

Heterocyclic carboxylic acid derivatives having a 2,5-substituted oxazolopyrimidine ring

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The present invention relates to heterocyclic carboxylic acid derivatives comprising a 2,5-substituted oxazolopyrimidine ring, and to physiologically acceptable salts thereof.

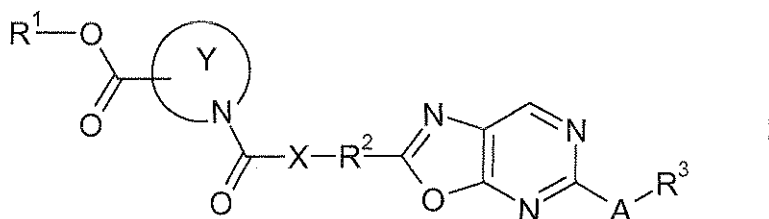
- 10 Structurally similar compounds are already described in the prior art (see WO 2009/154775), which are suitable for treating multiple sclerosis. The mode of action of these compounds consists in causing a desensitization of the EDG-1 signal pathway by activating the EDG-1 receptor (so-called superagonism), which is then equivalent to a functional antagonism of the EDG-1 signal pathway. Systemically
- 15 means that especially on lymphocytes, the EDG-1 signal pathway is permanently suppressed, as a result of which these cells can no longer chemotactically follow the S1P gradient between blood and lymph fluid. This means that the affected lymphocytes can no longer leave the secondary lymphatic tissue (increased homing) and the number of freely circulating lymphocytes in the plasma is greatly reduced.
- 20 This deficiency of lymphocytes in the plasma (lymphopenia) brings about immunosuppression which is obligatorily required for the mechanism of action of the EDG-1 receptor modulators described in WO 2009/154775.

The object of the present invention was to provide compounds which are suitable

25 specifically for wound healing and in particular for the treatment of wound healing disorders in patients with diabetes. In addition, it was desirable to provide compounds which are suitable for the treatment of diabetic foot syndrome (DFS). Furthermore, it was desirable to achieve a reproducible activation of the EDG-1 receptor signal pathway which thereby permits, in pharmacological terms, a

30 persistent activation of the EDG-1 signal pathway.

The present invention relates to oxazolopyrimidine compounds of the formula I,



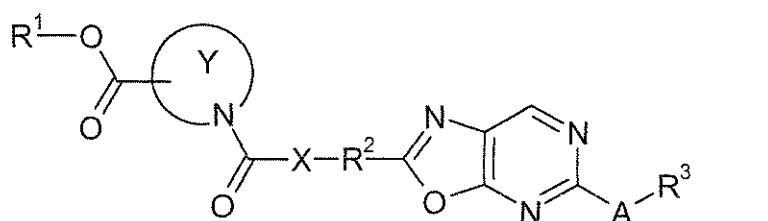
in which A, R¹, R², R³, X and Y are defined as indicated below. The mechanism of
5 action of the compounds of the formula I is not therefore based on desensitization of
the EDG-1 signal pathway and is thus in diametral opposition to the mechanism of
action described in WO 2009/154775. The invention furthermore relates to processes
for the preparation of compounds of the formula I, their use, in particular as active
ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

10 Compared with healthy people, patients with diabetes have delayed wound healing
and an increased rate of infection, especially in the case of long-term hyperglycemia,
caused for example by poor blood sugar regulation. The causes include circulation
disorders, especially in the area of the small vessels, which lead to impaired oxygen
15 and nutrient supply of the tissue. Moreover, the cell division and cell migration rate of
keratinocytes, fibroblasts and dermal endothelial cells is reduced. Additionally, the
activity of various defense cells (granulocytes) with reduced phagocytosis (engulfing
and destruction of bacteria) is restricted. The function of the antibodies (immuno-
globulins) against bacteria is also restricted in the event of high blood sugar values.
20 Accordingly, wounds and infections in patients with diabetes have to be cared for in a
particular way.

The Edg-1 receptor is a member of the endothelial differentiation gene (Edg) receptor
family of currently eight identified class A GPCRs (G-protein coupled receptors). This
25 family can be divided into subfamilies of sphingosine-1-phosphate (S1P)-activated
receptors (five members) and receptors activated by lysophosphatidic acid (LPA;
three members). The endogenous ligand S1P is a pluripotent lysophospholipid acting
on different cell types by activating GPCRs from the Edg receptor family, namely

Edg-1 (= S1P1), Edg-3 (= S1P3), Edg-5 (= S1P2), Edg-6 (= S1P4) and Edg-8 (S1P5). Although S1P is also described as an intracellular messenger, numerous cellular responses of S1P are mediated via the activation of Edg receptors. S1P is generated by the enzyme family of sphingosine kinases (SPHK) and degraded by
5 different phosphatases or lyases.

A subject of the present invention is an oxazolopyrimidine compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of
10 any of them,



15 wherein

A is chosen from NH, O and S;

X is chosen from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl, (C₂-C₆)-alkynediyl, (C₃-C₇)-cycloalkanediyl and (C₁-C₆)-alkanediyl-oxy, which all are optionally substituted by
20 one or more identical or different substituents chosen from fluorine and hydroxy, wherein the oxygen atom of the (C₁-C₆)-alkanediyl-oxy group is bonded to the group R²;

25 Y is 4-membered to 7-membered, saturated or partially unsaturated, monocyclic or bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0, 1, 2 or 3 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the additional ring nitrogen atoms can carry a hydrogen atom

or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

- 5 R¹ is chosen from hydrogen, (C₁-C₄)-alkyl and (C₃-C₇)-cycloalkyl-C_zH_{2z}-, wherein z is chosen from 0, 1 and 2;

R² is chosen from phenylene and a divalent residue of an aromatic, 5-membered to 6-membered monocyclic heterocycle which comprises 1, 2 or 3 identical or different
10 ring heteroatoms chosen from N, O and S, wherein one of the ring nitrogen atoms can carry a hydrogen atom or a substituent R²¹, and wherein the phenylene and divalent residue of an aromatic heterocycle are optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

- 15 R³ is chosen from (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1, 2, 3 or 4 identical or different ring heteroatoms chosen
20 from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one or two of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

- 25 R²¹ is chosen from (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl-C_wH_{2w}- and oxy, wherein w is chosen from 0, 1 and 2;

R²² is chosen from halogen, hydroxy, (C₁-C₄)-alkyl-, (C₁-C₄)-alkyloxy, (C₁-C₄)-alkyl-S(O)_m-, amino, nitro, cyano, hydroxycarbonyl, (C₁-C₄)-alkyloxycarbonyl, aminocarbonyl and aminosulfonyl;

- 30 R³¹ is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino,

(C₁-C₄)-alkylcarbonylamino, (C₁-C₄)-alkylsulfonylamino, nitro, cyano, (C₁-C₄)-alkylcarbonyl, aminosulfonyl, (C₁-C₄)-alkylaminosulfonyl and di((C₁-C₄)-alkyl)aminosulfonyl;

5 Het is a residue of a saturated, 4-membered to 7-membered, monocyclic heterocycle which comprises 1 or 2 identical or different ring heteroatoms chosen from N, O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from
10 fluorine and (C₁-C₄)-alkyl;

m is chosen from 0, 1 and 2, wherein all numbers m are independent of each other;

wherein all cycloalkyl and cycloalkanediyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more
15 identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl;

wherein all alkyl, alkanediyl, C_uH_{2u}, C_vH_{2v}, C_wH_{2w}, C_zH_{2z}, alkenyl, alkenediyl, alkynyl and alkynediyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

20 Structural elements such as groups, substituents, hetero ring members, numbers or other features, for example alkyl groups, groups like R²² or R³¹, numbers like m, u and v, which can occur several times in the compounds of the formula I, can all independently of one another have any of the indicated meanings and can in each
25 case be identical to or different from one another. For example, the alkyl groups in a dialkylamino group can be identical or different.

Alkyl, alkenyl and alkynyl groups can be linear, i.e. straight-chain, or branched. This also applies when they are part of other groups, for example alkyloxy groups (=
30 alkoxy groups, alkyl-O- groups), alkyloxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Depending on the respective definition, the number of carbon atoms in an alkyl group can be 1, 2, 3, 4, 5 or 6, or 1, 2, 3 or 4, or

- 1, 2 or 3. Examples of alkyl are methyl, ethyl, propyl including n-propyl and isopropyl, butyl including n-butyl, sec-butyl, isobutyl and tert-butyl, pentyl including n-pentyl, 1-methylbutyl, isopentyl, neopentyl and tert-pentyl, and hexyl including n-hexyl, 3,3-dimethylbutyl and isohexyl. Double bonds and triple bonds in alkenyl groups and alkynyl groups can be present in any positions. In one embodiment of the invention, alkenyl groups contain one double bond and alkynyl groups contain one triple bond. In one embodiment of the invention, an alkenyl group or alkynyl group contains at least three carbon atoms and is bonded to the remainder of the molecule via a carbon atom which is not part of a double bond or triple bond. Examples of alkenyl and alkynyl are ethenyl, prop-1-enyl, prop-2-enyl (= allyl), but-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, hex-3-enyl, hex-4-enyl, prop-2-ynyl (= propargyl), but-2-ynyl, but-3-ynyl, hex-4-ynyl or hex-5-ynyl. Substituted alkyl groups, alkenyl groups and alkynyl groups can be substituted in any positions, provided that the respective compound is sufficiently stable and is suitable for the desired purpose such as use as a drug substance. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable for the desired purpose such as use as a drug substance, applies in general with respect to the definitions of all groups in the compounds of the formula I.
- As far as applicable, the preceding explanations regarding alkyl, alkenyl and alkynyl groups apply correspondingly to divalent alkyl groups such as the groups alkanediyl, C_uH_{2u} , C_vH_{2v} , C_wH_{2w} and C_zH_{2z} and divalent alkenyl groups and alkynyl groups such as the groups alkenediyl and alkynediyl, which thus can likewise be linear and branched. The double bonds and triple bonds in alkenediyl and alkynediyl groups can be present in any positions. In one embodiment of the invention, alkenediyl groups contain one double bond and alkynediyl groups contain one triple bond. Examples of divalent alkyl groups are $-CH_2-$ (= methylene), $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-C(CH_3)_2-CH_2-$, $-CH_2-C(CH_3)_2-$, examples of divalent alkenyl groups are $-CH=CH-$, $-CH_2-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-C(CH_3)=C(CH_3)-$, and examples of divalent alkynyl groups are $-C\equiv C-$, $-CH_2-C\equiv C-$, $-C\equiv C-CH_2-$, $-C(CH_3)_2-C\equiv C-$, $-C\equiv C-C(CH_3)_2-$, $-CH_2-C\equiv C-CH_2-$, $-CH_2-CH_2-C\equiv C-$. If a number in a

divalent group such as the number z in the group C_zH_{2z} , for example, is 0 (= zero), the two groups which are attached to the contemplated group, such as C_zH_{2z} , are directly connected to one another via a single bond.

- 5 The number of ring carbon atoms in a cycloalkyl group can be 3, 4, 5, 6 or 7. In one embodiment of the invention, the number of ring carbon atoms in a cycloalkyl group, independently of the number of ring carbon atoms in any other cycloalkyl group, is 3, 4, 5 or 6, in another embodiment 3, 4 or 5, in another embodiment 3 or 4, in another embodiment 3, in another embodiment 5, 6 or 7, in another embodiment 5 or 6, in
- 10 another embodiment 6 or 7, in another embodiment 6. This applies accordingly to divalent cycloalkyl groups, i.e. cycloalkanediyl groups, which can be bonded to the adjacent groups via any one or two ring carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of divalent cycloalkyl groups are cyclopropane-1,1-diyl, cyclopropane-1,2-diyl,
- 15 cyclobutane-1,3-diyl, cyclopentane-1,1-diyl, cyclopentane-1,2-diyl, cyclopentane-1,3-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, cycloheptane-1,4-diyl. Independently of one another and independently of any other substituents, cycloalkyl groups and cycloalkanediyl groups are optionally substituted by one or more identical or different (C_1-C_4) -alkyl substituents which can
- 20 be located in any positions, i.e., cycloalkyl groups can be unsubstituted by alkyl substituents or substituted by alkyl substituents, for example by 1, 2, 3 or 4, or by 1 or 2, (C_1-C_4) -alkyl substituents, for example by methyl groups. Examples of alkyl-substituted cycloalkyl groups and cycloalkanediyl groups are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl, 2,2-dimethylcyclopropane-1,1-diyl,
- 25 2,2-dimethylcyclopropane-1,2-diyl, 2,2-dimethylcyclopentane-1,3-diyl, 6,6-dimethylcycloheptane-1,4-diyl. Examples of cycloalkylalkyl groups, which can represent groups such as (C_3-C_7) -cycloalkyl- C_2H_{2z} , for example, are cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclobutylethyl, 2-
- 30 cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl.

