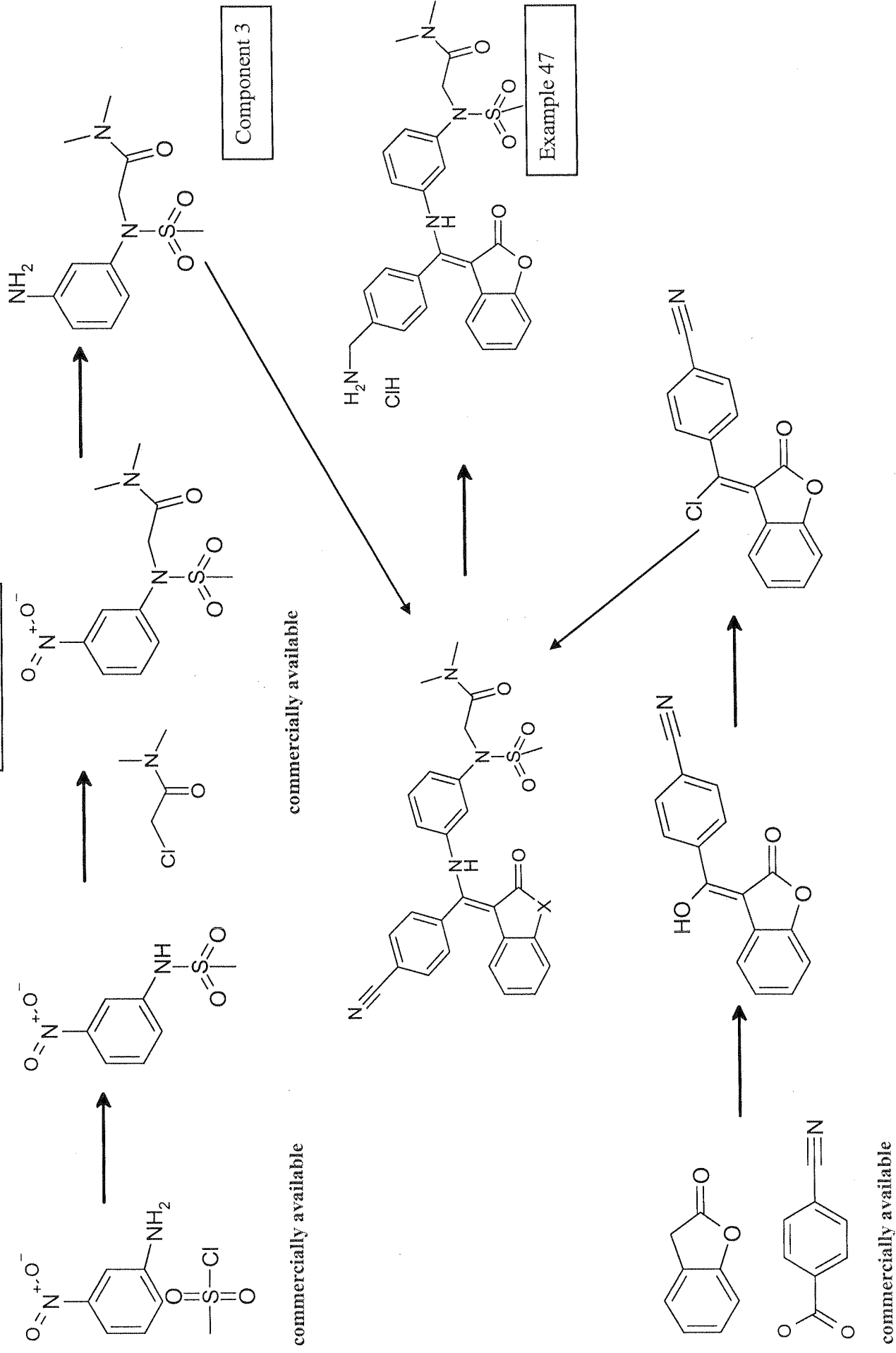
	67	x HCl	254-255
	74	x HCl	285-286
	77	x HCl	275-276
	78	x HCl	214-216
5	37k	x HCl	263-265
	37m	x HCl	> 270
	68	x HCl	286-287 decomp.
	97	x HCl	234-235
	102	base	196-197

10

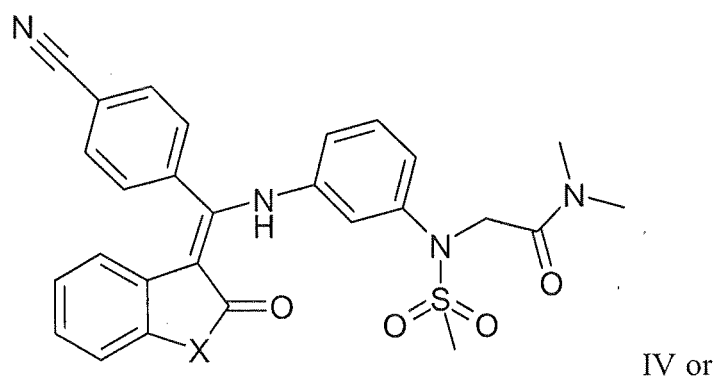
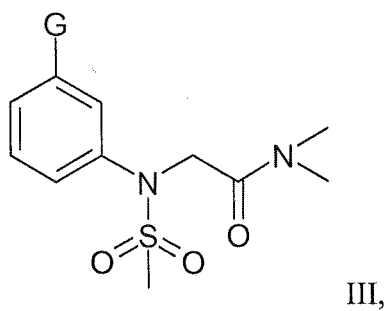
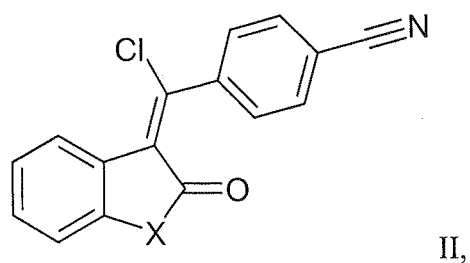
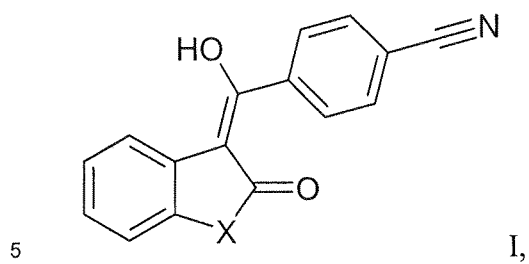
Scheme 2 shows the method of preparation for synthesising the compound according to Ex. 47. The majority of the compounds of formula 1 according to the invention (coumaranones and indolinones) may also be prepared analogously to this preparation method according to Scheme 2, particularly the compounds according to the invention

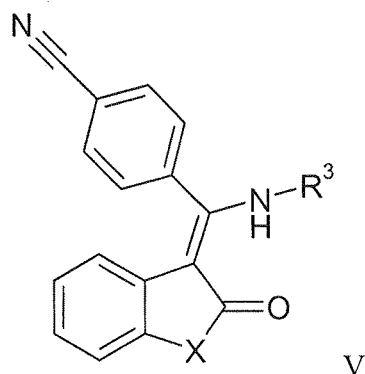
15 mentioned on the following pages.

Scheme 2



The present invention further relates to all the intermediate products of the process according to Scheme 2, particularly the intermediate products according to formulae I, II, III, IV or V





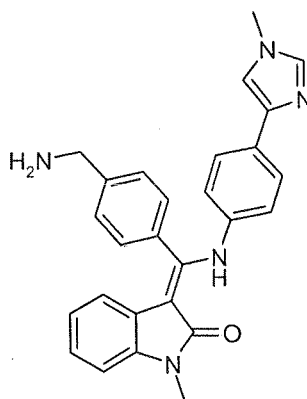
wherein G denotes NO₂ or NH₂ and wherein X and R³ have the meanings given above.

- 5 The methods of synthesising a number of example compounds are described hereinafter; they are substantially similar to synthesis scheme 2 described above.

EXAMPLE 36

10

2. 3-{{(4-AMINOMETHYL-PHENYL)-[4-(1-METHYL-1H-IMIDAZOL-4-YL)-PHENYLAMINO]-METHYLENE}-1-METHYL-1,3-DIHYDRO-INDOL-2-ONE



- 15 Starting from 4-cyano-benzoic acid, synthesis was carried out analogously to Example 40. Only the final step differed as follows. 6.15 g of 3-{{(4-cyano-phenyl)-[4-(1-methyl-1H-imidazol-4-yl)-phenylamino]-methylene}-1-methyl-1,3-dihydro-indol-2-one were dissolved in 200 ml of methanolic ammonia and tetrahydrofuran and hydrogenated with 5

g Raney nickel at RT and under a pressure of 50 psi. After about 10 h the catalyst was removed by suction filtering and the filtrate was again filtered through a glass filter, evaporated down and the crystalline residue was filtered with diisopropylether suction. The crystals were suspended in 400 ml methanol, adjusted to pH 1 with 10% ethanolic
 5 hydrochloric acid and heated to boiling temperature. The mixture was filtered, the filtrate was evaporated down to a residual volume of about 100 ml and combined with 300 ml ethanol. After further evaporation to approx. 100 ml residual volume the substance crystallised out. After cooling it was suction filtered and washed with ice-cold ethanol. Yield: 6.15 yellow crystals, melting point > 300°C. R_f value = 0.32
 10 (dichloromethane/methanol/ammonia 85:15:1).