Independently of one another and independently of any other substituents, alkyl groups, divalent alkyl groups, alkenyl groups, divalent alkenyl groups, alkynyl groups, divalent alkynyl groups, cycloalkyl groups and divalent cycloalkyl groups are optionally substituted by one or more fluorine substituents which can be located in any positions, i.e., the said groups can be unsubstituted by fluorine substituents or substituted by fluorine substituents, for example by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, or by 1, 2, 3, 4, 5, 6, 7, 8 or 9, or by 1, 2, 3, 4, 5, 6 or 7, or by 1, 2, 3, 4 or 5, or by 1, 2 or 3, or by 1 or 2, fluorine substituents. Examples of fluorine-substituted said groups are trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, 4,4,4-trifluorobutyl, heptafluoroisopropyl, -CHF-, -CF₂-, -CF₂-CH₂-, -CH₂-CF₂-, -CF₂-CF₂-, -CF(CH₃)-, -C(CF₃)₂-, 1-fluorocyclopropyl, 2,2-difluorocyclopropyl, 3,3-difluorocyclobutyl, 1-fluorocyclohexyl, 4,4-difluorocyclohexyl, 3,3,4,4,5,5-hexafluorocyclohexyl, 2,2-difluorocyclopropane-1,2-diyl. Examples of alkyloxy groups in which the alkyl moiety is fluorine-substituted, are trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and 3,3,3-trifluoropropoxy. In one embodiment of the invention, the total number of fluorine substituents and (C₁-C₄)-alkyl substituents, which independently of any other substituents are optionally present on cycloalkyl groups and cycloalkanediyl groups in the compounds of the formula I, is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, in another embodiment 1, 2, 3, 4, 5, 6, 7, 8 or 9, in another embodiment 1, 2, 3, 4 or 5, in another embodiment 1, 2, 3 or 4.

Groups like phenyl, naphthyl (= naphthalenyl) and residues of aromatic heterocycles which are optionally substituted by one or more substituents, can be unsubstituted or substituted, for example by 1, 2, 3, 4 or 5, or by 1, 2, 3 or 4, or by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions. In one embodiment of the invention the total number of nitro substituents in a compound of the formula I is not greater than two. Aromatic nitrogen heterocycles which in the parent ring system carry a hydrogen atom on a ring nitrogen atom in a 5-membered ring, such as a pyrrole, imidazole, indole or benzoimidazole ring, for example, can be substituted on the carbon atoms and/or on such ring nitrogen atoms. In one embodiment of the invention, substituents on such ring nitrogen atoms

are chosen from (C₁-C₄)-alkyl groups, i.e. such ring nitrogen atoms in aromatic heterocycles carry a hydrogen atom or a (C₁-C₄)-alkyl substituent. When it is stated with respect to ring nitrogen atoms in aromatic heterocycles and any other heterocycles that they can carry a hydrogen atom or a substituent, such ring nitrogen

5 atoms either carry a hydrogen atom or a substituent, or they do not carry a hydrogen atom or substituent. Ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in a nitrogen-containing aromatic 5-membered ring as is present in pyrrole, imidazole, indole or benzoimidazole, for example, and in a non-aromatic ring including a saturated ring. Ring nitrogen atoms which do not carry a hydrogen atom

10 or a substituent unless they are present in positively charged form, including any further ring nitrogen atoms in addition to ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in an aromatic ring as is present in thiazole, imidazole, pyridine or benzoimidazole, for example, and in a non-aromatic ring in which they are bridgehead atoms or are part of a double bond, and they occur as ring nitrogen

15 atoms via which a ring is bonded. Suitable ring nitrogen atoms in aromatic heterocycles in the compounds of the formula I, such as the ring nitrogen atom in a pyridine ring, specifically a ring nitrogen atom in an aromatic heterocycle representing R², can also carry an oxy substituent -O⁻ and be present as an N-oxide, and such ring nitrogen atoms can also be present as quaternary salt, for example as

20 N-(C₁-C₄)-alkyl salt such as N-methyl salt, wherein in one embodiment of the invention the counter anion in such quaternary salt is a physiologically acceptable anion which is derived from an acid that forms a physiologically acceptable salt. In monosubstituted phenyl groups, the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups, the substituents can be

25 located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups, the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Naphthyl can be 1-naphthyl (= naphthalen-1-yl) or 2-naphthyl (= naphthalen-2-yl). In monosubstituted 1-naphthyl groups, the substituent can be located in the 2-, 3-, 4-,

30 5-, 6-, 7- or 8-position. In monosubstituted 2-naphthyl groups, the substituent can be located in the 1-, 3-, 4-, 5-, 6-, 7- or 8-position. In disubstituted naphthyl groups, the substituents can likewise be located in any positions both in the ring via which the

naphthyl group is bonded and/or in the other ring. This statement relating to the monovalent residues applies accordingly to the respective divalent residues, such as phenylene groups representing R^2 , for example, which thus can likewise be unsubstituted or substituted, for example by 1, 2, 3 or 4, or by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions.

In residues of aromatic heterocycles representing R^2 or R^3 , which may be designated as heteroaryl and heteroarylene groups, as well as in all other heterocyclic rings in the compounds of the formula I including the group Het and non-aromatic heterocyclic groups representing R^3 , the ring heteroatoms are generally chosen from N, O and S, wherein N includes ring nitrogen atoms which carry a hydrogen atom or a substituent as well as ring nitrogen atoms which do not carry a hydrogen atom or a substituent. Ring heteroatoms can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms cannot be present in adjacent ring positions of any heterocycle, in another embodiment two ring heteroatoms chosen from oxygen and sulfur cannot be present in adjacent ring positions of any heterocycle. Saturated rings do not contain a double bond within the ring. Unsaturated ring systems can be aromatic or partially unsaturated including partially aromatic, in which latter case one ring in a bicyclic ring system is aromatic and the ring system is bonded via an atom in the non-aromatic ring. Depending on the respective group, unsaturated rings can contain one, two, three, four or five double bonds within the ring. Aromatic groups contain a cyclic system of six or ten delocalized pi electrons in the ring. Depending on the respective group, saturated and non-aromatic unsaturated heterocyclic rings, including Het and non-aromatic groups representing R^3 , can be 3-membered, 4-membered, 5-membered, 6-membered, 7-membered, 8-membered, 9-membered or 10-membered. In one embodiment of the invention, aromatic heterocyclic rings are 5-membered or 6-membered monocyclic rings or 8-membered, 9-membered or 10-membered bicyclic rings, in another embodiment 5-membered or 6-membered monocyclic rings or 9-membered or 10-membered bicyclic rings, in another embodiment 5-membered or 6-

membered monocyclic rings, wherein the 8-membered, 9-membered or 10-membered bicyclic rings are composed of two fused 5-membered rings, a 5-membered ring and a 6-membered ring which are fused to one another, and two fused 6-membered rings, respectively. In bicyclic aromatic heterocyclic groups, one or both rings can contain hetero ring members, and one or both rings can be aromatic. In general, bicyclic ring systems containing an aromatic ring and a non-aromatic ring are regarded as aromatic when they are bonded via a carbon atom in the aromatic ring, and as non-aromatic when they are bonded via a carbon atom in the non-aromatic ring. Unless stated otherwise, heterocyclic groups including aromatic heterocyclic groups can be bonded via any suitable ring carbon atom and, in the case of nitrogen heterocycles, via any suitable ring nitrogen atom. In one embodiment of the invention, an aromatic heterocyclic group in a compound of the formula I, independently of any other aromatic heterocyclic group, is bonded via a ring carbon atom, in another embodiment via a ring nitrogen atom. Depending on the definition of the respective heterocyclic group, in one embodiment of the invention the number of ring heteroatoms which can be present in a heterocyclic group, independently of the number of ring heteroatoms in any other heterocyclic group, is 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 1, wherein the ring heteroatoms can be identical or different. Heterocyclic groups which are optionally substituted, can independently of any other heterocyclic group be unsubstituted or substituted by one or more identical or different substituents, for example by 1, 2, 3, 4 or 5, or by 1, 2, 3 or 4, or by 1, 2 or 3, or by 1 or 2, or by 1 substituents, which are indicated in the definition of the respective group. Substituents on heterocyclic groups can be located in any positions. For example, in a pyridin-2-yl group substituents can be located in the 3-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-3-yl group substituents can be located in the 2-position and/or 4-position and/or 5-position and/or 6-position, and in a pyridin-4-yl group substituents can be located in the 2-position and/or 3-position and/or 5-position and/or 6-position.

Examples of parent heterocycles, from which heterocyclic groups including aromatic heterocyclic groups, saturated heterocyclic groups and non-aromatic unsaturated

- heterocyclic groups can be derived, are azete, oxete, pyrrole, furan, thiophene, imidazole, pyrazole, [1,3]dioxole, oxazole (= [1,3]oxazole), isoxazole (= [1,2]oxazole), thiazole (= [1,3]thiazole), isothiazole (= [1,2]thiazole), [1,2,3]triazole, [1,2,4]triazole, [1,2,4]oxadiazole, [1,3,4]oxadiazole, [1,2,4]thiadiazole, [1,3,4]thiadiazole, tetrazole,
- 5 pyridine, pyran, thiopyran, pyridazine, pyrimidine, pyrazine, [1,3]oxazine, [1,4]oxazine, [1,3]thiazine, [1,4]thiazine, [1,2,3]triazine, [1,3]dithiine, [1,4]dithiine, [1,2,4]triazine, [1,3,5]triazine, [1,2,4,5]tetrazine, azepine, [1,3]diazepine, [1,4]diazepine, [1,3]oxazepine, [1,4]oxazepine, [1,3]thiazepine, [1,4]thiazepine, azocine, azecine, cyclopenta[b]pyrrole, 2-azabicyclo[3.1.0]hexane, 3-
- 10 azabicyclo[3.1.0]hexane, 2-oxa-5-azabicyclo[2.2.1]heptane, indole, isoindole, benzothiophene, benzofuran, [1,3]benzodioxole (= 1,2-methylenedioxybenzene), [1,3]benzoxazole, [1,3]benzothiazole, benzoimidazole, thieno[3,2-c]pyridine, chromene, isochromene, [1,4]benzodioxine, [1,4]benzoxazine, [1,4]benzothiazine, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine,
- 15 thienothiophene, [1,8]naphthyridine and other naphthyridines, pteridine, and the respective saturated and partially saturated heterocycles in which one or more, for example one, two, three, four or all double bonds within the ring system including double bonds in aromatic ring are replaced with single bonds, such as azetidine, oxetane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, imidazolidine, oxazolidine,
- 20 thiazolidine, dihydropyridine, piperidine, tetrahydropyran, piperazine, morpholine, thiomorpholine, azepane, chroman, isochroman, [1,4]benzodioxane (= 1,2-ethylenedioxybenzene), 2,3-dihydrobenzofuran, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, for example.
- 25 Examples of residues of aromatic heterocycles, which can occur in the compounds of the formula I, are thiophenyl (= thienyl) including thiophen-2-yl and thiophen-3-yl, pyridinyl (= pyridyl) including pyridin-2-yl (= 2-pyridyl), pyridin-3-yl (= 3-pyridyl) and pyridin-4-yl (= 4-pyridyl), imidazolyl including, for example, 1H-imidazol-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl and 1H-imidazol-5-yl, [1,2,4]triazolyl including 1H-
- 30 [1,2,4]-triazol-1-yl and 4H-[1,2,4-triazol-3-yl, tetrazolyl including 1H-tetrazol-1-yl and 1H-tetrazol-5-yl, quinolinyl (= quinolyl) including quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl and quinolin-8-yl, which all are optionally