The following were prepared analogously:

	Example	salt form	melting point(°C)	R _f value
	1	base		
15	2	x TFA		0.38 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
	3	x TFA		0.5 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 4:1:0.1)
	4	base		0.34 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
	5	x TFA		0.25 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 4:1:0.1)
	6	base		0.27 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
20	7	base		0.54 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 4:1:0.1)
	8	base		0.33 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
	9	base		0.21 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
	10	x HCl	294 decomp.	
	11	base		0.27 (CH ₂ Cl ₂ /CH ₃ OH/NH ₃ 9:1:0.1)
25	12	x HCl	272	
	13	x HCl	> 250	
	15	x HCl	278	
	16	x HCl	214-215 decomp.	
	17	x HCl	> 245 decomp.	
30	18	base	225 decomp.	
	19	x HCl	295-296	

	20	x HCl	265-267
	21	x HCl	274-275
	22	x HCl	259-260 decomp.
	23	x HCl	281 decomp.
5	24	x HCl	245-246 decomp.
	26	x HCl	> 260 decomp.
	27	base	230-232
	28	base	153-155
	29	base	168-171
10	30	base	233-238
	31	base	194-197
	32	x HCl	210-212
	33	base	157-159
	34	base	229
15	35	base	228
	36	base	214-217
	37a	base	204-206
	37b	base	214-216
	37c	base	186-188
20	37d	base	227-229
	37e	base	263-265
	37f	base	198-200
	37g	x HCl	255-256
	37h	x HCl	284
25	37i	x HCl	251-252
	37j	x HCl	226-227
	37l	base	172-173
	37n	x HCl	195-198
	37o	x HCl	297-298
30	39	x HCl	> 290
	41	base	167-169

	42	base	201-203
	43	x HCl	95-97 decomp.
	44	base	222-224
	45	base	208-210
5	46	base	186-188
	47	x HCl	274
	48	x HCl	186-188
	49	base	171-173
	50	base	164-166
10	51	base	177-179
	52	x HCl	232-233
	53	x HCl	> 285
	54	x HCl	245-247
	55	base	149-151
15	57	base	161-164
	58	base	168-172
	59	base	153-156
	62	x HCl	285-286
	63	x HCl	289-290
20	66	base	215-217
	69	base	204-205
	70	x HCl	285-286
	71	x HCl	> 290
	72	x HCl	289
25	73	base	163-166
	76	x HCl	288
	79	base	182-184
	80	base	135-137
	81	x HCl	294-295
30	82	x HCl	254-255
	83	x HCl	> 275

	84	x HCl	215-220
	85	base	135-137
	86	x HCl	207
	87	x HCl	253-254
5	88	x HCl	> 290
	89	x HCl	> 270
	90	x HCl	85-88 (amorphous?)
	91	x HCl	283-284
	92	x TFA	amorphous
10	93	base	161-162
	94	x HCl	271-272
	95	x HCl	188
	96	x HCl	268-269
	98	x HCl	241 decomposition
15	99	x HCl	196
	100	-	140
	101	x HCl	253-254
	103	x TFA	amorphous

20

	Example #	m+H	Rf value	retention time [min]
	104		0.5	
	105	380		
25	106		0.5	
	107		0.4	
	108		0.5	
	109		0.2	
	110		0.4	
30	111		0.5	
	112		0.3	

	113	352	
	114		0.3
	115		0.6
	116		0.4
5	117		0.4
	118		0.2
	119		0.3
	120		0.3
	121		0.3
10	122		1.7
	123		0.6
	124	539	
	125		0.2

15 METHOD OF CARRYING OUT THIN LAYER CHROMATOGRAPHY TO
DETERMINE THE RF VALUES:

The solid phase used was silica gel 60 F254 (made by Merck) and the liquid phase - unless otherwise specified - was a 9 : 1 : 0.1 mixture of dichloromethane: methanol: ammonia.

20

Chromolith method:

HPLC-MS-1 Waters ZMD, Alliance 2690/2695 HPLC, Waters 2700 Autosampler, Waters 996/2996 diode array detector

25

The mobile phase used was:

A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

30	time in min	%A	%B	flow rate in ml/min
	0.00	95	5	2.00

0.10	95	5	2.00
2.10	2	98	2.00
3.00	2	98	2.00
3.25	95	5	2.00

5

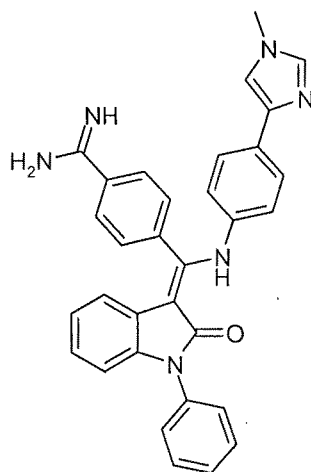
The stationary phase used was a Merck Chromolith™ SpeedROD RP-18e column, 4.6 mm x 50 mm (column temperature: constant at 25°C).

The diode array detection took place in a wavelength range of 210-400 nm.

10

15 **Example 14**

3. 4-[[4-(1-METHYL-1H-IMIDAZOL-4-YL)-PHENYLAMINO]-(2-OXO-1-PHENYL-1,2-DIHYDRO-INDOL-3-YLIDENE)-METHYL]-BENZAMIDINE



20

Starting from 4-cyano-benzoic acid synthesis was carried out analogously to Example 40. Only the last step differed as follows. 0.6 g 3-{{(4-cyano-phenyl)-[4-(1-methyl-1H-imidazol-4-yl)-phenylamino]-methylene}-1-phenyl-1,3-dihydro-indol-2-one were

dissolved in 20 ml dichloromethane and 30 ml 40% ethanolic hydrochloric acid and stored in the refrigerator for 12 h. The solution was evaporated down to the residue, combined with 50 ml 6 N ethanolic ammonia solution and refluxed for 3 h. The solution was evaporated down with silica gel and purified by chromatography with
5 dichloromethane/methanol 8:2 on silica gel 70 (flow rate 20 ml/min). The clean fractions were evaporated down and the crystals with acetone, suction filtered and washed.
Yield: 0.2 g yellow crystals, melting point 241°C (decomp.).

Example 25 was prepared analogously (melting point 230-232°C as hydrochloride), as was
10 Example 38 (melting point > 275°C with decomp. as hydrochloride).

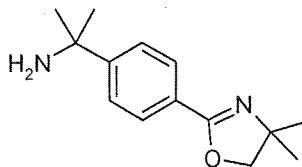
15

EXAMPLE 56

4. 3-{[4-(1-AMINO-1-METHYL-ETHYL)-PHENYL]-[4-(1-METHYL-1H-
IMIDAZOL-4-YL)-PHENYLAMINO]-METHYLENE}-3H-BENZOFURAN-2-ONE

20

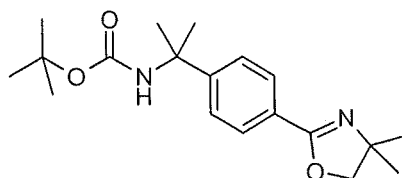
4.1 1-[4-(4,4-DIMETHYL-4,5-DIHYDRO-OXAZOL-2-YL)-PHENYL]-1-METHYL-
ETHYLAMINE



25 130 g anhydrous cerium(III)chloride were suspended in 1 l THF and stirred for 1 h, cooled to -60°C with thorough mechanical stirring and combined dropwise with 330 ml of a 1.5 M methyl lithium solution in THF/cumene, while the internal temperature did not rise above -50°C. The yellow suspension was stirred for 30 min and at -50°C combined with a

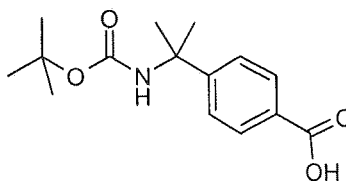
solution of 34.4 g 2-(4-cyanophenyl)-4,4-dimethyl-4,5-dihydro-oxazole in 50 ml THF. After another 12 h, 330 ml conc. ammonia solution was added dropwise at -55°C, whereupon a violet precipitate was formed. It was allowed to come up to RT, filtered and the residue was washed with 1 l THF. The organic phase was evaporated down. The oily yellow residue was purified by chromatography (dichloromethane/methanol 9:1, silica gel 70, flow rate 50 ml/min). The clean fractions yielded 33.3 g of yellow oil with an R_f value 0.20 (dichloromethane/methanol 7:3).

4.2 TERT-BUTYL {1-[4-(4,4-DIMETHYL-4,5-DIHYDRO-OXAZOL-2-YL)-PHENYL]-1-METHYL-ETHYL}-CARBAMATE



A solution of 0.4 g sodium carbonate in 4 ml water was added to a solution of 0.8 g 1-[4-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-1-methyl-ethylamine in 15 ml dioxane. Then within 10 min a solution of 0.83 g Boc-anhydride in dioxane was added dropwise. The yellow solution was stirred for 12 h at RT. The dioxane was distilled off and the aqueous residue was extracted 2x with ethyl acetate. The organic phases were combined, dried on $MgSO_4$, filtered and evaporated down to the residue. After crystallisation 0.87 g yellowish-white product was obtained.

4.3 4-(1-TERT-BUTOXYCARBONYLAMINO-1-METHYL-ETHYL)-BENZOIC ACID

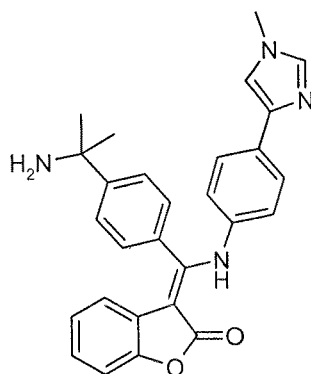


A solution of 0.83 g tert-butyl {1-[4-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-phenyl]-1-methyl-ethyl}-carbamate and 3.1 ml methyl iodide in 2 ml DMF were stirred for 12 h at 60°C in a pressure tube reactor and after cooling evaporated down to the residue. The oil was stirred with 15 ml of 1 M NaOH for 3h at RT. The suspension was extracted with ether. The aqueous phase was acidified to pH 2 with 1 M HCl and the precipitate formed was taken up in ether. After the aqueous phase had been extracted twice more with ether the organic phases were combined, dried on MgSO₄, filtered and the filtrate was evaporated down to the residue.

Yield: 0.4 g crystals, R_f value 0.41 (dichloromethane/methanol 9:1).

The process used in Example 40 hereinbefore was used to cleave the Boc protecting group.

4.4 3-{[4-(1-AMINO-1-METHYL-ETHYL)-PHENYL]-[4-(1-METHYL-1H-IMIDAZOL-4-YL)-PHENYLAMINO]-METHYLENE}-3H-BENZOFURAN-2-ONE



2.5 g tert-butyl (1-methyl-1-{4-[[4-(1-methyl-1H-imidazol-4-yl)-phenylamino]-(2-oxo-benzofuran-3-ylidene)-methyl]-phenyl}ethyl)-carbamate (N-Boc derivative of Example 56) were dissolved in 50 ml dioxane and combined with 50 ml of a 4 N solution of hydrogen chloride in dioxane. The solution was stirred for 1 h at RT and evaporated down. The residue was dissolved in 50 ml methanol and evaporated down with another 150 ml

isopropanol almost to the residue and then crystallised. After diluting with acetone the product was suction filtered and washed with acetone.

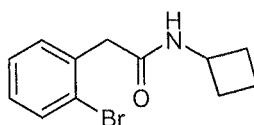
Yield: 1.9 g yellow crystals of melting point $>280^{\circ}\text{C}$ as hydrochloride.

R_f value: 0.18 (dichloromethane/methanol 8:2).