substituted as indicated in the definition of the respective group. Examples of residues of saturated and partially unsaturated heterocycles, which can occur in the compounds of the formula I, are azetidiny, pyrrolidiny including pyrrolidin-1-yl, pyrrolidin-2-yl and pyrrolidin-3-yl, 2,5-dihydro-1H-pyrrolyl, piperidiny including piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and piperidin-4-yl, 1,2,3,4-tetrahydropyridiny, 1,2,5,6-tetrahydropyridiny, 1,2-dihydropyridiny, azepanyl, azocanyl, azecanyl, octahydrocyclopenta[b]pyrrolyl, 2,3-dihydrobenzofuranyl including 2,3-dihydrobenzofuran-7-yl, 2,3-dihydro-1H-indoly, octahydro-1H-indoly, 2,3-dihydro-1H-isoindoly, octahydro-1H-isoindoly, 1,2-dihydroquinoliny, 1,2,3,4-tetrahydroquinoliny, decahydroquinoliny, 1,2-dihydroisoquinoliny, 1,2,3,4-tetrahydroisoquinoliny, 1,2,3,4-tetrahydroisoquinoliny, decahydroisoquinoliny, decahydroisoquinoliny, 4,5,6,7-tetrahydrothieno[3,2-c]pyridiny, pyrazolidiny, imidazolidiny, hexahydropyrimidiny, 1,2-dihydropyrimidiny, piperaziny, [1,3]diazepanyl, [1,4]diazepanyl, oxazolidiny, [1,3]oxazinanyl, [1,3]oxazepanyl, morpholiny including morpholin-2-yl, morpholin-3-yl and morpholin-4-yl, [1,4]oxazepanyl, thiazolidiny, [1,3]thiazinanyl, thiomorpholiny including thiomorpholin-2-yl, thiomorpholin-3-yl and thiomorpholin-4-yl, 3,4-dihydro-2H-[1,4]thiaziny, [1,3]thiazepanyl, [1,4]thiazepanyl, [1,4]thiazepanyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, isoxazolidiny, isothiazolidiny, oxazolidiny, [1,2,4]-oxadiazolidiny, [1,2,4]-thiadiazolidiny, [1,2,4]triazolidiny, [1,3,4]oxadiazolidiny, [1,3,4]thiadiazolidiny, [1,3,4]triazolidiny, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, 2,3-dihydrothienyl, 2,5-dihydrothienyl, 2,3-dihydropyrrolyl, 2,3-dihydroisoxazolyl, 4,5-dihydroisoxazolyl, 2,5-dihydroisoxazolyl, 2,3-dihydroisothiazolyl, 4,5-dihydroisothiazolyl, 2,5-dihydroisothiazolyl, 2,3-dihydropyrazolyl, 4,5-dihydropyrazolyl, 2,5-dihydropyrazolyl, 2,3-dihydrooxazolyl, 4,5-dihydrooxazolyl, 2,5-dihydrooxazolyl, 2,3-dihydrothiazolyl, 4,5-dihydrothiazolyl, 2,5-dihydrothiazolyl, 2,3-dihydroimidazolyl, 4,5-dihydroimidazolyl, 2,5-dihydroimidazolyl, tetrahydropyridaziny, tetrahydropyrimidiny, tetrahydropyraziny, tetrahydro[1,3,5]triaziny, [1,3]dithianyl, tetrahydropyrany, tetrahydrothiopyrany, [1,3]dioxolany, 3,4,5,6-tetrahydropyridiny, 4H-[1,3]thiaziny, 1,1-dioxo-2,3,4,5-tetrahydrothienyl, 2-azabicyclo[3.1.0]hexyl including 2-azabicyclo[3.1.0]hex-2-yl, 3-azabicyclo[3.1.0]hexyl including 3-azabicyclo[3.1.0]hex-3-yl, 2-oxa-5-

azabicyclo[2.2.1]-heptyl including 2-oxa-5-azabicyclo[2.2.1]-hept-5-yl, which all are bonded via any suitable ring carbon atom or ring nitrogen atom and are optionally substituted as indicated in the definition of the respective group.

Halogen is fluorine, chlorine, bromine or iodine. In one embodiment of the invention,

- 5 any halogen in a compound of the formula I is independently of any other halogen chosen from fluorine, chlorine and bromine, in another embodiment from fluorine and chlorine.

- 10 When an oxo group is bonded to a carbon atom, it replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH_2 group in a chain or a ring is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a $\text{C}(\text{O})$ ($=\text{C}(\text{=O})$) group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring such as in a phenyl group, for example. When a ring sulfur atom in a heterocyclic group can carry one or two oxo groups, it is a non-oxidized
- 15 sulfur atom S in case it does not carry any oxo group, or it is an $\text{S}(\text{O})$ group ($=$ sulfoxide group, S-oxide group) in case it carries one oxo group, or it is an $\text{S}(\text{O})_2$ group ($=$ sulfone group, S,S-dioxide group) in case it carries two oxo groups.

- 20 The present invention includes all stereoisomeric forms of the compounds of the formula I and their salts and solvates. With respect to each chiral center, independently of any other chiral center, the compounds of the formula I can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and
- 25 mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or
- 30 cis/trans isomerism, for example on double bonds or rings such as cycloalkyl rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. In one embodiment of the invention, a

compound which can occur in two or more stereoisomeric forms is a pure, or substantially pure, individual stereoisomer. The preparation of individual stereoisomers can be carried out, for example, by separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective synthesis. Optionally, a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formula I or at the stage of a starting material or an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of the formula I and their salts and solvates.

In case the compounds of the formula I contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also includes their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts. Thus, the compounds of the formula I which contain an acidic group, such as a hydroxycarbonyl group (= carboxy group = C(O)-OH group), can be present on such groups, and can be used according to the invention, as alkaline metal salts, alkaline earth metal salts or as ammonium salts, for example. More specific examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts, quaternary ammonium salts such as tetraalkylammonium salts, or acid addition salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula I which contain a basic group, i.e. a group which can be protonated such as an amino group or a nitrogen heterocycle, can be present on such groups, and can be used according to the invention, in the form of their addition salts with inorganic and organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, methanesulfonic acid, oxalic acid, acetic acid, trifluoroacetic acid, tartaric acid, lactic acid, benzoic acid, malonic acid, fumaric acid, maleic acid, citric acid, and other acids known to the person skilled in the art. If a compound of the formula I simultaneously contains an acidic group and a basic group in the molecule, the compound also includes, in addition to the salt forms mentioned, inner salts (= betaines, zwitterions). The salts of

- the compounds of the formula I can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting the compound of the formula I with an organic or inorganic acid or base in a solvent or diluent, or by anion exchange or cation exchange from another salt. The invention also includes all
- 5 salts of the compounds of the formula I which, owing to low physiological compatibility of the salt-forming acid or base, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of physiologically acceptable salts.
- 10 The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols such as (C₁-C₄)-alkanols, active metabolites of the compounds of the formula I, and also prodrugs and derivatives of the compounds of the formula I which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active
- 15 compounds, for example esters or amides of carboxylic acid groups.

In one embodiment of the invention, A is chosen from NH and O, in another embodiment, A is chosen from NH and S, in another embodiment A is chosen from O and S, in another embodiment A is NH, in another embodiment A is O, in another

20 embodiment A is S.

The alkanediyl, alkenediyl and alkynediyl groups occurring in the group X can be linear or branched, as already indicated with respect to such groups in general, and these groups as well as cycloalkanediyl groups representing X can be bonded to the

25 adjacent groups, i.e. to the heterocycle Y and to the group R² or, in the case of the group alkanediyl-oxy, to the oxygen atom of the alkanediyl-oxy group via any positions. The said adjacent groups can be bonded to the same carbon atom or to different carbon atoms in the group X. In one embodiment, the chain of carbon atoms in an alkanediyl, alkenediyl and alkynediyl groups occurring in the group X which

30 directly connects the heterocycle Y to the group R² or, in the case of the group alkanediyl-oxy, to the oxygen atom of the alkanediyl-oxy group, consists of 1, 2, 3 or 4 carbon atoms, in another embodiment of 1, 2 or 3 carbon atoms, in another

embodiment of 1 or 2 carbon atoms, in another embodiment of 1 carbon atom. In the case of a cycloalkanediyl group representing X, in one embodiment the heterocycle Y and the group R² are bonded to two ring carbon atoms which are in 1,2-position, 1,3-position or 1,4-position with respect to each other, in another embodiment in 1,2-position or 1,3-position with respect to each other, in another embodiment in 1,2-position with respect to each other, in another embodiment in 1,4-position with respect to each other. In one embodiment, X is chosen from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl, (C₃-C₇)-cycloalkanediyl and (C₁-C₆)-alkanediyl-oxy, in another embodiment from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl and (C₁-C₆)-alkanediyl-oxy, in another embodiment from (C₁-C₆)-alkanediyl, (C₃-C₇)-cycloalkanediyl and (C₁-C₆)-alkanediyl-oxy, in one embodiment from (C₁-C₆)-alkanediyl and (C₁-C₆)-alkanediyl-oxy, in another embodiment from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl, (C₂-C₆)-alkynediyl and (C₃-C₇)-cycloalkanediyl, in another embodiment from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl and (C₃-C₇)-cycloalkanediyl, in another embodiment from (C₁-C₆)-alkanediyl and (C₂-C₆)-alkenediyl, in another embodiment X is (C₁-C₆)-alkanediyl, in another embodiment X is (C₂-C₆)-alkenediyl, in another embodiment X is (C₃-C₇)-cycloalkanediyl, and in another embodiment X is (C₁-C₆)-alkanediyl-oxy, which all are optionally substituted as indicated. In one embodiment a (C₁-C₆)-alkanediyl group occurring in X is a (C₁-C₄)-alkanediyl group, in another embodiment a (C₁-C₃)-alkanediyl group, in another embodiment a (C₁-C₂)-alkanediyl group. In one embodiment, the (C₂-C₆)-alkenediyl and (C₂-C₆)-alkynediyl groups representing X are (C₂-C₄)-alkenediyl and (C₂-C₄)-alkynediyl groups, in another embodiment (C₂-C₃)-alkenediyl and (C₂-C₃)-alkynediyl groups. In one embodiment, a (C₃-C₇)-cycloalkanediyl group representing X is a (C₃-C₆)-cycloalkanediyl group, in another embodiment a (C₃-C₄)-cycloalkanediyl group, in another embodiment a cyclopropanediyl group, in another embodiment a cyclohexanediyl group. Examples of groups X from any one or more of which the respective group representing X can be chosen in the aforementioned embodiments, or from any one or more of which X is chosen in another embodiment of the invention, are methylene, -CH(CH₃)- (ethane-1,1-diyl), -CH₂-CH₂- (ethane-1,2-diyl, 1,2-ethylene), -C(CH₃)₂- (1-methylethane-1,1-diyl), -CH₂-CH₂-CH₂- (propane-1,3-diyl, 1,3-propylene), -CH₂-CH(CH₃)- and

-CH(CH₃)-CH₂- (propane-1,2-diyl, 1,2-propylene), which exemplify the group (C₁-C₆)-alkanediyl, -CH=CH- (ethene-1,2-diyl), -CH=CH-CH₂- and -CH₂-CH=CH- (prop-1-ene-1,3-diyl and prop-2-ene-1,3-diyl) and -CH=C(CH₃)- and -C(CH₃)=CH- (prop-1-ene-1,2-diyl) which exemplify the group (C₂-C₆)-alkenediyl, -C≡C- (ethynediyl) and -CH₂-C≡C- and -C≡C-CH₂- (prop-1-yne-1,3-diyl and prop-2-yne-1,3-diyl) which exemplify the group (C₂-C₆)-alkynediyl, cyclopropane-1,1-diyl, cyclopropane-1,2-diyl and cyclohexane-1,4-diyl which exemplify the group (C₃-C₇)-cycloalkanediyl, -CH₂-O- (methylene-oxy), -CH₂-CH₂-O- (ethane-1,2-diyl-oxy), -CH(CH₃)-O- (ethane-1,1-diyl-oxy), -C(CH₃)₂-O- (1-methyl-ethane-1,1-diyl-oxy), -CH₂-CH₂-CH₂-O- (propane-1,3-diyl-oxy) and -CH₂-CH₂-CH₂-CH₂-O- (butane-1,4-diyl-oxy) which exemplify the group (C₁-C₆)-alkanediyl-oxy, all of which are optionally substituted as indicated. Thus, in one embodiment X is chosen from -CH₂-O-, -CH₂-CH₂-O-, -CH(CH₃)-O- and -C(CH₃)₂-O-, in another embodiment from -CH₂-O-, -CH₂-CH₂-O- and -CH(CH₃)-O-, in another embodiment from -CH₂-O- and -CH(CH₃)-O-, and in another embodiment X is -CH₂-O-, all of which are optionally substituted as indicated, and in which the oxygen atom is bonded to the group R². In one embodiment, the number of substituents which are optionally present in X, is 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 1, and in another embodiment the group X is not substituted by substituents chosen from fluorine and hydroxy. In one embodiment, the number of hydroxy substituents in X is not greater than 2, in another embodiment not greater than 1. In one embodiment, no more than one hydroxy substituent is present on an individual carbon atom in X. In one embodiment, hydroxy substituents are not present on carbon atoms which are part of a double bond in the group (C₂-C₆)-alkenediyl. In one embodiment, hydroxy substituents are not present on the carbon atom in the group (C₁-C₆)-alkanediyl-oxy which is bonded to the oxygen atom, in another embodiment no substituents are present on the carbon atom in the group (C₁-C₆)-alkanediyl-oxy which is bonded to the oxygen atom, i.e. in this latter embodiment all carbon atoms which are not linked to the said oxygen atom are optionally substituted by one or more identical or different substituents chosen from fluoro and hydroxy. The double bond in the group (C₂-C₆)-alkenediyl can have E configuration or Z configuration. In one embodiment it has E configuration, in another embodiment it has Z configuration.

The 4-membered to 7-membered saturated or partially unsaturated, monocyclic or bicyclic heterocycle Y comprises the ring nitrogen atom depicted in formula I, which carries the carbonyl group bonded to the group X, as ring heteroatom, and in addition comprises 0, 1, 2 or 3, in one embodiment of the invention 0, 1 or 2, in another embodiment 0 or 1, in another 1 or 2, in another embodiment 1, in another embodiment 0, identical or different further ring heteroatoms chosen from N, O and S, wherein one or two of the additional ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents. In one embodiment, the additional heteroatoms which can be present in Y, are chosen from N and O, in another embodiment from N and S, in another embodiment from O and S, in another embodiment they are N atoms, in another embodiment they are O atoms, and in another embodiment they are S atoms. As applies to the compounds of the formula I in general, ring heteroatoms in Y can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms in Y cannot be present in adjacent ring positions, in another embodiment two ring heteroatoms in Y chosen from oxygen and sulfur cannot be present in adjacent ring positions, and in another embodiment two ring heteroatoms in Y, including the ring nitrogen atom which is depicted in formula I, cannot be present in adjacent ring positions. In case Y is saturated, the heterocycle Y does not contain double bonds within the ring. In case Y is partially unsaturated, i.e. the heterocycle Y contains one or more double bonds within the ring but is non-aromatic, in one embodiment the heterocycle contains one or two, in another embodiment one, double bonds within the ring which can be present in any suitable positions. In one embodiment, Y is saturated, in another embodiment Y is partially unsaturated.

In one embodiment, Y is a 4-membered to 6-membered, in another embodiment a 4-membered to 5-membered, in another embodiment a 5-membered to 6-membered,

in another embodiment a 4-membered, in another embodiment a 5-membered, in another embodiment a 6-membered heterocycle which is saturated or partially unsaturated and monocyclic or bicyclic, and which is otherwise defined as indicated with respect to Y in general, as far as applicable. In one embodiment, the number of ring members in a monocyclic heterocycle representing Y is as indicated in the general definition of Y or in the afore-mentioned embodiments, and a bicyclic heterocycle representing Y is 6-membered to 7-membered, in another embodiment 6-membered, in another embodiment 7-membered. In bicyclic heterocycles representing Y the bridgehead atoms can be nitrogen atoms, which are any of the ring nitrogen atoms which can be present in addition to the ring nitrogen atom depicted in formula I, and/or ring carbon atoms. In one embodiment, one of the bridgehead atoms in a bicyclic heterocycle representing Y is a carbon atom and the other is a carbon atom or a nitrogen atom, in another embodiment both bridgehead atoms are carbon atoms. Examples of bicyclic ring systems from any one or more of which bicyclic heterocycles representing Y are chosen in one embodiment, are bicyclo[3.1.0], bicyclo[3.2.0], bicyclo[4.1.0], bicyclo[2.2.1] and bicyclo[2.1.1] ring systems which comprise the ring nitrogen atom depicted in formula I and any additional ring heteroatoms which are optionally present in Y, and which are saturated or partially unsaturated and are otherwise defined as indicated with respect to Y in general, as far as applicable. In one embodiment, a bicyclic heterocycle representing Y is saturated. In one embodiment Y is a monocyclic heterocycle, in another embodiment Y is a bicyclic heterocycle. In one embodiment, the number of (C₁-C₄)-alkyl substituents which are optionally present on ring carbon atoms in Y, is one, two, three or four, in another embodiment one or two, and in another embodiment Y is not substituted on ring carbon atoms by (C₁-C₄)-alkyl substituents.

In one embodiment, Y is a 4-membered to 7-membered, saturated, monocyclic or bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0 or 1 ring heteroatoms chosen from N, O and S, wherein an additional ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and a ring sulfur atom can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring carbon atoms by identical or different (C₁-

C₄)-alkyl substituents. In another embodiment, Y is a 4-membered to 6-membered, saturated, monocyclic heterocycle which does not comprise further ring heteroatoms in addition to the ring nitrogen atom depicted in formula I, wherein the ring is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents. In another embodiment, Y is chosen from any one or more of the heterocycles azetidine, pyrrolidine and piperidine, the ring nitrogen atom of which is the ring nitrogen atom of Y depicted in formula I which carries the carbonyl group bonded to the group X, wherein these heterocycles are optionally substituted on ring carbon atoms by one or more identical or different (C₁-C₄)-alkyl substituents, and in another embodiment these heterocycles do not carry alkyl substituents.

The group R¹-O-C(O)- can be bonded to the heterocycle Y in any suitable position. In one embodiment, the group R¹-O-C(O)- is bonded to a ring carbon atom of Y in any position, in another embodiment it is bonded to a ring carbon atom in Y which is in a ring position adjacent to the ring nitrogen atom in Y depicted in formula I, in another embodiment it is bonded to a ring carbon atom in Y which is adjacent to the said ring nitrogen atom or separated from the said ring nitrogen atom by one or two ring members, in another embodiment it is bonded to a ring carbon atom which is adjacent to the said ring nitrogen or separated from the said ring nitrogen atom by at least one ring member, in another embodiment it is bonded to a ring carbon atom in Y which is separated from the said ring nitrogen atom by one or two ring members, and in another embodiment it is bonded to a ring carbon atom which is separated from the said ring nitrogen atom by at least one ring member. For example, in case of a heterocycle Y which does not contain further ring heteroatoms in addition to the nitrogen atom depicted in formula I and in which the said ring nitrogen atom thus is in position 1 of the heterocycle, in one embodiment the group R¹-O-C(O)- is bonded to a ring carbon atom in any position, in another embodiment it is bonded in position 2, in another embodiment in position 3, in another embodiment in position 4, in another embodiment in position 2 or 3, in another embodiment in position 3 or 4, in another embodiment in position 2, 3 or 4. In one embodiment, in a partially unsaturated heterocycle Y the group R¹-O-C(O)- is bonded to a ring atom which is not part of a double bond. In one embodiment, in case of a bicyclic heterocycle Y the group R¹-O-

C(O)- is bonded to a ring atom which is not a bridgehead atom. The group Y can be present on the heterocycle Y in any stereochemical position, for example in endo position or exo position in the case of a bicyclic ring Y, or in cis position or in trans position with respect to a substituent on Y, or on a carbon atom having S

- 5 configuration or a carbon atom having R configuration. For example, in the case of a ring Y which is chosen from azetidine, pyrrolidine, piperidine and perhydroazepine, the ring nitrogen atom of which is the ring nitrogen atom of Y depicted in formula I, and which carries the group $R^1-O-C(O)-$ in position 2, in one embodiment the carbon atom carrying the group $R^1-O-C(O)-$ is present in S configuration. Examples of the
- 10 moiety $R^1O-C(O)-Y-$, from any one or more of which this moiety in the compounds of the formula I is chosen in one embodiment, are 2-hydroxycarbonyl-azetidin-1-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-azetidin-1-yl, (S)-2-hydroxycarbonyl-azetidin-1-yl, (S)-2-((C₁-C₄)-alkyloxycarbonyl)-azetidin-1-yl, 3-hydroxycarbonyl-azetidin-1-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-azetidin-1-yl, 2-hydroxycarbonyl-pyrrolidin-1-yl, 2-((C₁-C₄)-
- 15 alkyloxycarbonyl)-pyrrolidin-1-yl, (S)-2-hydroxycarbonyl-pyrrolidin-1-yl, (S)-2-((C₁-C₄)-alkyloxycarbonyl)-pyrrolidin-1-yl, 3-hydroxycarbonyl-pyrrolidin-1-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-pyrrolidin-1-yl, 2-hydroxycarbonyl-piperidin-1-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-piperidin-1-yl, (S)-2-hydroxycarbonyl-piperidin-1-yl, (S)-2-((C₁-C₄)-alkyloxycarbonyl)-piperidin-1-yl, 3-hydroxycarbonyl-piperidin-1-yl, 3-((C₁-C₄)-
- 20 alkyloxycarbonyl)-piperidin-1-yl, 4-hydroxycarbonyl-piperidin-1-yl, 4-((C₁-C₄)-alkyloxycarbonyl)-piperidin-1-yl, 2-hydroxycarbonyl-perhydroazepin-1-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-perhydroazepin-1-yl, (S)-2-hydroxycarbonyl-perhydroazepin-1-yl, (S)-2-((C₁-C₄)-alkyloxycarbonyl)-perhydroazepin-1-yl, 3-hydroxycarbonyl-perhydroazepin-1-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-perhydroazepin-1-yl, 4-
- 25 hydroxycarbonyl-perhydroazepin-1-yl, 4-((C₁-C₄)-alkyloxycarbonyl)-perhydroazepin-1-yl, 2-hydroxycarbonyl-morpholin-4-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-morpholin-4-yl, 3-hydroxycarbonyl-morpholin-4-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-morpholin-4-yl, 2-hydroxycarbonyl-thiomorpholin-4-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-thiomorpholin-4-yl, 3-hydroxycarbonyl-thiomorpholin-4-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-thiomorpholin-4-
- 30 yl, 2-hydroxycarbonyl-1,1-dioxo-thiomorpholin-4-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-1,1-dioxo-thiomorpholin-4-yl, 3-hydroxycarbonyl-1,1-dioxo-thiomorpholin-4-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-1,1-dioxo-thiomorpholin-4-yl, 2-hydroxycarbonyl-4-methyl-

piperazin-1-yl, 2-((C₁-C₄)-alkyloxycarbonyl)-4-methyl-piperazin-1-yl, 3-hydroxycarbonyl-4-methyl-piperazin-1-yl, 3-((C₁-C₄)-alkyloxycarbonyl)-1-methyl-piperazin-1-yl.