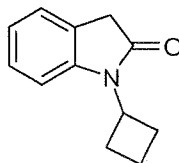
5

The components of the synthesis described above are known in the literature, commercially available or prepared as follows:

10 COMPONENT 1



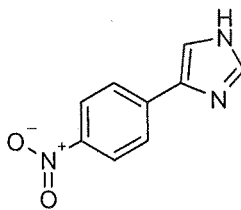
26.3 g 2-bromophenylacetic acid were dissolved in 200 ml dichloromethane and combined with 15 ml oxalyl chloride and one drop of DMF. After 1 h at RT the solution was
15 evaporated down and the acid chloride was further used directly. The acid chloride was dissolved in 40 ml dichloromethane and added dropwise to a solution of 9 g cyclobutylamine and 27 ml diisopropylethylamine in dichloromethane at $15-20^{\circ}\text{C}$. After 12 h at RT the dichloromethane was distilled off, the residue was dissolved in 600 ml ethyl acetate and extracted 2x with 4 N HCl, 2x with 4 N NaOH and 3x with water. The organic
20 phase was dried on MgSO_4 , filtered and evaporated down to the crystalline residue. After the addition of diisopropylether the mixture was suction filtered and 24.1 g of 2-bromo-phenylacetic acid-cyclobutylamide were obtained, melting point $159-161^{\circ}\text{C}$.
 R_f value: 0.67 (dichloromethane/methanol 9:1).



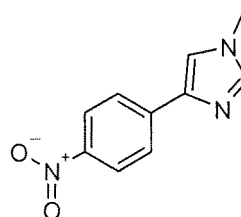
25

400 ml toluene were degassed with argon and then 13.4 g of 2-bromo-phenylacetic acid-cyclobutylamide, 9.7 g powdered K_2CO_3 , 0.9 g tris(dibenzylideneacetone)dipalladium(0) and 1.2 g tri-*o*-tolylphosphine were added. After 72 stirring at 100°C and cooling the mixture was diluted to 2 l with diethyl ether, filtered to remove insoluble matter and
5 evaporated down to the residue. After crystallisation in diisopropylether the mixture was suction filtered and the filtrate was evaporated down to the residue with silica gel. The purification was carried out by chromatography on silica gel 60 (eluant dichloromethane). Yield: 3.75 g oil, R_f value: 0.18 (dichloromethane).

10
COMPONENT 2

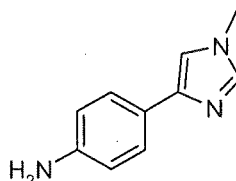


100 g p-nitro-phenacylbromide and 400 ml formamide were stirred for 2 h at 175°C. After
15 cooling the mixture was made alkaline with 20 ml ammonia, stirred into 800 ml water and the precipitate was suction filtered. The crystals were recrystallised from methanol and suction filtered. Yield: 46.5 g, melting point 217-219°C.



20
45 g 1H-4-(4-nitro-phenyl)-imidazole were placed in 300 ml DMSO and 30 g potassium tert. butoxide were added batchwise while cooling with ice. The mixture was heated to RT and stirred for 1 h. Then 16.5 ml methyl iodide was added dropwise between 20-25°C and

stirred for a further 2 h at RT. Then the mixture was poured onto 300 g ice, stirred, the precipitate formed was suction filtered and washed thoroughly with water. Yield: 39.8 g.



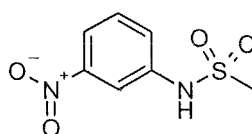
5

22 g of 1-methyl-4-(4-nitro-phenyl)-imidazole were dissolved in 1.6 l methanol and combined with 4 g Pd/C (10 %). The mixture was hydrogenated at 50 psi and RT for approx. 5 h. Then another gram of catalyst was added and the mixture was hydrogenated for 18 h, then for a further 12 h with the addition of another 2 g of catalyst. Finally, the catalyst was suction filtered and the filtrate was evaporated down. The residue was taken up in toluene and some methanol, and evaporated down somewhat until a dark-grey precipitate formed. This was suction filtered, taken up in methanol, combined with 4 g activated charcoal and filtered off. The filtrate was combined with 100 ml toluene, concentrated by rotary evaporation and crystallised.

Yield: 22 g, R_f value: 0.34 (dichloromethane/methanol 9:1).

10
15

COMPONENT 3



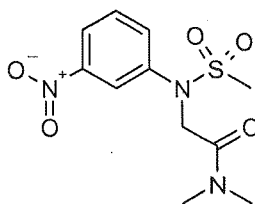
20

100 g of 3-nitroaniline were dissolved in 400 ml pyridine and 57 ml methanesulphonic acid chloride were added dropwise while cooling gently with ice. After 12 h at RT the red reaction mixture was poured onto 1.2 l of ice, stirred, suction filtered, the solid was suspended with copious amounts of water, washed and dried.

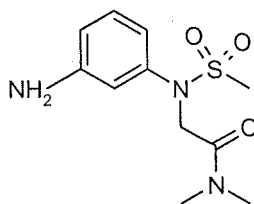
Yield: 148 g solid with a melting point 165-166°C.

R_f value. 0.65 (dichloromethane/methanol 9:1).

25

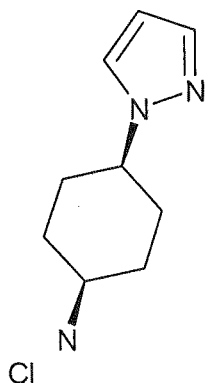


50 g of 3-methanesulphonylamino-nitrobenzene were placed in 200 ml DMF, 31 g
5 potassium tert. butoxide were added and the reaction mixture was stirred for 1 h at RT.
After the addition of 28.5 g of 2-chloro-N,N-dimethylacetamide the mixture was stirred for
12 h at 60°C. After cooling to RT water was added and the mixture was extracted 5x with
ethyl acetate. The organic phases were washed with water, dried on MgSO₄, filtered and
the filtrate was evaporated down to the residue. The residue was crystallised from
10 diisopropylether. Yield: 31.5 g.



31.5 g of 2-(N-methanesulphonyl-N-(3-nitrophenyl)-amino)-N,N-dimethylacetamide were
15 hydrogenated with 3 g Pd/C at RT and 50 psi in ammoniacal methanol for 24 h. Then the
catalyst was suction filtered while warm and washed several times with ethyl acetate. The
filtrate was evaporated down to the residue. Yield: 20 g of solid with a melting point of
143-144°C.

20 **COMPONENT 4:**



9.25 g (47 mmol) 4-aminophenylpyrazole hydrochloride are placed in 150 ml methanol and hydrogenated with 1.00 g Nishimura catalyst at ambient temperature under a pressure of 50 psi. Then the catalyst is filtered off, the filtrate is concentrated by evaporation. The
5 residue is crystallised from acetonitrile, the enantiomers are obtained by chromatographic separation.

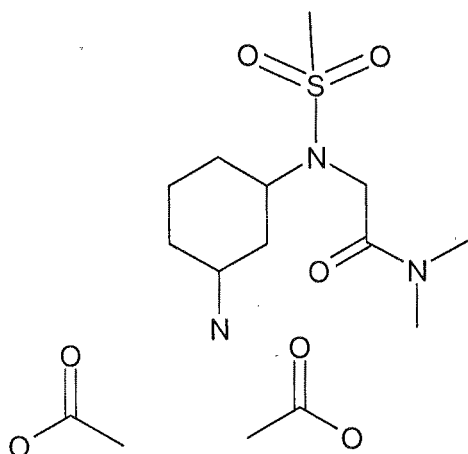
Yield: 1.89 g (20%) *cis* compound

NMR: LH201668

MP: 175°-177° C

10

COMPONENT 5:



4.00 g (15 mmol) **Component 3** are placed in 60 ml glacial acetic acid and hydrogenated with 0.600 g Nishimura catalyst at ambient temperature under a pressure of 50 psi. Then
15 the catalyst is filtered off and the filtrate is concentrated by evaporation. The residue is

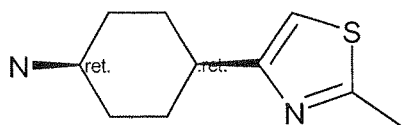
dissolved in a little water, treated with activated charcoal and filtered. The filtrate is lyophilised.

Yield: 4.90 g (84%)

NMR: LH201565

5

Component 6:



10

2-methyl-2-(4-nitro-phenyl)-[1,3]dioxolane:

33.03 g (200 mmol) 4-nitroacetophenone, 12.30 ml (220 mmol) ethyleneglycol and 1.00 g (5 mmol) p-toluenesulphonic acid are placed in 250 ml toluene, then refluxed for 16 hours using the water separator. Then the reaction mixture is cooled and extracted with water. The organic phase is dried and evaporated to dryness. The residue is extracted with diisopropylether and suction filtered.

15

Yield: 34.45 g (82%)

20

4-(2-methyl-[1,3]dioxolan-2-yl)-cyclohexylamine:

8.37 g (40 mmol) 2-methyl-2-(4-nitro-phenyl)-[1,3]dioxolane are placed in 160 ml methanol and hydrogenated with 1.00 g Nishimura catalyst at ambient temperature under a pressure of 50 psi. Then the catalyst is filtered off and the filtrate is concentrated by evaporation. The residue is dissolved in cyclohexane, filtered to remove insoluble matter and the filtrate is evaporated to dryness.

25

Yield: 7.00 g (94%), *cis/trans* ratio 77:23

NMR: LG201616

9H-fluoren-9-ylmethyl [4-(2-methyl-[1,3]dioxolan-2-yl)-cyclohexyl]-carbamate :

A solution of 12.72 g (120 mmol) sodium carbonate is placed in 120 ml water and
5 combined with a solution of 7.00 g (38 mmol) 4-(2-methyl-[1,3]dioxolan-2-yl)-
cyclohexylamine (cis/trans mixture) in 50 g dioxane. After cooling to 0°C a solution of
10.09 g (39 mmol) Fmoc-chloride in 100 g dioxane is added dropwise within 0.2 hours.
The reaction mixture is stirred for 16 hours, with the cooling removed. Then the mixture is
poured onto water and extracted with ethyl acetate. The organic phase is washed with
10 water, dried and evaporated to dryness. The residue is purified by chromatography.
Yield: 13.10 g (85%) *cis/trans* ratio 4:1
NMR: LH201618

15 9H-fluoren-9-ylmethyl (4-acetyl-cyclohexyl)-carbamate:

13.10 g (32 mmol) 9H-fluoren-9-ylmethyl [4-(2-methyl-[1,3]dioxolan-2-yl)-cyclohexyl]-
carbamate (*cis/trans* mixture) and 1.30 g p-toluenesulphonic acid are refluxed in 25 ml
water and 500 ml acetone for 16 hours with stirring. Then the reaction mixture is
20 concentrated by evaporation, the residue is dissolved in ethyl acetate and extracted with
water. The organic phase is dried and evaporated to dryness. The residue is extracted with
diisopropylether and suction filtered.
Yield: 7.77 g (89%) *cis* compound
NMR: LH201628

25

9H-fluoren-9-ylmethyl [4-(2-bromo-acetyl)-cyclohexyl]-carbamate:

7.77 g (21 mmol) 9H-fluoren-9-ylmethyl (4-acetyl-cyclohexyl)-carbamate (*cis* compound)
are dissolved in 100 ml methanol at ambient temperature and combined with 1.09 ml (21
30 mmol) bromine. The mixture is stirred for 16 hours at ambient temperature, cooled and the
crystals precipitated are suction filtered.