- 5 In one embodiment of the invention, the number z is chosen from 0 and 1, in another embodiment it is 0, in another embodiment it is 1. In one embodiment of the invention, the group R¹ is chosen from hydrogen and (C₁-C₄)-alkyl, in another embodiment R¹ is chosen from hydrogen, methyl, ethyl, n-propyl, n-butyl and isopropyl, in another embodiment from hydrogen, methyl and ethyl, in another
- 10 embodiment R¹ is hydrogen, in another embodiment R¹ is (C₁-C₄)-alkyl, in another embodiment R¹ is methyl, and in another embodiment R¹ is ethyl. In one embodiment, a (C₃-C₇)-cycloalkyl group occurring in R¹ is (C₃-C₆)-cycloalkyl, in another embodiment it is cyclopropyl.
- 15 In one embodiment of the invention, the number of ring heteroatoms in an aromatic heterocycle representing R² is 1 or 2, in another embodiment it is 1. In one embodiment of the invention, R² is chosen from phenylene and a divalent residue of an aromatic, 6-membered monocyclic heterocycle which comprises 1, 2 or 3 ring nitrogen atoms, in another embodiment 1 or 2 ring nitrogen atoms, in another
- 20 embodiment 1 ring nitrogen atom, wherein one of the ring nitrogen atoms can carry a substituent R²¹ which is oxy, i.e. wherein one of the ring nitrogen atoms can be oxidized to the N-oxide, and wherein the phenylene and divalent residue of an aromatic heterocycle are optionally substituted on one or more ring carbon atoms by identical or different substituents R²². In another embodiment, R² is phenylene,
- 25 wherein the phenylene is optionally substituted on one or more ring atoms by identical or different substituents R²², and in another embodiment R² is pyridinediyl, wherein the ring nitrogen atom can carry a substituent R²¹ which is oxy, i.e. wherein the ring nitrogen atom can be oxidized to the N-oxide, and wherein the pyridinediyl is optionally substituted on one or more ring carbon atoms by identical or different
- 30 substituents R²². In another embodiment, R² is a divalent residue of an aromatic 5-membered heterocycle which comprises 1, 2 or 3 identical or different ring heteroatoms chosen from N, O and S, wherein one of the ring nitrogen atoms can

carry a hydrogen atom or a substituent R^{21} , and wherein the divalent residue of an aromatic heterocycle is optionally substituted on one or more ring carbon atoms by identical or different substituents R^{22} . In one embodiment, a divalent residue of an aromatic heterocyclic group representing R^2 is chosen from furandiyl, thiophenediyl, oxazolediyl, thiazole-diyl, pyridinediyl, pyridazinediyl, pyrimidinediyl and pyrazinediyl, in another embodiment from furandiyl, thiophenediyl, thiazole-diyl, pyridinediyl, pyridazinediyl, pyrimidinediyl and pyrazinediyl, in another embodiment from furandiyl, thiophenediyl, pyridinediyl, pyridazinediyl, pyrimidinediyl and pyrazinediyl, in another embodiment from furandiyl, thiophenediyl, pyridinediyl and pyrimidinediyl, in another embodiment from furandiyl, thiophenediyl and pyridinediyl, which are all optionally substituted as indicated with respect to R^2 .

The ring carbon atoms via which the phenylene group and the divalent residue of an aromatic heterocycle representing R^2 are bonded to the oxazolopyrimidine ring and to the group X, can be in any positions. A phenylene group representing R^2 can be 1,2-phenylene, i.e. the oxazolopyrimidine ring and the group X can be bonded in 1,2-position, or ortho position, with respect to each other, it can be 1,3-phenylene, i.e. the oxazolopyrimidine ring and the group X can be bonded in 1,3-position, or meta position, with respect to each other, and it can be 1,4-phenylene, i.e. the oxazolopyrimidine ring and the group X can be bonded in 1,4-position, or para position, with respect to each other. In one embodiment, a phenylene group representing R^2 is chosen from 1,3-phenylene and 1,4-phenylene, in another embodiment it is 1,3-phenylene, and in another embodiment it is 1,4-phenylene, which all are optionally substituted as indicated with respect to R^2 . In one embodiment, R^2 is chosen from one or more of the groups phenylene, furan-2,5-diyl, thiophen-2,4-diyl, thiophene-2,5-diyl, pyridine-2,4-diyl, pyridine-2,5-diyl, pyridine-3,5-diyl, pyridine-2,6-diyl and pyrimidine-2,5-diyl, in another embodiment from the groups furan-2,5-diyl, thiophene-2,4-diyl, thiophene-2,5-diyl, pyridine-2,4-diyl, pyridine-2,5-diyl, pyridine-3,5-diyl, pyridine-2,6-diyl and pyrimidine-2,5-diyl, in another embodiment from pyridine-2,4-diyl, pyridine-2,5-diyl, pyridine-3,5-diyl and pyridine-2,6-diyl, in another embodiment from phenylene, pyridine-2,4-diyl, pyridine-2,5-diyl, pyridine-3,5-diyl and pyridine-2,6-diyl, which all are optionally substituted as indicated

with respect to R^2 . In one embodiment, the number of substituents R^{22} which are optionally present on ring carbon atoms in R^2 , is 1, 2, 3, 4 or 5, in another embodiment 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 1. Ring carbon atoms in R^2 which do not carry a substituent R^{22} , carry a hydrogen atom.

In one embodiment of the invention, R^3 is chosen from (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl and (C_2-C_6) -alkynyl, in another embodiment R^3 is (C_1-C_6) -alkyl, in another embodiment R^3 is (C_2-C_5) -alkyl, and in another embodiment R^3 is (C_1-C_4) -alkyl. In another embodiment R^3 is chosen from (C_1-C_6) -alkyl, (C_3-C_7) -cycloalkyl- C_uH_{2u} - and Het- C_vH_{2v} -, in another embodiment from (C_3-C_7) -cycloalkyl- C_uH_{2u} - and Het- C_vH_{2v} -, in another embodiment R^3 is (C_3-C_7) -cycloalkyl- C_uH_{2u} -, and in another embodiment R^3 is Het- C_vH_{2v} -, wherein in this embodiment u and v independently of each other are chosen from 1 and 2. In one embodiment u is 1, in another embodiment u is 2. In one embodiment v is 1, in another embodiment v is 2. In one embodiment, the group (C_3-C_7) -cycloalkyl- C_uH_{2u} - representing R^3 is chosen from cyclopropyl- C_uH_{2u} -, cyclobutyl- C_uH_{2u} - and cyclopentyl- C_uH_{2u} - and the group Het- C_vH_{2v} - representing R^3 is tetrahydrofuranyl- C_vH_{2v} -. In one embodiment, R^3 is chosen from cyclopropyl- C_uH_{2u} -, cyclobutyl- C_uH_{2u} - and cyclopentyl- C_uH_{2u} -.

In one embodiment, R^3 is chosen from (C_3-C_7) -cycloalkyl- C_uH_{2u} - and Het- C_vH_{2v} -, or R^3 is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1, 2, 3 or 4 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent and one or two of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R^{31} , and in another embodiment R^3 is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1, 2, 3 or 4 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent and one or two of the ring sulfur atoms can carry one or two oxo

groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R^{31} . In one embodiment, the number of ring heteroatoms in the ring representing R^3 is 0, 1, 2 or 3, in another embodiment it is 0, 1 or 2, in another embodiment it is 0 or 1, in another embodiment it is 0, in another embodiment it is 1, 2, 3 or 4, in another embodiment it is 1, 2 or 3, in another embodiment it is 1 or 2, in another embodiment it is 1. The residue of the ring representing R^3 can thus be carbocyclic or heterocyclic. In one embodiment, the ring heteroatoms in R^3 are chosen from N and O, in another embodiment from N and S, in another embodiment from O and S, in another embodiment they are N, wherein ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent as occurs in saturated or partially unsaturated heterocycles or in 5-membered aromatic rings in heterocycles such as pyrrole or benzoimidazole, for example, or not carry a hydrogen atom or a (C_1-C_4) -alkyl substituent as occurs in aromatic heterocycles such as imidazole or pyridine, for example. In a residue of a heterocycle representing R^3 which comprises one or more ring sulfur atoms, in one embodiment one of the ring sulfur atoms is non-oxidized or carries one or two oxo groups, and any other ring sulfur atoms are non-oxidized. The residue of a monocyclic or bicyclic ring representing R^3 can be bonded to the group A via any suitable ring carbon atom or ring nitrogen atom. In one embodiment it is bonded via a ring carbon atom, in another embodiment it is bonded via a ring carbon atom or, in case A is NH, via a ring nitrogen atom, and in another embodiment it is bonded via a ring nitrogen atom. The residue of a monocyclic or bicyclic ring representing R^3 can be unsaturated and in this case contain 1, 2, 3, 4 or 5, or 1, 2, 3 or 4, or 1, 2 or 3, or 1 or 2, or 1, double bonds within the ring and can in any of the one or two rings be aromatic or non-aromatic, or it can be saturated and in this latter case contain no double bonds within the ring. In one embodiment, the residue of the ring representing R^3 is saturated or aromatic, in another embodiment it is saturated, and in another embodiment it is aromatic. In one embodiment, the residue of the 3-membered or 4-membered ring representing R^3 is saturated. If R^3 comprises ring nitrogen atoms which can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent, one of such ring nitrogen atoms or two of such ring nitrogen atoms can be present. In one embodiment, the number of optional substituents R^{31} on ring carbon atoms in the ring representing R^3 is 1, 2, 3,

4, 5 or 6, in another embodiment 1, 2, 3, 4 or 5, in another embodiment 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 1.

- 5 The ring which can represent R^3 can be 3-membered, 4-membered, 5-membered, 6-membered, 7-membered, 8-membered, 9-membered or 10 membered. In one embodiment, R^3 is 4-membered to 10-membered, in another embodiment 4-membered to 9-membered, in another embodiment 4-membered to 8-membered, in another embodiment 4-membered to 7-membered, in another embodiment 5-membered to 7-membered, in another embodiment 5-membered or 6-membered, in another embodiment 6-membered, in another embodiment 8-membered to 10-membered, in another embodiment 9-membered to 10-membered. In one embodiment, a 3-membered ring representing R^3 does not comprise any ring heteroatoms. In one embodiment, R^3 is monocyclic, in another embodiment bicyclic.
- 10 In one embodiment, a bicyclic group representing R^3 is at least 7-membered. Among others, the residue of a ring representing R^3 can be a cycloalkyl group, a phenyl group, a naphthyl group, a residue of an unsaturated, aromatic or non-aromatic heterocyclic group or a residue of a saturated heterocyclic group, which all are optionally substituted on ring carbon atoms and ring nitrogen atoms as specified with respect to R^3 . As far as applicable, all explanations given above with respect to such groups apply correspondingly to R^3 . Another example of groups which can represent R^3 , are cycloalkenyl groups such as (C₅-C₇)-cycloalkenyl groups which can be bonded via any ring carbon atom and are optionally substituted as specified with respect to R^3 . In one embodiment, optional substituents R^{31} on a cycloalkenyl group representing R^3 are chosen from fluorine and (C₁-C₄)-alkyl. In one embodiment, cycloalkenyl groups contain one double bond within the ring which can be present in any position. Examples of cycloalkenyl are cyclopentenyl including cyclopent-1-enyl, cyclopent-2-enyl and cyclopent-3-enyl, cyclohexenyl including cyclohex-1-enyl, cyclohex-2-enyl and cyclohex-3-enyl, and cycloheptenyl including cyclohept-1-enyl, cyclohept-2-enyl, cyclopent-3-enyl and cyclohept-4-enyl. Examples of residues of rings, from any one or more of which R^3 is chosen in one embodiment of the invention, are cyclobutyl, cyclopentyl, cyclohexyl, phenyl, oxetanyl including oxetan-
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3-yl, tetrahydrofuranyl including tetrahydrofuran-3-yl, tetrahydrothiophenyl including tetrahydrothiophen-3-yl, tetrahydropyranyl including tetrahydropyran-4-yl, azetidiny including azetidin-1-yl, pyrrolidinyl, piperidinyl, imidazolidinyl, piperazin-yl, morpholinyl including morpholin-1-yl, thiomorpholinyl, furanyl including furan-3-yl, thiophenyl including thiophen-3-yl, pyrazolyl including pyrazol-3-yl, imidazolyl, thiazolyl including thiazol-2-yl, pyridinyl including pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, pyridazinyl including pyridazin-3-yl, wherein in all of them, if applicable, one or two of the ring nitrogen atoms can carry a hydrogen atom or (C₁-C₄)-alkyl, and wherein all of them are optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹, and wherein in all of them, if applicable, a ring sulfur atom can be non-oxidized, i.e. be present as a sulfur atom, or carry one or two oxo groups, i.e. be present in the form of a sulfoxide or sulfone.

In one embodiment, R³ is chosen from phenyl and a residue of a saturated or unsaturated 3-membered to 7-membered, monocyclic ring, in another embodiment from phenyl and a residue of a saturated or unsaturated 5-membered to 7-membered, monocyclic ring, in another embodiment from phenyl, pyridinyl and a residue of a saturated 3-membered to 7-membered, monocyclic ring, in another embodiment from phenyl, pyridinyl and a residue of a saturated 5-membered to 7-membered, monocyclic ring, in another embodiment from phenyl and pyridinyl, in another embodiment from phenyl and a residue of a saturated 3-membered to 7-membered, monocyclic ring, in another embodiment from phenyl and a residue of a saturated 5-membered to 7-membered, monocyclic ring, in another embodiment from any one or more of the groups phenyl, cyclobutyl, cyclopentyl, cyclohexyl and pyridinyl, in another embodiment from any one or more of the groups phenyl, cyclopentyl and cyclohexyl, in another embodiment from any one or both of the groups phenyl and cyclohexyl, wherein in all these embodiments the monocyclic ring comprises 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one or two of the ring sulfur atoms can carry one or two oxo groups, and wherein the phenyl, pyridinyl, residue of a ring, cyclobutyl, cyclopentyl and cyclohexyl are optionally substituted on one or more ring carbon atoms by

identical or different substituents R^{31} , and wherein pyridinyl includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl. In another embodiment, R^3 is phenyl which is optionally substituted by one or more identical or different substituents R^{31} .

- 5 In one embodiment of the invention, the number w is chosen from 0 and 1, in another embodiment it is 0, in another embodiment it is 1. In one embodiment, a (C_3-C_7) -cycloalkyl group present in R^{21} is (C_3-C_6) -cycloalkyl, in another embodiment (C_3-C_5) -cycloalkyl, in another embodiment cyclopropyl. In one embodiment, R^{21} is chosen from (C_1-C_4) -alkyl and oxy, in another embodiment R^{21} is (C_1-C_4) -alkyl, in another
10 embodiment it is (C_1-C_3) -alkyl, in another embodiment it is methyl, and in another embodiment it is oxy.

- In one embodiment of the invention, the substituents R^{22} which are optionally present on the group R^2 , are chosen from halogen, hydroxy, (C_1-C_4) -alkyl-, (C_1-C_4) -alkyloxy-,
15 (C_1-C_4) -alkyl-S(O) $_m$ -, amino, nitro and cyano, in another embodiment from halogen, hydroxy, (C_1-C_4) -alkyl-, (C_1-C_4) -alkyloxy-, amino and cyano-, in another embodiment from halogen, hydroxy, (C_1-C_4) -alkyl- and (C_1-C_4) -alkyloxy-, in another embodiment from fluorine, chlorine, hydroxy, (C_1-C_4) -alkyl- and (C_1-C_4) -alkyloxy-, in another
20 embodiment from fluorine, chlorine and (C_1-C_4) -alkyl-, and in another embodiment they are (C_1-C_4) -alkyl substituents.

- In one embodiment, 1, 2 or 3 of the substituents R^{22} , in another embodiment 1 or 2 of the substituents R^{22} , and in another embodiment 1 of the substituents R^{22} , which are optionally present on the group R^2 , are defined as in the general definition of R^{22} and
25 thus are chosen from halogen, hydroxy, (C_1-C_4) -alkyl-, (C_1-C_4) -alkyloxy-, (C_1-C_4) -alkyl-S(O) $_m$ -, amino, nitro, cyano, hydroxycarbonyl, (C_1-C_4) -alkyloxycarbonyl, aminocarbonyl and aminosulfonyl-, and any further substituents R^{22} which are optionally present on the group R^2 , for example 1, 2 or 3 further substituents R^{22} , or 1
30 or 2 further substituents R^{22} , or 1 further substituent R^{22} , are chosen from halogen, hydroxy, (C_1-C_4) -alkyl-, (C_1-C_4) -alkyloxy-, (C_1-C_4) -alkyl-S(O) $_m$ -, amino, nitro and cyano, wherein all alkyl groups independently of each other are optionally substituted by one or more fluorine substituents as generally applies to alkyl groups. In one

- embodiment, the said substituents R^{22} which are optionally present on the group R^2 and which in the afore-mentioned embodiment are defined as in the general definition of R^{22} , for example 1 or 2 such substituents R^{22} , or 1 such substituent R^{22} , are chosen from halogen, hydroxy, (C₁-C₄)-alkyl-, (C₁-C₄)-alkyloxy-, (C₁-C₄)-alkyl-S(O)_m-, amino and cyano. In one embodiment, the said substituents R^{22} which are optionally present on the group R^2 and which in the afore-mentioned embodiment are defined as in the general definition of R^{22} , for example 1 or 2 such substituents R^{22} , or 1 such substituent R^{22} , are not located on ring carbon atoms within the group R^2 which are adjacent to the atom via which the group R^2 is bonded to the
- oxazolopyrimidine ring depicted in formula I. In one embodiment, the said further substituents R^{22} which are optionally present on the group R^2 , for example 1, 2 or 3 further substituents R^{22} , or 1 or 2 further substituents R^{22} , or 1 further substituent R^{22} , are chosen from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy-, amino and cyano, in another embodiment from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy-, in another embodiment from halogen, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy-, in another embodiment from halogen and (C₁-C₄)-alkyl-, wherein in all these embodiments all alkyl groups independently of each other are optionally substituted by one or more fluorine substituents.
- In one embodiment of the invention, R^{31} is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, (C₁-C₄)-alkylcarbonylamino, (C₁-C₄)-alkylsulfonylamino, cyano, (C₁-C₄)-alkylcarbonyl, aminosulfonyl, (C₁-C₄)-alkylaminosulfonyl and di((C₁-C₄)-alkyl)aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano, aminosulfonyl, (C₁-C₄)-alkylaminosulfonyl and di((C₁-C₄)-alkyl)aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano and aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano and aminosulfonyl, in another embodiment from

halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, amino, (C₁-C₄)-alkylamino and di((C₁-C₄)-alkyl)amino, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, (C₁-C₄)-alkyloxy and di((C₁-C₄)-alkyl)amino, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy, in another embodiment from halogen, (C₁-C₄)-alkyl and (C₁-C₄)-alkyloxy, in another embodiment from fluorine, chlorine, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy, wherein in all these embodiments all alkyl groups independently of each other are optionally substituted by one or more fluorine substituents.

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In one embodiment, the optional substituents R³¹ on the residue of an aromatic ring representing R³, for example on a phenyl group or pyridinyl group representing R³, are chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, (C₁-C₄)-

15 alkylcarbonylamino, (C₁-C₄)-alkylsulfonylamino, cyano, (C₁-C₄)-alkylcarbonyl, aminosulfonyl, (C₁-C₄)-alkylaminosulfonyl and di((C₁-C₄)-alkyl)aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano, aminosulfonyl, (C₁-C₄)-alkylaminosulfonyl and di((C₁-C₄)-alkyl)aminosulfonyl,

20 in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, (C₁-C₄)-alkyl-S(O)_m-, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano and aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, cyano and aminosulfonyl, in another embodiment from halogen, (C₁-C₄)-

25 alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, amino, (C₁-C₄)-alkylamino and di((C₁-C₄)-alkyl)amino, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, (C₁-C₄)-alkyloxy and di((C₁-C₄)-alkyl)amino, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy, in another embodiment from halogen, (C₁-C₄)-alkyl and (C₁-C₄)-alkyloxy, in another embodiment from fluorine, chlorine, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy, wherein in all these embodiments all alkyl groups independently of each other are optionally substituted by one or more fluorine substituents.

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- In one embodiment, the optional substituents R^{31} on the residue of a saturated or non-aromatic unsaturated ring representing R^3 are chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, (C₁-C₄)-alkyl-S(O)_m, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino, (C₁-C₄)-alkylcarbonylamino, (C₁-C₄)-alkylsulfonylamino and cyano, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy, oxo, amino, (C₁-C₄)-alkylamino, di((C₁-C₄)-alkyl)amino and cyano, in another embodiment from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy, (C₁-C₄)-alkyloxy and oxo, in another embodiment from halogen, (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkyloxy and oxo, in another embodiment from fluorine, chlorine, (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkyloxy and oxo, in another embodiment from (C₁-C₄)-alkyl, hydroxy and oxo, in another embodiment from alkyl and hydroxy, and in another embodiment they are (C₁-C₄)-alkyl, wherein in all these embodiments all alkyl groups independently of each other are optionally substituted by one or more fluorine substituents. In case the residue of a ring representing R^3 contains any oxo groups as substituents R^{31} , in one embodiment not more than two such oxo substituents are present, and in another embodiment not more than one such oxo substituent is present.
- In one embodiment of the invention, the ring heteroatoms in Het are chosen from N and O, in another embodiment from O and S, in another embodiment they are O atoms. In another embodiment, the number of ring heteroatoms in Het is 1. In one embodiment, two ring oxygen atoms in Het are not present in adjacent ring positions, in another embodiment two ring heteroatoms chosen from O and S are not present in adjacent ring positions, in another embodiment two ring heteroatoms are not present in adjacent ring positions. Ring nitrogen atoms in Het carry a hydrogen atom or a substituent as specified. In one embodiment, optional substituents on ring nitrogen atoms in Het are (C₁-C₄)-alkyl substituents. In one embodiment, optional substituents on ring nitrogen atoms and ring carbon atoms in Het are (C₁-C₄)-alkyl substituents. In one embodiment, the number of optional substituents on Het is 1, 2, 3, 4 or 5, in another embodiment 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 1. Het can be bonded via any suitable

ring carbon atom. In one embodiment, Het is bonded via a ring carbon atom which is not adjacent to a ring heteroatom. Het can be 4-membered, 5-membered, 6-membered or 7-membered. In one embodiment, Het is 4-membered or 5-membered, in another embodiment 5-membered to 7-membered, in another embodiment 5-membered or 6-membered, in another embodiment 4-membered. Examples of Het, from any one or more of which Het is chosen in one embodiment, are oxetanyl including oxetan-2-yl and oxetan-3-yl, tetrahydrofuranyl including tetrahydrofuran-2-yl and tetrahydrofuran-3-yl, tetrahydropyranyl including tetrahydropyran-2-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl, oxepanyl including oxepan-2-yl, oxepan-3-yl and oxepan-4-yl, [1,3]dioxolanyl including [1,3]dioxolan-2-yl and [1,3]dioxolan-4-yl, [1,4]dioxanyl including [1,4]dioxan-2-yl, thietanyl including thietan-2-yl and thietan-3-yl, tetrahydrothiophenyl including tetrahydrothiophen-2-yl and tetrahydrothiophen-3-yl, tetrahydrothiopyranyl including tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl and tetrahydrothiopyran-4-yl, [1,4]dithianyl including [1,4]dithian-2-yl, azetidinyI including azetidin-2-yl and azetidin-3-yl, pyrrolidinyl including pyrrolidinyl-2-yl and pyrrolidinyl-3-yl, piperidinyl including piperidinyl-2-yl, piperidinyl-3-yl and piperidinyl-4-yl, azepanyl including azepan-2-yl, azepan-3-yl and azepan-4-yl, oxazolidinyl including oxazolidin-2-yl, oxazolidin-4-yl and oxazolidin-5-yl, thiazolidinyl including thiazolidin-2-yl, thiazolidin-4-yl and thiazolidin-5-yl, morpholinyl including morpholin-2-yl and morpholin-3-yl, thiomorpholinyl including thiomorpholin-2-yl and thiomorpholin-3-yl, which all are optionally substituted as specified with respect to Het.

A subject of the invention are all compounds of the formula I wherein any one or more structural elements such as groups, substituents and numbers are defined as in any of the specified embodiments or definitions of the elements or have any one or more of the specific meanings which are mentioned herein as examples of elements, wherein all combinations of one or more specified embodiments and/or definitions and/or specific meanings of the elements are a subject of the present invention. Also with respect to all such compounds of the formula I, all their stereoisomeric forms and mixtures of stereoisomeric forms in any ratio, and their physiologically

acceptable salts, and the physiologically acceptable solvates of any of them, are a subject of the present invention.