Yield: 6.35 g (50%)

NMR: LG201641

5 9H-fluoren-9-ylmethyl [4-(2-methyl-thiazol-4-yl)-cyclohexyl]-carbamate:

4.00 g (7 mmol) 9H-fluoren-9-ylmethyl [4-(2-bromo-acetyl)-cyclohexyl]-carbamate (*cis* compound) and 0.700 g (9 mmol) thioacetamide are refluxed in 50 ml acetonitrile for 72 hours with stirring. Then the reaction mixture is concentrated by evaporation, the residue is
10 purified by chromatography. Corresponding fractions are combined and evaporated to dryness. The crystalline residue is extracted with diisopropylether and suction filtered.

Yield: 1.10 g (39%) *cis* compound

NMR: LH201648

MP: 140°-141° C

15

4-(2-methyl-thiazol-4-yl)-cyclohexylamine (**Component 6**):

1.10 g (2 mmol) 9H-fluoren-9-ylmethyl [4-(2-methyl-thiazol-4-yl)-cyclohexyl]-carbamate
20 (*cis* compound) and 15 ml diethylamine are stirred in 30 ml tetrahydrofuran for 16 hours at ambient temperature. Then the reaction mixture is concentrated by evaporation, the residue is combined with tetrahydrofuran and concentrated again by evaporation. The residue is purified by chromatography.

Yield: 0.13 g (36%)

25

INDICATIONS

As has been found, the compounds of formula 1 are characterised by their wide range of applications in the therapeutic field. Particular mention should be made of those applications for which the compounds according to the invention of formula 1 are preferably suited on account of their pharmaceutical efficacy as PDE4 inhibitors. Examples include respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints, skin or eyes, cancers, and also diseases of the peripheral or central nervous system.

Particular mention should be made of the prevention and treatment of diseases of the airways and of the lung which are accompanied by increased mucus production, inflammations and/or obstructive diseases of the airways. Examples include acute, allergic or chronic bronchitis, chronic obstructive bronchitis (COPD), coughing, pulmonary emphysema, allergic or non-allergic rhinitis or sinusitis, chronic rhinitis or sinusitis, asthma, alveolitis, fibrosing alveolitis, idiopathic pulmonary fibrosis, ulcerative colitis, Farmer's disease, hyperreactive airways, infectious bronchitis or pneumonitis, paediatric asthma, bronchiectases, pulmonary fibrosis, ARDS (acute adult respiratory distress syndrome), bronchial oedema, pulmonary oedema, bronchitis, pneumonia or interstitial pneumonia triggered by various causes, such as aspiration, inhalation of toxic gases, or bronchitis, pneumonia or interstitial pneumonia as a result of heart failure, irradiation, chemotherapy, cystic fibrosis or mucoviscidosis, or alpha1-antitrypsin deficiency.

Also deserving special mention is the treatment of inflammatory diseases of the gastrointestinal tract. Examples include acute or chronic inflammatory changes in gall bladder inflammation, Crohn's disease, ulcerative colitis, inflammatory pseudopolyps, juvenile polyps, colitis cystica profunda, pneumatosis cystoides intestinales, diseases of the bile duct and gall bladder, e.g. gallstones and conglomerates, for the treatment of inflammatory diseases of the joints such as rheumatoid arthritis or inflammatory diseases of the skin and eyes.

Preferential mention should also be made of the treatment of cancers. Examples include all forms of acute and chronic leukaemias such as acute lymphatic and acute myeloid leukaemia, chronic lymphatic and chronic myeloid leukaemia, and bone tumours such as osteosarcoma and all types of glioma such as oligodendroglioma and glioblastoma.

5

Preferential mention should also be made of the prevention and treatment of diseases of the peripheral or central nervous system. Examples of these include depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

10

Particularly preferably the present invention relates to the use of compounds of formula 1 for preparing a pharmaceutical composition for the treatment of inflammatory or obstructive diseases of the upper and lower respiratory tract including the lungs, such as for example allergic rhinitis, chronic rhinitis, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, fibrosing alveolitis, COPD, chronic bronchitis, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis, particularly COPD, chronic bronchitis and asthma.

15

It is most preferable to use the compounds of formula 1 for the treatment of inflammatory and obstructive diseases such as COPD, chronic bronchitis, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis, particularly COPD, chronic bronchitis and asthma.

20

It is also preferable to use the compounds of formula 1 for the treatment of diseases of the peripheral or central nervous system such as depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

25

An outstanding aspect of the present invention is the reduced profile of side effects. This means, within the scope of the invention, being able to administer a dose of a

30

pharmaceutical composition without inducing vomiting, preferably nausea and most preferably malaise in the patient. It is particularly preferable to be able to administer a therapeutically effective quantity of substance without inducing emesis or nausea, at every stage of the disease.

5

COMBINATIONS

- The compounds of formula 1 may be used on their own or in conjunction with other active substances of formula 1 according to the invention. If desired the compounds of formula 1 may also be used in combination with other pharmacologically active substances. It is preferable to use for this purpose active substances selected for example from among betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof, such as for example combinations of
- betamimetics with corticosteroids, PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists,
 - anticholinergics with betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists,
 - corticosteroids with PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists
 - PDE4-inhibitors with EGFR-inhibitors or LTD4-antagonists
 - EGFR-inhibitors with LTD4-antagonists
 - MRP4-inhibitors.

The invention also encompasses combinations of three active substances, each selected from one of the above-mentioned categories of compounds.

Suitable betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenol, sulphonterol, tiaramide, terbutaline,

tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Preferably the betamimetics are selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide,

5 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-

10 benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyl-oxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-

15 butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl-4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-

20 (4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-

25 (4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-

30 hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates,

enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Particularly preferred betamimetics are selected from among fenoterol, formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinoline-2-one, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butylxyphenyl)-2-methyl-2-propylamino]ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Of these betamimetics the particularly preferred ones according to the invention are formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinoline-2-one, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

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According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. Of the above-mentioned acid addition salts the salts of hydrochloric acid, methanesulphonic acid, benzoic acid and acetic acid are particularly preferred according to the invention.

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The anticholinergics used are preferably compounds selected from among the tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium

salts, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate -methobromide, tropenol 9-fluoro-fluorene-9-carboxylate -methobromide, scopine 9-hydroxy-fluorene-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine 2,2-diphenylpropionate methobromide, cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide, methyl cyclopropyltropine 4,4'-difluorobenzilate methobromide, tropenol 9-hydroxy-xanthene-9-carboxylate -methobromide, scopine 9-hydroxy-xanthene-9-carboxylate methobromide, tropenol 9-methyl-xanthene-9-carboxylate methobromide, scopine 9-methyl-xanthene-9-carboxylate methobromide, tropenol 9-ethyl-xanthene-9-carboxylate methobromide, tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide, scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide, optionally in the form of the solvates or hydrates thereof.

In the above-mentioned salts the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and trospium are the pharmacologically active ingredients. As anions, the above-mentioned salts may preferably contain chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts, the chlorides, bromides, iodides and methanesulphonate are particularly preferred.

Of particular importance is tiotropium bromide. In the case of tiotropium bromide the pharmaceutical combinations according to the invention preferably contain it in the form of the crystalline tiotropium bromide monohydrate, which is known from WO 02/30928. If the tiotropium bromide is used in anhydrous form in the pharmaceutical combinations
5 according to the invention, it is preferable to use anhydrous crystalline tiotropium bromide, which is known from WO 03/000265.

Corticosteroids used here are preferably compounds selected from among prednisolone, prednisone, butixocortpropionate, flunisolide, beclomethasone, triamcinolone, budesonide,
10 fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, betamethasone, deflazacort, RPR-106541, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate and (S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates,
15 enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferred is the steroid selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide,
20 dexamethasone, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate and (S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates
25 and/or hydrates thereof.

Particularly preferred is the steroid selected from among budesonide, fluticasone, mometasone, ciclesonide and (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate, optionally in the form
30 of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates thereof.

Other PDE4 inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4396 (Sch-351591), AWD-12-281 (GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440, T-2585, V-11294A, CI-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, (-)-p-[(4aR*.10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1.6]naphthyridin-6-yl]-N,N-diisopropylbenzamide, (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone, 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, (S)-(-)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Particularly preferably the PDE4-inhibitor is selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, CI-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, cis[4-cyano-4-

(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

10 Particularly preferably the PDE4-inhibitor is selected from among roflumilast, ariflo (cilomilast), arofyllin, AWD-12-281 (GW-842470), 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], atizoram, Z-15370, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

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By acid addition salts with pharmacologically acceptable acids which the above-mentioned PDE4-inhibitors might be in a position to form are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

LTD4-antagonists which may be used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321, 1-(((R)-(3-(2-(6,7-difluoro-2-

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quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2.3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane-acetic acid and [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, optionally
5 in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Preferably the LTD4-antagonist is selected from among montelukast, pranlukast,
10 zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

15 Particularly preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001 and MEN-91507 (LM-1507), optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

20

By acid addition salts with pharmacologically acceptable acids which the LTD4-antagonists may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate,
25 hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. By salts or derivatives which the LTD4-antagonists may be capable of forming are meant, for example: alkali metal salts, such as, for example, sodium or potassium salts, alkaline earth metal salts,
30 sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

The EGFR-inhibitors used are preferably compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}}-7-

5 cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}}-7-

cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-

10 phenyl)amino]-6-{{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}}-7-cyclopropylmethoxy-quinazoline, 4-

15 [(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}}-7-

cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-

20 yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-

25 fluorophenyl)amino]-6-{{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-

30 2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}}-7-cyclopentyloxy-

quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-

fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetyl-amino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-

5 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-

10 [(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-

15 fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-

20 4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-

25 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetyl-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

30 phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-

methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropylloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-

yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, cetuximab,

10 trastuzumab, ABX-EGF and Mab ICR-62, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Preferred EGFR-inhibitors are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-

15 {[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-

20 cyclopentylloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-

25 yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-([4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl]amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino]-7-cyclopentylloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-[[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-

30 yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-([4-[N-(2-

methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl} amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl} amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl} amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl} amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl} amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl} amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl} amino}-7-ethoxy-quinoline, 4-{{3-chloro-4-(3-fluoro-benzyloxy)-phenyl} amino}-6-(5-{{(2-methanesulphonyl-ethyl)amino} methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl} amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{{4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-

(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-

5 7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-

10 methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetyl-amino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-

15 [(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-

20 1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-

25 [(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline,

4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

30 phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-

[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetyl-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropylloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and cetuximab, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

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It is particularly preferable within the scope of the present invention to use those EGFR-inhibitors which are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-

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quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{{4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-

quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or

diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Particularly preferred EGFR-inhibitors according to the invention are the compounds
5 selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-
10 fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{{4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-
15 yl}amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-
20 piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-
25 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-
30 methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-

methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the EGFR-inhibitors may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Examples of dopamine agonists which may be used preferably include compounds selected from among bromocriptine, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, terguride and viozan. Any reference to the above-mentioned dopamine agonists within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts and optionally hydrates thereof which may exist. By the physiologically acceptable acid addition salts which may be formed by the above-mentioned dopamine agonists are meant, for example, pharmaceutically acceptable salts which are selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

Examples of H1-antihistamines preferably include compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifen, emedastine, dimetinden, clemastine, bamipin, cexchlorpheniramine, pheniramine, doxylamine, chlorphenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and meclozine. Any reference to the above-mentioned H1-antihistamines within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts which may exist.