An example of compounds of the invention which with respect to any structural elements are defined as in specified embodiments of the invention or definitions of such elements, and which are a subject of the invention, are compounds of the formula I, in any of their stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, and the physiologically acceptable salts thereof, and the physiologically acceptable solvates of any of them, wherein

R^3 is chosen from (C_1-C_6) -alkyl, (C_3-C_7) -cycloalkyl- C_uH_{2u} - and Het- C_vH_{2v} -, wherein u and v are chosen from 1 and 2, or R^3 is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R^{31} ;

Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle which comprises 1 ring heteroatom chosen from N, O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C_1-C_4) -alkyl; and all other groups and numbers are defined as in the general definition of the compounds of the formula I or in any specified embodiments of the invention or definitions of structural elements.

Another such example are compounds of the formula I, in any of their stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, and the physiologically acceptable salts thereof, and the physiologically acceptable solvates of any of them, wherein

A is chosen from O and S;

X is chosen from (C_1-C_6) -alkanediyl, (C_2-C_6) -alkenediyl and (C_1-C_6) -alkanediyl-oxy;

Y is a 4-membered to 7-membered, saturated, monocyclic or bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0 or 1 ring heteroatoms chosen from N, O and S, wherein an additional ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and a ring sulfur atom can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring nitrogen atoms by identical or different (C₁-C₄)-alkyl substituents; R² is chosen from phenylene and pyridinediyl, wherein the phenylene and the pyridinediyl are optionally substituted on one or more ring nitrogen atoms by identical or different substituents R²²;

R³ is chosen from (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle which comprises 1 ring heteroatom chosen from N, O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl; and all other groups and numbers are defined as in the general definition of the compounds of the formula I or in any specified embodiments of the invention or definitions of structural elements.

Another such example are compounds of the formula I, in any of their stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, and the physiologically acceptable salts thereof, and the physiologically acceptable solvates of any of them, wherein

A is O;

X is chosen from (C₁-C₆)-alkanediyl and (C₁-C₆)-alkanediyl-oxy;

Y is a 4-membered to 6-membered, saturated, monocyclic heterocycle which does not comprise further ring heteroatoms in addition to the ring nitrogen atom depicted in formula I, wherein the ring is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

5 R¹ is chosen from hydrogen and (C₁-C₄)-alkyl;

R² is phenylene which is optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

R³ is chosen from (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to

10 7-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or

15 different substituents R³¹;

R²² is chosen from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy;

R³¹ is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy;

Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle
20 which comprises 1 ring heteroatom chosen from O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl; wherein all cycloalkyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more identical or different
25 substituents chosen from fluorine and (C₁-C₄)-alkyl;

wherein all alkyl, alkanediyl, C_uH_{2u} and C_vH_{2v} groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

30 Another such example are compounds of the formula I, in any of their stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, and the physiologically

acceptable salts thereof, and the physiologically acceptable solvates of any of them, wherein

A is O;

X is chosen from (C₁-C₆)-alkanediyl and (C₁-C₆)-alkanediyl-oxy;

- 5 Y is a 4-membered to 6-membered, saturated, monocyclic heterocycle which does not comprise further ring heteroatoms in addition to the ring nitrogen atom depicted in formula I, wherein the ring is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

R¹ is chosen from hydrogen and (C₁-C₄)-alkyl;

- 10 R² is phenylene which is optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

R³ is a residue of a saturated or unsaturated, 3-membered to 7-membered, monocyclic ring which comprises 0 or 1 ring heteroatom chosen from N, O and S, wherein a ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent
15 and a ring sulfur atom can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

R²² is chosen from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy;

- 20 R³¹ is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy;

wherein all cycloalkyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl;

- 25 wherein all alkyl, alkanediyl, C_uH_{2u} and C_vH_{2v} groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

- Likewise, also with respect to all specific compounds disclosed herein, such as the example compounds which represent embodiments of the invention wherein the
30 various groups and numbers in the general definition of the compounds of the formula I have the specific meanings present in the respective specific compound, it applies that they are a subject of the present invention in any of their stereoisomeric

forms and or a mixture of stereoisomeric forms in any ratio, and in the form of their physiologically acceptable salts, and in the form of the physiologically acceptable solvates of any of them. Irrespective thereof whether a specific compound is disclosed herein as a free compound and/or as a specific salt, it is a subject of the invention both in the form of the free compound and in the form of all its physiologically acceptable salts, and if a specific salt is disclosed, additionally in the form of this specific salt, and in the form of the physiologically acceptable solvates of any of them. Thus, a subject of the invention also is a compound of the formula I which is chosen from any one or more of the specific compounds of the formula I disclosed herein, including the example compounds specified below, and the physiologically acceptable salts thereof, and the physiologically acceptable solvates of any of them, wherein the compound of the formula I is a subject of the invention in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, if applicable. As an example mentioned is a compound of the formula I, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, which is chosen from

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid,

(S)-1-((E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid, and

(S)-1-(3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-propionyl)-pyrrolidine-2-carboxylic acid,

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

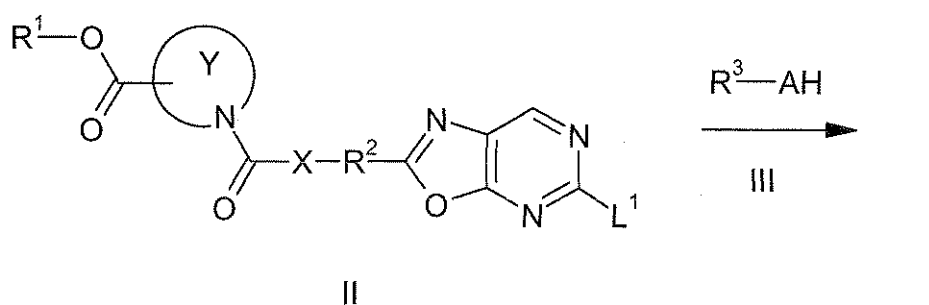
1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-

piperidine-4-carboxylic acid, and

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid,

wherein the compounds (S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid and (S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid can be present in the 1-substituted propionyl moiety in S configuration or R configuration or a mixture of these two forms of the said moiety in any ratio.

Another subject of the present invention are processes for the preparation of the compounds of the formula I and their salts and solvates, by which the compounds are obtainable and which are outlined in the following. In one process, a compound of the formula II is reacted with a compound of the formula III to give a compound of the formula I,



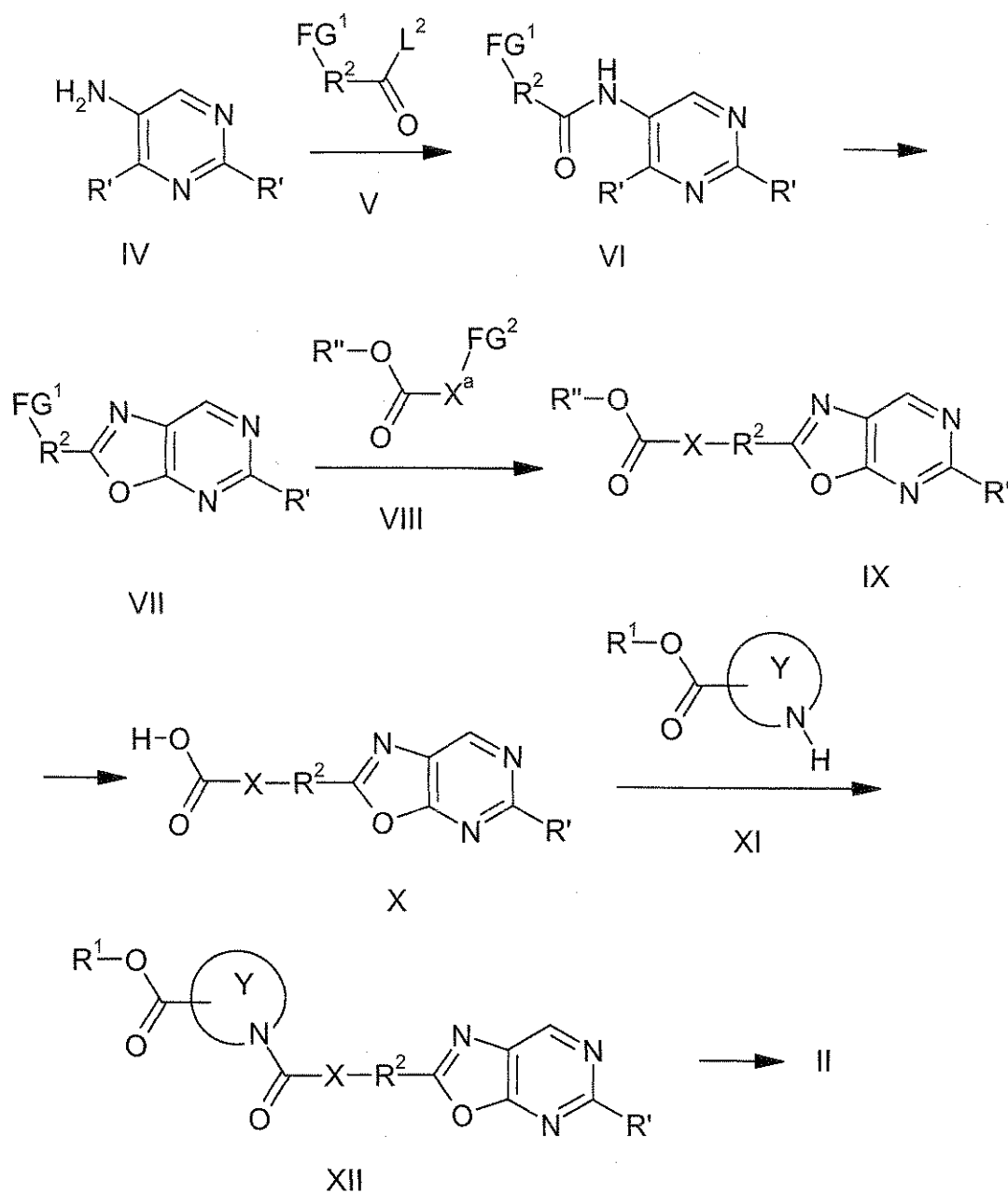
wherein the groups A, X, Y, R¹, R² and R³ in the compounds of the formulae II and III are defined as in the compounds of the formula I and additionally functional groups can be present in protected form or in the form of a precursor group which is later converted into the final group. The group L¹ in the compounds of the formula II is a leaving group which can be replaced in a nucleophilic aromatic substitution reaction, such as a halogen atom, for example chlorine or bromine, or a sulfoxide group or a sulfone group, for example a group of the formula -S(O)-Alk or -S(O)₂-Alk wherein Alk is a (C₁-C₄)-alkyl group, for example methyl or ethyl.

The reaction of the compounds of the formulae II and III is a nucleophilic aromatic substitution reaction at the carbon atom in the 5-position of oxazolo[5,4-d]pyrimidine ring, i.e. in the pyrimidine moiety, and can be carried out under standard conditions for such reactions which are well known to a person skilled in the art. Generally the

reaction is carried out in an inert solvent, for example a hydrocarbon or chlorinated hydrocarbon such as benzene, toluene, xylene, chlorobenzene, dichloromethane, chloroform or dichloroethane, an ether such as tetrahydrofuran (THF), dioxane, dibutyl ether, diisopropyl ether or 1,2-dimethoxyethane (DME), a ketone such as acetone or butan-2-one, an ester such as ethyl acetate or butyl acetate, a nitrile such as acetonitrile, an amide such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or N-methylpyrrolidin-2-one (NMP), or a mixture of solvents, at temperatures from about 20 °C to about 160 °C, for example at temperatures from about 40 °C to about 100 °C, depending on the particulars of the specific case. Generally it is favorable for enhancing the nucleophilicity of the compound of the formula III to add a base, for example a tertiary amine, such as triethylamine, ethyldiisopropylamine or N-methylmorpholine, or an inorganic base such as an alkaline earth metal hydride, hydroxide, carbonate or hydrogencarbonate like sodium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate or sodium hydrogencarbonate, or an alkoxide or amide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium tert-butoxide, sodium amide or lithium diisopropylamide. A compound of the formula III can also be treated with a base and converted into a salt separately before the reaction with the compound of the formula II.