Examples of PAF-antagonists preferably include compounds selected from among 4-(2-chlorophenyl)-9-methyl-2-[3(4-morpholinyl)-3-propanon-1-yl]-6H-thieno-[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepines, 6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclo-penta-[4,5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepines.

MRP4-inhibitors used are preferably compounds selected from among *N*-acetyl-dinitrophenyl-cysteine, cGMP, cholate, diclofenac, dehydroepiandrosterone 3-glucuronide, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-*s*-glutathione, estradiol 17- β -glucuronide, estradiol 3,17-disulphate, estradiol 3-glucuronide, estradiol 3-sulphate, estrone 3-sulphate, flurbiprofen, folate, N5-formyl-tetrahydrofolate, glycocholate, clycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, ketoprofen, lithocholic acid sulphate, methotrexate, MK571 ((*E*)-3-[[[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-[3-dimethylamino)-3-oxopropyl]thio]methyl]thio]-propanoic acid), β -naphthyl- β -D-glucuronide, nitrobenzyl mercaptopurine riboside, probenecid, PSC833, sildenafil, sulfinpyrazone, taurochenodeoxycholate, taurocholate, taurodeoxycholate, tauroolithocholate, tauroolithocholic acid sulphate, topotecan, trequinsin and zaprinast, dipyrindamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

Preferably the invention relates to the use of MRP4-inhibitors for preparing a pharmaceutical composition for the treatment of respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors, the MRP4-inhibitors preferably being selected from among *N*-acetyl-dinitrophenyl-cysteine, dehydroepiandrosterone 3-sulphate, dilazep,
5 dinitrophenyl-*S*-glutathione, estradiol 3,17-disulphate, flurbiprofen, glycocholate, glycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, lithocholic acid sulphate, MK571, PSC833, sildenafil, taurochenodeoxycholate, taurocholate, tauroolithocholate, tauroolithocholic acid sulphate, trequinsin and zaprinast, dipyridamole, optionally in the form of the racemates, enantiomers, diastereomers and the
10 pharmacologically acceptable acid addition salts and hydrates thereof.

The invention relates more preferably to the use of MRP4-inhibitors for preparing a pharmaceutical composition for treating respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors according to the invention, the MRP4-inhibitors preferably
15 being selected from among dehydroepiandrosterone 3-sulphate, estradiol 3,17-disulphate, flurbiprofen, indomethacin, indoprofen, MK571, taurocholate, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof. The separation of enantiomers from the racemates can be carried out using methods known from the art (e.g. chromatography on chiral phases, etc.) .

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By acid addition salts with pharmacologically acceptable acids are meant, for example, salts selected from among the hydrochlorides, hydrobromides, hydroiodides, hydrosulphates, hydrophosphates, hydromethanesulphonates, hydronitrates, hydromaleates, hydroacetates, hydrobenzoates, hydrocitrate, hydrofumarates,
25 hydrotartrates, hydrooxalates, hydrosuccinates, hydrobenzoates and hydro-*p*-toluenesulphonates, preferably the hydrochlorides, hydrobromides, hydrosulphates, hydrophosphates, hydrofumarates and hydromethanesulphonates.

The invention further relates to pharmaceutical preparations which contain a triple
30 combination of the PDE4B-inhibitors, MRP4-inhibitors and another active substance according to the invention, such as, for example, an anticholinergic, a steroid, an LTD4-

antagonist or a betamimetic, and the preparation thereof and the use thereof for treating respiratory complaints.

FORMULATIONS

Suitable forms for administration are for example tablets, capsules, solutions, syrups, emulsions or inhalable powders or aerosols. The content of the pharmaceutically effective compound(s) in each case should be in the range from 0.1 to 90 wt.%, preferably 0.5 to 50 wt.% of the total composition, i.e. in amounts which are sufficient to achieve the dosage range specified hereinafter.

The preparations may be administered orally in the form of a tablet, as a powder, as a powder in a capsule (e.g. a hard gelatine capsule), as a solution or suspension. When administered by inhalation the active substance combination may be given as a powder, as an aqueous or aqueous-ethanolic solution or using a propellant gas formulation.

Preferably, therefore, pharmaceutical formulations are characterised by the content of one or more compounds of formula 1 according to the preferred embodiments above.

It is particularly preferable if the compounds of formula 1 are administered orally, and it is also particularly preferable if they are administered once or twice a day. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also
5 contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.

Capsules containing one or more active substances or combinations of active substances
10 may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

15 Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and
20 glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral administration the tablets may, of course, contain, apart from the abovementioned
25 carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in
30 addition to the excipients mentioned above.

It is also preferred if the compounds of formula 1 are administered by inhalation, particularly preferably if they are administered once or twice a day. For this purpose, the compounds of formula 1 have to be made available in forms suitable for inhalation.

Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions, which are optionally present in admixture with conventional physiologically acceptable excipients.

Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile ready-to-use inhalable solutions. The preparations which may be used according to the invention are described in more detail in the next part of the specification.

Inhalable powders

If the active substances of formula 1 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare the inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred. Methods of preparing the inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

Propellant-containing inhalable aerosols

The propellant-containing inhalable aerosols which may be used according to the invention may contain 1 dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such

as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are fluorinated alkane derivatives selected from
5 TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof. The propellant-driven inhalation aerosols used within the scope of the use according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

10

Propellant-free inhalable solutions

The compounds of formula **1** according to the invention are preferably used to prepare propellant-free inhalable solutions and inhalable suspensions. Solvents used for this purpose include aqueous or alcoholic, preferably ethanolic solutions. The solvent may be
15 water on its own or a mixture of water and ethanol. The solutions or suspensions are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic
20 acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may also be used,
25 particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions
30 used for the purpose according to the invention. Preferred co-solvents are those which

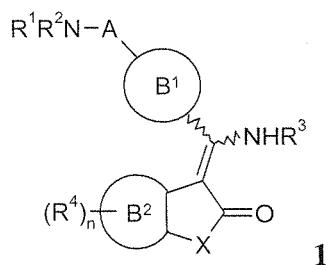
contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body. Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art.

For the treatment forms described above, ready-to-use packs of a medicament for the treatment of respiratory complaints are provided, containing an enclosed description including for example the words respiratory disease, COPD or asthma, a pteridine and one or more combination partners selected from those described above.

PATENT CLAIMS

1. Compounds of formula 1,

5



wherein

A denotes CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene

10

B¹ denotes phenyl or an aromatic or non-aromatic ring which may optionally contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and which may optionally be mono- or polysubstituted by one or more groups selected from among OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

15

B² denotes phenyl or a heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen;

20 **X** denotes O or CR⁶R⁷;

n denotes 0, 1, 2 or 3;

R¹ denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, COR^{1.1}, COOR^{1.1} CH₂COOR^{1.1};

25

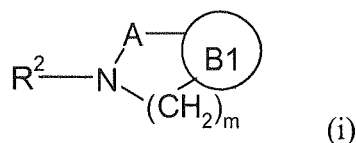
R^{1.1} denotes H or C₁₋₆-alkyl;

R^2 denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

or R^1 and R^2 together with the nitrogen form a non-aromatic heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen;

5

or R^2 , N, A and B¹ together form a bicyclic group of formula (i)



wherein

10 A denotes CO, C=NH or C₁₋₃-alkyl

m denotes 1, 2 or 3,

and

R^3 denotes H or a group selected from among OH, C₁₋₆-haloalkyl, a C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, while the C₃₋₁₀-heterocycle and the C₅₋₁₀-heteroaryl may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl, optionally bridged C₃₋₈-cycloalkyl and C₁₋₆-haloalkyl, which may optionally be substituted by a group selected from C₁₋₆-alkyl, C₁₋₆-haloalkyl, OH, halogen and C₆₋₁₀-aryl ;

15

20

or R^3 denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂,

25

or R^3 denotes a group selected from among C_{3-8} -cycloalkyl, C_{5-8} -cycloalkenyl, C_{1-6} -alkyl and C_{1-6} -alkanol, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{3-8} -cycloalkyl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among C_{1-6} -alkyl,

5 C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, CO_2 -aryl, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH , $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, while the C_{5-10} -heteroaryl and the C_{3-10} -heterocycle may optionally be

10 substituted by a group selected from oxo, hydroxyl, halogen, C_{1-6} -alkyl and C_{1-6} -haloalkyl;

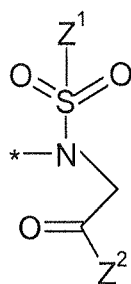
or R^3 denotes a group selected from among C_{6-10} -aryl, a C_{6-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from

15 among aryl, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH , $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$ and $N-(SO_2-C_{1-4}-alkyl)(R^{3,4})$;

20

or R^3 denotes a group selected from among C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{3-7} -cycloalkyl, C_{6-10} -aryl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from among B, halogen, OH , C_{1-6} -alkyl and oxo, while B is a compound of formula 2

25



2,

wherein Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}$ -alkyl), C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$, or C_{3-7} -cycloalkyl;
 and Z^2 denotes OH, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$, $O(C_{1-6}$ -alkyl), mono- or
 5 bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic C_{3-10} -heterocycle, mono- or bicyclic C_{5-10} -heteroaryl or C_{6-10} -aryl;

or R^3 denotes a group selected from among C_{6-10} -aryl and a C_{5-10} -heteroaryl, which may
 10 optionally be substituted by C_{1-6} -alkyl, which may optionally be substituted by a group selected from among $COOR^{3.3}$, $NR^{3.3}R^{3.4}$, $NHCOR^{3.3}$, $NHCOOR^{3.3}$, phenyl, while phenyl may optionally be substituted by a group selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, CN, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, OH , $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH,
 15 $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}$ -alkyl) $_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and $N(C_{1-6}$ -alkyl) $_2$, a C_{3-10} -heterocycle and a C_{5-10} -heteroaryl, while the C_{3-10} -heterocycle and the C_{5-10} -heteroaryl may optionally be substituted by an oxo group or a methyl group;

while

20 $R^{3.3}$ denotes H or C_{1-6} -alkyl;
 $R^{3.4}$ denotes H, C_{1-6} -alkyl or C_{7-11} -aralkyl, $-C_{1-6}$ -alkylene or C_{5-10} -heteroaryl- C_{1-6} -alkylene,

or R^3 denotes a group selected from among C_{6-10} -aryl and a C_{5-10} -heteroaryl, which may optionally be substituted by $NR^{3.1}R^{3.2}$;

25 wherein

$R^{3.1}$ denotes H, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{1-6} -haloalkyl, $COR^{3.1.1}$, $COOR^{3.1.1}$, $CONR^{3.1.1}R^{3.1.2}$ or $SO_2-R^{3.1.1}$;

and

30 $R^{3.1.1}$ denotes H, C_{1-6} -alkyl, C_{1-6} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl; and

$R^{3.1.2}$ denotes H, C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₃₋₆-cycloalkyl or C₆₋₁₀-aryl;

and

$R^{3.2}$ denotes H or a group selected from among C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₁₋₆-haloalkyl, which may optionally be substituted by one or more groups selected from among NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, oxo and a non-aromatic C₃₋₁₀-heterocycle, which may contain one or two heteroatoms selected from among nitrogen, oxygen and sulphur, while the non-aromatic C₃₋₁₀-heterocycle may optionally be substituted by C₁₋₄-alkyl;

or R^3 denotes a group selected from among C₆₋₁₀-aryl and a C₅₋₁₀-heteroaryl, which may optionally be substituted by a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, CN, C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, oxo, OH, O-C₁₋₆-alkyl, halogen, SH, S-C₁₋₆-alkyl, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

or R^3 denotes benzimidazolyl, which may optionally be substituted by a group selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl and C₃₋₆-cycloalkyl;

and

R^4 denotes C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₁₋₆-haloalkyl, OR^{4.1}, NR^{4.1}R^{4.2}, CN or halogen; wherein

$R^{4.1}$ denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

$R^{4.2}$ denotes H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₁₋₆-haloalkyl;

and

R⁶ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

R⁷ denotes H, C₁₋₆-alkyl or C₁₋₆-haloalkyl;

5

or **R⁶** and **R⁷** together form a 3-6 membered carbocycle;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
10 as well as deuterated forms thereof.

2. Compounds of formula 1 according to claim 1, wherein

15 **A** CO, C=NH, C₁₋₆-alkylene or C₃₋₈-cycloalkylene,

B¹ denotes phenyl or an aromatic or non-aromatic ring, which may optionally contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen and which may optionally be mono- or polysubstituted by one or more groups selected from
20 among OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

B² denotes phenyl or pyridinyl;

X denotes O or CR⁶R⁷;

n denotes 0, 1, 2 or 3;

R¹ denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;

5

R² denotes H, C₁₋₄-alkyl or C₁₋₄-haloalkyl;

or **R¹** and **R²** together with the nitrogen form a non-aromatic heterocycle, which may contain one or two nitrogen atoms;

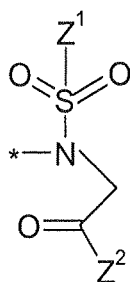
10

R³ denotes H, OH, C₁₋₆-haloalkyl or a group selected from among C₆₋₁₀-aryl, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by a methyl group, oxo or OH;

15 or **R³** denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, COaryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂,
20 SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and N(C₁₋₆-alkyl)₂;

or **R³** denotes a group selected from among C₃₋₈-cycloalkyl, a C₃₋₈-cycloalkyl bridged by C₁₋₃-alkylene, C₅₋₈-cycloalkenyl, C₁₋₆-alkyl and C₁₋₆-alkanol, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₃₋₈-
25 cycloalkyl, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among C₁₋₆-alkyl, C₁₋₆-haloalkyl, CN, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂, a C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, while the C₅₋₁₀-heteroaryl and the C₃₋₁₀-heterocycle may optionally be substituted
30 by a group selected from oxo, hydroxyl, halogen, C₁₋₆-alkyl and C₁₋₆-haloalkyl;

or R^3 denotes a group selected from among C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{3-7} -cycloalkyl, C_{6-10} -aryl, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which is substituted by one or more groups selected from among B, halogen, OH, C_{1-6} -alkyl, oxo, where B is a compound of formula 2



2,

wherein

Z^1 denotes H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol, $O(C_{1-6}$ -alkyl), C_{6-10} -aryl, $O-C_{6-10}$ -aryl, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$ or C_{3-7} -cycloalkyl;

and Z^2 denotes OH, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$, $O(C_{1-6}$ -alkyl), mono- or bicyclic C_{3-7} -cycloalkyl, a mono- or bicyclic C_{3-10} -heterocycle, a mono- or bicyclic C_{5-10} -heteroaryl or C_{6-10} -aryl;

or R^3 denotes phenyl, which may be substituted by one or more groups selected from among C_{6-10} -aryl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}$ -alkyl) $_2$, $COOH$, $COO-C_{1-6}$ -alkyl, COH , $CO-C_{1-6}$ -alkyl, $COaryl$, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-4}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-4}$ -haloalkyl, SO_2-C_{1-6} -alkyl, SO_2-C_{1-4} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}$ -alkyl) $_2$, NO_2 , NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and $N(C_{1-6}$ -alkyl) $_2$;

or R^3 denotes phenyl which is substituted by C_{1-4} -alkyl, which may optionally be substituted by a group selected from among $COOR^{3.3}$, $NR^{3.3}R^{3.4}$, $NHCOR^{3.3}$, $NHCOOR^{3.3}$ and phenyl, which may optionally be substituted by one or more groups selected from among methyl, *t*-butyl, F, Cl, Br, CN, OH, and a heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen, while the heterocycle may optionally be substituted by an oxo group or a methyl group;

wherein

$R^{3.3}$ denotes H or C_{1-6} -alkyl;

$R^{3.4}$ denotes H, C_{1-6} -alkyl or C_{6-10} -aryl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene;

5 or R^3 denotes phenyl, substituted with $NR^{3.1}R^{3.2}$;

wherein

$R^{3.1}$ denotes H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, $COR^{3.1.1}$, $COOR^{3.1.1}$, $CONR^{3.1.1}R^{3.1.2}$ or $SO_2-R^{3.1.1}$;

and

10 $R^{3.1.1}$ denotes H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

$R^{3.1.2}$ denotes H, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl or C_{6-10} -aryl;

and

15 $R^{3.2}$ denotes H, C_{1-4} -alkyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NH(C_{1-4}$ -alkyl), $N(C_{1-4}$ -alkyl)₂, oxo or a non-aromatic C_{3-10} -heterocycle, which may contain one or two nitrogen atoms and may optionally be substituted by a methyl group;

20

or R^3 denotes C_{6-10} -aryl, which may be substituted by a C_{5-10} -heteroaryl containing one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-4} -alkyl, C_{3-6} -cycloalkyl, CN, C_{1-4} -haloalkyl, $CONH_2$, $CONH-C_{1-4}$ -alkyl, $CON(C_{1-4}$ -alkyl)₂, COOH, 25 $COO-C_{1-4}$ -alkyl, COH, $CO-C_{1-4}$ -alkyl, OH, $O-C_{1-4}$ -alkyl, halogen, SH, $S-C_{1-4}$ -alkyl, NH_2 , $NH-C_{1-4}$ -alkyl and $N(C_{1-4}$ -alkyl)₂;

or R^3 denotes C_{6-10} -aryl, which may be substituted by a non-aromatic C_{3-10} -heterocycle, which may contain one or two heteroatoms, selected from among oxygen, sulphur and 30 nitrogen, while the C_{3-10} -heterocycle may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo;

or R^3 denotes benzimidazolyl, which may optionally be substituted by one group or more groups selected from among C_{1-4} -alkyl, C_{1-4} -haloalkyl and C_{3-6} -cycloalkyl;

and

5 R^4 denotes C_{1-4} -alkyl, C_{3-6} -cycloalkyl, C_{1-4} -haloalkyl, $OR^{4.1}$, $NR^{4.1}R^{4.2}$, CN or halogen;

$R^{4.1}$ denotes H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl or C_{1-4} -haloalkyl;

$R^{4.2}$ denotes H, C_{1-4} -alkyl, C_{3-6} -cycloalkyl or C_{1-4} -haloalkyl;

and

10 R^6 denotes H, C_{1-6} -alkyl or C_{1-6} -haloalkyl;

R^7 denotes H, C_{1-6} -alkyl or C_{1-6} -haloalkyl;

or R^6 and R^7 together form a 3-6 membered carbocycle;

15

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

3. Compounds of formula 1 according to claim 1 or 2, wherein

5 R^3 denotes C_{1-6} -alkyl, which may optionally be substituted by one or more groups selected from among halogen, OH, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, COOH, $COO-C_{1-6}$ -alkyl, COH, $CO-C_{1-6}$ -alkyl, COaryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl, SO_2-C_{1-6} -alkanol; SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl and
10 $N(C_{1-6}-alkyl)_2$,

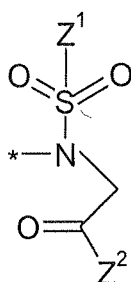
or R^3 denotes a group selected from among C_{3-8} -cycloalkyl, a C_{3-8} -cycloalkyl bridged with C_{1-3} -alkylene, a C_{5-8} -cycloalkenyl, C_{1-6} -alkyl, and C_{1-6} -alkanol, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl,
15 C_{3-8} -cycloalkyl, a C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which in turn may optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, CN, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, COOH, $COO-C_{1-6}$ -alkyl, COH, $CO-C_{1-6}$ -alkyl, $CO-C_{6-10}$ -aryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl,
20 SO_2-C_{1-6} -alkanol, SO_2-C_{1-6} -alkyl, SO_2-C_{1-6} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-6} -alkyl, $SO_2-N(C_{1-6}-alkyl)_2$, NO_2 , NH_2 , $NH-C_{1-6}$ -alkyl, $N(C_{1-6}-alkyl)_2$, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may optionally be substituted by one or more groups selected from oxo, hydroxyl, halogen or C_{1-6} -alkyl and C_{1-6} -haloalkyl;

25

or R^3 denotes a group selected from among C_{6-10} -aryl, C_{5-10} -heteroaryl and a C_{3-10} -heterocycle, which may be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -haloalkyl, $CONH_2$, $CONH-C_{1-6}$ -alkyl, $CON(C_{1-6}-alkyl)_2$, COOH, $COO-C_{1-6}$ -alkyl, COH, $CO-C_{1-6}$ -alkyl, $CO-$
30 C_{6-10} -aryl, OH, $O-C_{1-6}$ -alkyl, $O-C_{1-6}$ -haloalkyl, halogen, SH, $S-C_{1-6}$ -alkyl, $S-C_{1-6}$ -haloalkyl,

SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂ and N-(SO₂-C₁₋₄-alkyl)(R^{3,4});

or R³ denotes a group selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, C₆₋₁₀-aryl, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from among B, halogen, OH, C₁₋₆-alkyl and oxo, while B is a compound of formula 2



2

wherein

Z¹ denotes H, OH, halogen, C₁₋₆-alkyl, C₁₋₆-alkanol, O(C₁₋₆-alkyl), C₆₋₁₀-aryl, O-C₆₋₁₀-aryl, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ or C₃₋₇-cycloalkyl and

Z² denotes OH, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, O(C₁₋₆-alkyl), mono- or bicyclic C₃₋₇-cycloalkyl, mono- or bicyclic C₅₋₁₀-heteroaryl, mono- or bicyclic C₃₋₁₀-heterocycle or C₆₋₁₀-aryl;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

4. Compounds of formula 1 according to claim 3, wherein

A denotes CH₂, CD₂, C=NH, CHMe, CMe₂, 1,1'-cyclopropylene or 1,1'-cyclobutylidene;

B¹ denotes phenyl;

B² denotes phenyl;

X denotes O

5 and wherein

n denotes 0 or 1;

R¹ denotes H;

10

R² denotes H,

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally
in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates
15 thereof, as well as deuterated forms thereof.

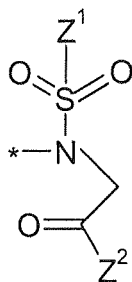
5. Compounds of formula **1** according to claim 3 or 4,

R³ denotes C₁₋₆-alkyl, which may optionally be substituted by one or more groups
20 selected from among halogen, OH, CN, CONH₂, CONH-C₁₋₆-alkyl,
CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl,
OH, O-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol; SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂,
SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl and
N(C₁₋₆-alkyl)₂,

25

or **R³** denotes a group selected from among C₃₋₈-cycloalkyl, a C₃₋₈-cycloalkyl bridged by
C₁₋₃-alkylene and C₁₋₆-alkyl, which may optionally be substituted by one or more
groups selected from among C₆₋₁₀-aryl, C₃₋₈-cycloalkyl, a C₅₋₁₀-heteroaryl and a
C₃₋₁₀-heterocycle, which may in turn optionally be substituted by one or more

- groups selected from among C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-haloalkyl, CN, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SH, S-C₁₋₆-alkyl, S-C₁₋₆-haloalkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂, C₅₋₁₀-heteroaryl and a C₃₋₁₀-heterocycle, which may optionally be substituted by one or more groups selected from oxo, hydroxyl, halogen or C₁₋₆-alkyl and C₁₋₆-haloalkyl;
- 10 or R³ denotes a group selected from among C₆₋₁₀-aryl, a C₃₋₈-heterocycle with 1 to 4 heteroatoms selected from N, O, S and a C₅₋₁₀-heteroaryl with 1 to 2 heteroatoms selected from N, O, S, which may optionally be substituted by one or more groups selected from among C₆₋₁₀-aryl, C₁₋₆-alkyl, C₁₋₆-haloalkyl, CONH₂, CONH-C₁₋₆-alkyl, CON(C₁₋₆-alkyl)₂, COOH, COO-C₁₋₆-alkyl, COH, CO-C₁₋₆-alkyl, CO-C₆₋₁₀-aryl, OH, O-C₁₋₆-alkyl, O-C₁₋₆-haloalkyl, halogen, SO₂-C₁₋₆-alkyl, SO₂-C₁₋₆-alkanol, SO₂-C₁₋₆-haloalkyl, SO₂-NH₂, SO₂-NH-C₁₋₆-alkyl, SO₂-N(C₁₋₆-alkyl)₂, NO₂, NH₂, NH-C₁₋₆-alkyl, N(C₁₋₆-alkyl)₂ and N-(SO₂-C₁₋₄-alkyl)(R^{3,4}), wherein R^{3,4} is a C₅₋₁₀-heteroaryl-C₁₋₆-alkylene;
- 20 or R³ denotes a group selected from among C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene, C₅₋₁₀-heteroaryl-C₁₋₆-alkylene, C₃₋₇-cycloalkyl, C₆₋₁₀-aryl, C₃₋₈-heterocycle with 1 to 4 heteroatoms selected from N, O, S, and a C₅₋₁₀-heteroaryl with 1 to 2 heteroatoms selected from N, O, S, which may optionally be substituted in each case by one or more groups selected from among B, halogen, OH, C₁₋₆-alkyl, oxo, wherein B is a
- 25 compound of formula 2



wherein

Z^1 is H, OH, halogen, C_{1-6} -alkyl, C_{1-6} -alkanol or $O(C_{1-6}$ -alkyl) and

Z^2 is OH, NH_2 , $NH(C_{1-6}$ -alkyl), $N(C_{1-6}$ -alkyl) $_2$, $O(C_{1-6}$ -alkyl), mono- or bicyclic C_{3-7} -cycloalkyl, mono- or bicyclic C_{5-10} -heteroaryl, mono- or bicyclic C_{3-10} -

5 heterocycle or C_{6-10} -aryl;

and wherein R^4 denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the
10 form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof,
as well as deuterated forms thereof.

6. Compounds of formula **1** according to one of claims 1 to 3, wherein

15

A denotes CO, C=NH, C_{1-4} -alkylene or C_{3-6} -cycloalkylene, C_{1-6} -alkylene or C_{3-8} -cycloalkylene,

20

B^1 denotes phenyl or pyridinyl;

B^2 denotes phenyl or pyridinyl;

X denotes O;

25

n denotes 0, 1, 2 or 3;

R^1 denotes H, methyl, ethyl or propyl;

R^2 denotes H, methyl, ethyl or propyl;

30

R^3 denotes H, OH, C_{1-6} -haloalkyl or C_{6-10} -aryl or a group selected from among a C_{5-10} -heteroaryl and a C_{3-10} -cycloalkyl, which may contain one, two or three nitrogen atoms and which may optionally be substituted by a methyl group;

5 or R^3 denotes a group selected from among cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methyl, ethyl, propyl and butyl, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl and a C_{5-10} -heterocycle, which may in turn optionally be substituted by one or more groups selected from among C_{1-6} -alkyl, C_{1-6} -haloalkyl, CN, OH, O- C_{1-6} -alkyl, O- C_{1-6} -haloalkyl, halogen,
10 S- C_{1-6} -alkyl, S- C_{1-6} -haloalkyl, NO_2 , NH_2 , NH- C_{1-6} -alkyl and N(C_{1-6} -alkyl)₂;

or R^3 denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, C_{1-4} -haloalkyl, $CONH_2$, $CONH-C_{1-4}$ -alkyl, $CON(C_{1-4}-alkyl)_2$, $COOH$, $COO-C_{1-4}$ -alkyl, COH ,
15 $CO-C_{1-4}$ -alkyl, $CO-C_{6-10}$ -aryl, OH, O- C_{1-4} -alkyl, O- C_{1-4} -haloalkyl, halogen, SH, S- C_{1-4} -alkyl, S- C_{1-4} -haloalkyl, SO_2-C_{1-4} -alkyl, SO_2-C_{1-4} -haloalkyl, SO_2-NH_2 , SO_2-NH-C_{1-4} -alkyl, $SO_2-N(C_{1-4}-alkyl)_2$, NO_2 , NO_2 , NH_2 , NH- C_{1-4} -alkyl and N(C_{1-4} -alkyl)₂;

20 or R^3 denotes phenyl, which may optionally be substituted by C_{1-4} -alkyl, which may in turn optionally be substituted by a group selected from among $COOR^{3.3}$, $NR^{3.3}R^{3.4}$, $NHCOR^{3.3}$, $NHCOOR^{3.3}$, *p*-fluorophenyl and a heterocycle, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen and which may optionally be substituted by an oxo group;

25 wherein

$R^{3.3}$ denotes H or C_{1-4} -alkyl;

$R^{3.4}$ denotes H, C_{1-4} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene or C_{5-10} -heteroaryl- C_{1-6} -alkylene;

30 or R^3 denotes phenyl, which may be substituted by $NR^{3.1}R^{3.2}$;
wherein

$R^{3.1}$ denotes H, C_{1-4} -alkyl, $COR^{3.1.1}$, $COOR^{3.1.1}$, $CONR^{3.1.1}R^{3.1.2}$ or $SO_2-R^{3.1.1}$;

and

$R^{3.1.1}$ denotes H, C_{1-4} -alkyl or C_{6-10} -aryl;

5 $R^{3.1.2}$ denotes H, C_{1-4} -alkyl or C_{6-10} -aryl;

$R^{3.2}$ denotes H, C_{1-4} -alkyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NH(C_{1-4}\text{-alkyl})$, $N(C_{1-4}\text{-alkyl})_2$, oxo or a C_{3-10} -heterocycle, which may contain one or
10 two nitrogen atoms and which may optionally be substituted by a methyl group;

or R^3 denotes phenyl, which may be substituted by a C_{5-10} -heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while
15 the C_{5-10} -heteroaryl may optionally be substituted by one or more groups selected from among C_{6-10} -aryl, C_{1-4} -alkyl, C_{1-4} -haloalkyl, C_{3-6} -cycloalkyl, CN, $CONH_2$, $CONH-C_{1-4}$ -alkyl, $CON(C_{1-4}\text{-alkyl})_2$, $COOH$, $COO-C_{1-4}$ -alkyl, COH , $CO-C_{1-4}$ -alkyl, OH , $O-C_{1-4}$ -alkyl, halogen, NH_2 and $N(C_{1-4}\text{-alkyl})_2$;

20 or R^3 denotes phenyl, which may be substituted by a C_{5-10} -heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C_{5-10} -heteroaryl may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo;

25 or R^3 denotes benzimidazolyl, which may optionally be substituted by one or more groups selected from among methyl, ethyl, propyl, CF_3 , CH_2CF_3 , cyclopropyl, cyclopentyl and cyclohexyl;

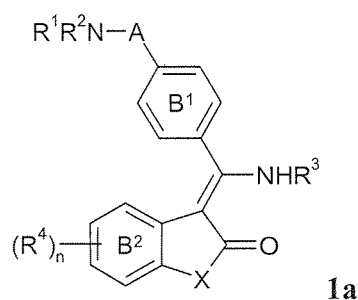
and

R^4 denotes C_{1-4} -alkyl, C_{1-4} -haloalkyl or halogen;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

5

7. Compounds of formula **1a**,



10 wherein A, X, n, R¹, R², R³ and R⁴ have the meanings given in claims 1 to 3, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

15

8. Compounds of formula **1** or **1a** according to one of claims 1 to 7 wherein

X denotes O;

5 optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

10

9. Compounds of formula **1** or **1a** according to one of claims 1 to 7 wherein

X denotes CR^6R^7 ;

15 optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

20 10. Compounds of formula **1** or **1a** according to one of claims 1 to 7, wherein

A denotes CH_2 , CHMe , CMe_2 , C=NH , 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

- B¹** denotes phenyl;
- B²** denotes phenyl;
- 5 **X** denotes O;
- n** denotes 0, 1 or 2;
- R¹** denotes H, methyl or ethyl;
- 10 **R²** denotes H, methyl or ethyl;
- R³** denotes H, cyclopropyl, cyclobutyl, N-methyl-piperidinyl, pyridinyl, phenyl or 4-phenyl-cyclohexane or
- 15 **R³** denotes phenyl, which may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, CF₃, CONH₂, CONHMe, CONMe₂, COOH, COOMe, COOEt, COH, COMe, OH, OMe, OEt, F, Cl, Br, SH, SO₂Me, SONH₂, SONMe₂, NO₂, NH₂, NHMe and NMe₂;
- or
- 20 **R³** denotes phenyl, which is optionally substituted by a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among COOH, COOMe, NH₂, NMe₂, NHCOMe, NHCOO-*tert*-butyl, NMe(benzyl), *p*-fluorophenyl, pyrrolidinyl, piperidinyl,
- 25 morpholinyl, pyrrolidin-2-onyl, imidazolyl and triazolyl;
- or
- R³** denotes phenyl, which is substituted by NR^{3.1}R^{3.2},
wherein
- 30 **R^{3.1}** denotes H, methyl, COH, COMe, COOMe, CONH₂, CONMe₂, SO₂Me, SO₂CF₃ or SO₂-phenyl,

and wherein

$R^{3.2}$ denotes H or a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NHMe$, NMe_2 , N-piperidinyl, N-morpholinyl and N-methyl-piperazinyl, wherein the N-piperidinyl, N-morpholinyl and the N-methyl-piperazinyl may optionally be substituted by a further oxo;

or

R^3 denotes phenyl, which may be substituted by a C_{5-10} -heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C_{5-10} -heteroaryl may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF_3 , CN, $CONH_2$, $CONMe_2$, $CONEt_2$, $COOH$, $COOMe$, $COOEt$, COH , $COMe$, OH , OMe , OEt , F, Cl, Br, NH_2 , NMe_2 , NEt_2 and NPr_2 ;

or

R^3 denotes phenyl, which is substituted by a C_{3-10} -heterocycle, which may contain one or two heteroatoms selected from among oxygen and nitrogen, while the C_{3-10} -heterocycle may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo;

or R^3 denotes benzimidazolyl, which may optionally be substituted by one or more groups selected from among methyl, propyl, CF_3 , CH_2CF_3 , cyclopropyl and cyclohexyl;

and wherein

R^4 denotes methyl, ethyl, propyl, butyl, CF_3 , CH_2CF_3 , F, Cl, or Br;

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

5

11. Compounds of formula **1** or **1a** according to one of claims 1 to 7 or 10, wherein

A denotes CH₂, CHMe, CMe₂, 1,1'-cyclopropylene, 1,1'-cyclobutylidene;

10 **B¹** denotes phenyl;

B² denotes phenyl;

X denotes O;

15

n denotes 0 or 1;

R¹ denotes H;

20 **R²** denotes H;

R³ denotes H, 4-phenyl-cyclohexanyl or

R³ denotes phenyl, which may optionally be substituted by NR^{3.1}R^{3.2};
25 wherein

R^{3.1} denotes H, methyl, SO₂Me, SO₂CF₃, or SO₂-phenyl;

and

$R^{3,2}$ denotes H or a group selected from among methyl and ethyl, which may optionally be substituted by one or more groups selected from among NH_2 , $NHMe$, NMe_2 , oxo, N-piperidinyl, N-morpholinyl and N-methyl-piperazinyl,

or

R^3 denotes phenyl, which is substituted by a C_{5-10} -heteroaryl, which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, while the C_{5-10} -heteroaryl may optionally be substituted by one or more groups selected from among phenyl, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, CF_3 , CN, $CONH_2$, $CONMe_2$, $CONEt_2$, $COOH$, $COOMe$, $COOEt$, COH , $COMe$, OH , OMe , OEt , F, Cl, Br, SO_2Me , $SONH_2$, $SONMe_2$, NO_2 , NH_2 , NMe_2 , NEt_2 and NPr_2 ,

or

R^3 denotes phenyl, which may be substituted by a C_{3-10} -heterocycle, which may contain one or two heteroatoms selected from among oxygen and nitrogen, while the C_{3-10} -heterocycle may optionally be substituted by one or more groups selected from among C_{1-4} -alkyl and oxo,

and wherein

R^4 denotes H, F or Cl;

optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof, as well as deuterated forms thereof.

25

12. Compounds according to one of claims 1 to 11 as pharmaceutical compositions.

13. Use of compounds according to one of claims 1 to 11 for preparing a medicament for the treatment of inflammatory and obstructive diseases such as COPD, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis.

5 **14.** Use of compounds according to one of claims 1 to 11 for preparing a medicament for the prevention and treatment of diseases of the peripheral or central nervous system such as depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke,
10 hypoxia or craniocerebral trauma.

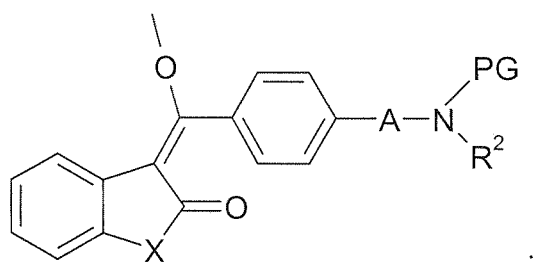
15. Pharmaceutical formulations, characterised in that they contain one or more compounds of formula **1** or **1a** according to one of claims 1 to 11.

16. Pharmaceutical formulation suitable for administration by inhalation, characterised in that it contains a compound of formula **1** or **1a** according to one of claims 1 to 11.

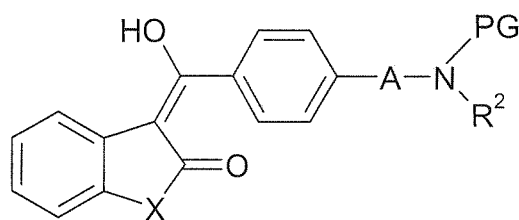
17. Pharmaceutical combinations which contain as an additional active substance, in addition to one or more compounds of formula **1** or **1a** according to one of claims 1 to 11, one or more compounds selected from the categories of the betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof.

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18. Intermediate products of the process according to Scheme 1 of the formulae i, ii or iii

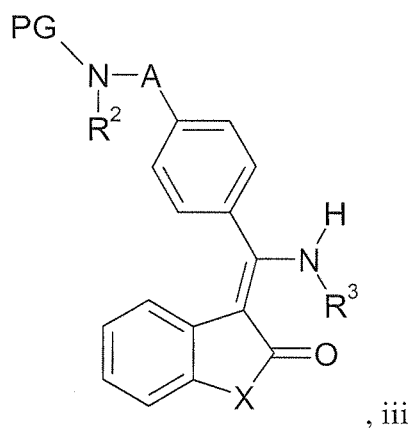


i,



ii, or

15



, iii

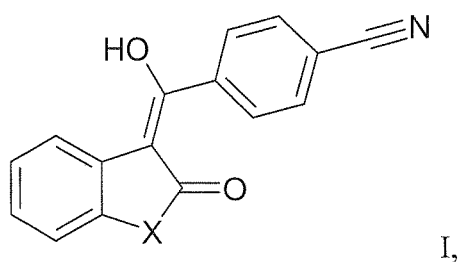
wherein X, A, R² and R³ have the meanings defined in claims 1 to 11 and PG is hydrogen or a suitable protecting group.

5

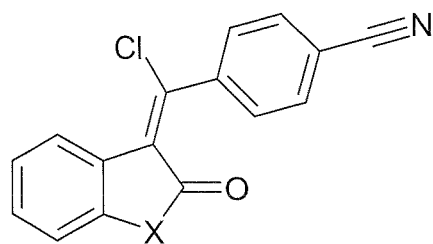
19. Intermediate products according to claim 18, wherein PG is the allyloxycarbonyl protecting group or the tert-butyloxycarbonyl protecting group and wherein X is either O or NR⁵, wherein R⁵ is defined as in claim 1.

10

20. Intermediate products of the process according to Scheme 2 of the formulae I, II, III, IV or V

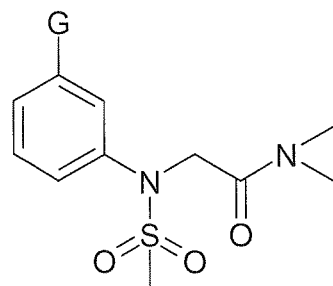


I,

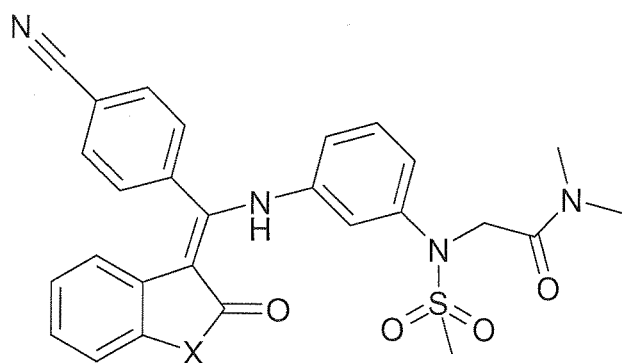


II,

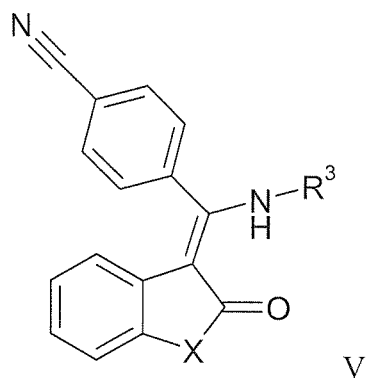
15



III,



IV, or



wherein G denotes NO_2 or NH_2 and wherein X and R^3 have the meanings defined in claims

5 1 to 11.