The starting compounds of the formulae II and III can be obtained by procedures described in the literature or analogously to procedures described in the literature, and in many cases are commercially available. For example, the compounds of the formula II can be obtained by reacting a 5-amino-pyrimidine derivative of the formula IV with an activated carboxylic acid derivative of the formula V to give a compound of the formula VI, cyclizing the latter compound with formation of the oxazolo[5,4-d]pyrimidine ring system to give a compound of the formula VII, introducing the moiety $R''O-C(O)-X-$ into the compound of the formula VII by reaction with a compound of the formula VIII, deprotecting the obtained compound of the formula IX to give the carboxylic acid of the formula X, introducing the moiety $R^1O-C(O)-Y-$ by reaction with a compound of the formula XI to give a compound of the formula XII which can already be a compound of the formula II depending on the

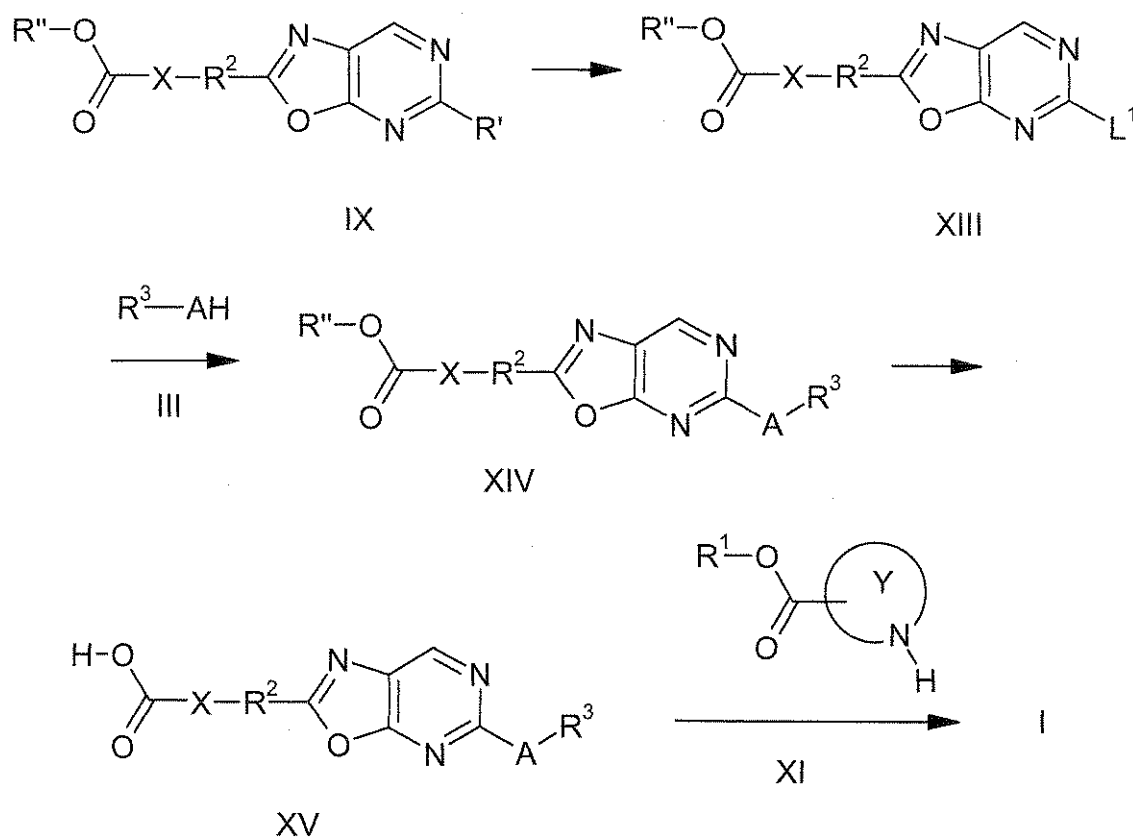
meaning of R' and L^1 , and optionally modifying the group R' in the compound of the formula XII to give a compound of the formula II.



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The sequence in which structural moieties are introduced during the synthesis of a compound of the formula I can also be different and, for example, in a compound of the formula IX, or a compound of the formula XIII which has been obtained from a compound of the formula IX by modification of the group R' , first the group $-A-R^3$

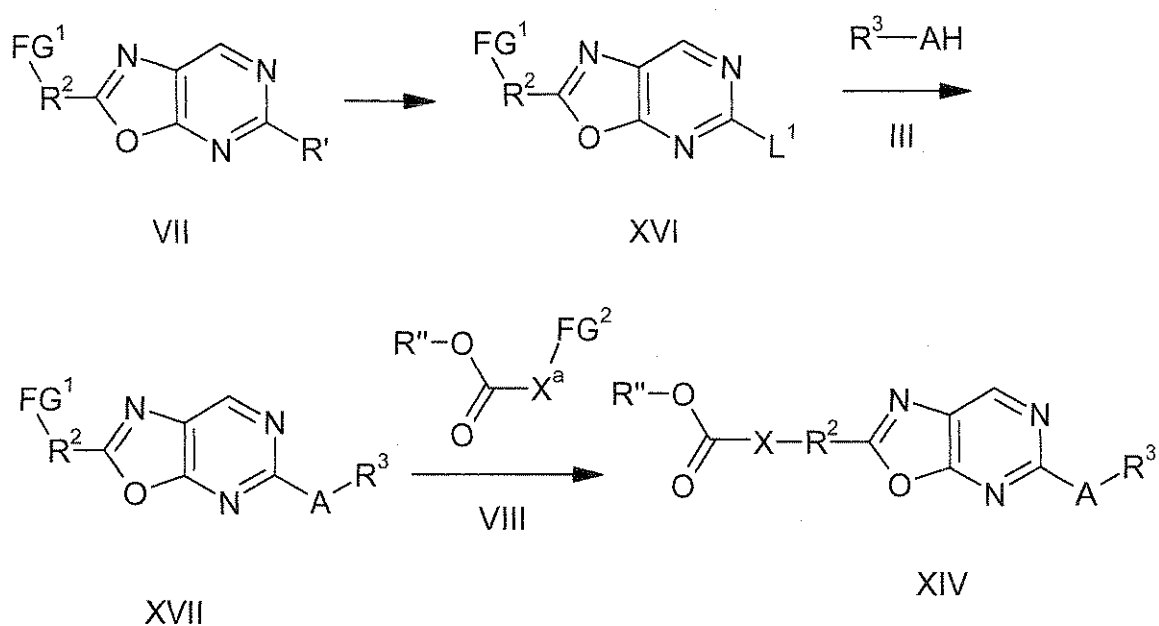
introduced by reaction with a compound of the formula III, the obtained compound of the formula XIV deprotected to give the carboxylic acid of the formula XV, and then the moiety $R^1O-C(O)-Y-$ introduced by reaction with a compound of the formula XI.



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In a further way of synthesizing compounds of the formula I, the group $-A-R^3$ is introduced into a compound of the formula VII, or a compound of the formula XVI which has been obtained from a compound of the formula VII by modification of the group R' , by reaction with a compound of the formula III, the obtained compound of the formula XVII reacted with a compound of the formula VIII, and the obtained compound of the formula XIV reacted further as indicated above.



The groups A, X, Y, R^1 , R^2 and R^3 in the compounds of the formulae V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI and XVII are defined as in the compounds of the formula I and additionally functional groups can be present in protected form or in the form of a precursor group which is later converted into the final group. The group X^a in the compounds of the formula VIII is defined as the group X in the compounds of the formula I, or comprises a part of the group X in the desired compound of the formula II, such that after the reaction of the compounds of the formulae VII and VIII, or the compounds of the formulae VIII and XVII, the group X^a and any parts of the groups FG^1 and FG^2 remaining in the compound of the formulae IX and XIV together form the desired group X. For example, in case the group X is an alkanediyl-oxy group, the group X^a in the compound of the formula VIII can be the desired alkanediyl-oxy group and the group FG^2 can be a hydrogen atom attached to the oxygen atom, or the group X^a can be the alkanediyl part, the group FG^2 is a leaving group, and the group FG^1 in the compounds of the formulae VII and XVII is a hydroxy group the oxygen atom of which together with the alkanediyl part then forms the desired alkanediyl-oxy group after the reaction of the compound of the formula VII or the formula XVII and the compound of the formula VIII.

The groups FG^1 and FG^2 in the compounds of the formulae V, VI, VII, VIII, XVI and XVII are functional groups suitable for the type of coupling used to form the desired group X from the group X^a and any part of the groups FG^1 and FG^2 remaining in the compounds of the formulae IX and XIV. For example, if the group X^a is attached to the group R^2 or to an atom in the group FG^1 , such as an oxygen atom in a hydroxy group representing FG^1 as mentioned afore, via a nucleophilic substitution reaction, FG^2 can be a leaving group such as a halogen atom like chlorine, bromine or iodine or a sulfonyloxy group like methanesulfonyloxy, trifluoromethanesulfonyloxy or toluenesulfonyloxy. If the group X^a is attached to the group R^2 via a transition metal-catalyzed reaction, FG^2 can be a leaving group such as a boronic acid, boronic acid ester, dialkyl borane or stannane group, and in this case FG^1 can be halogen. FG^2 can also be a hydrogen atom or a carbon atom being part of a double bond in an alkenediyl group representing X^a if a Heck reaction is used for attaching X^a to R^2 , and in this case FG^1 can be halogen. If a Wittig reaction or Wittig-Horner reaction is used for attaching X^a to R^2 , FG^2 can be a phosphonio group such as triphenylphosphonio or a phosphoryl group such as diethyl phosphoryl, and the compound of the formula VIII can be a phosphonium salt or a phosphonic acid ester, and in this case FG^1 can be an aldehyde group $-C(O)-H$ or ketone group $-C(O)-alkyl$, and vice versa. Generally, the group FG^1 is present on the carbon atom in the phenylene group or heterocyclic group representing R^2 which in the compounds of the formulae II and I carries the group X. The group FG^1 in the compounds of the formulae V, VI, VII and XVI can also be present in protected form or in the form of a precursor group which is later converted into the group which in the compound of the formula VII or the formula XVII, respectively, reacts with the compound of the formula VIII. For example, a hydroxy group representing FG^1 in the compound of the formulae VII and XVII can be present in the compounds of the formulae V, VI, VII and XVI in protected form, for example in the form of an etherified hydroxy group such as a benzyl ether or an alkyl ether like a methyl ether. Such ethers can then be cleaved before the reaction with the compound of the formula VIII by using methods well known to a person skilled in the art. A summary of methods for the removal of protecting groups can be found in the literature, for example in P. J. Kocienski, Protecting Groups

(Thieme Verlag, 1994) or T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis (John Wiley & Sons, 1999).

5 The group L^1 in the compounds of the formulae XIII and XVI is defined as specified above. The group L^2 in the compounds of the formula V is a nucleophilically substitutable leaving group and can in particular be a halogen atom, such as chlorine or bromine, and the compound of the formula V can thus be a carboxylic acid halide. L^2 can also be a group of the formula $FG^1-R^2-C(O)-O$ and the compound of the formula V can thus be a carboxylic acid anhydride, for example. The groups R' in the
10 compounds of the formulae IV, VI, VII, IX, X and XII can be a hydroxy group or a halogen atom, such as chlorine or bromine.

The group R'' in the compounds of the formulae VIII, IX, XIII and XIV is a group suitable for protecting the carboxylic acid function as an ester, for example a (C_1-C_4) -alkyl group such as methyl, ethyl or tert-butyl, or a benzyl group. Compounds
15 occurring in the synthesis of the compounds of the formula I, such as the compound of the formula IV, may also be present in another tautomeric form, for example in the keto form in case the groups R' in the compound of the formula IV are hydroxy groups. Compounds occurring in the synthesis of the compounds of the formula I,
20 including starting compounds, intermediates and products, can also be employed or obtained in the form of a salt. For example, compounds of the formulae XI can be employed in the form of an acid addition salt such as the hydrochloride.

25 The reaction of the compounds of the formulae IV and V can be carried out under standard conditions for the acylation of an amine with an activated carboxylic acid derivative like an acid halide or anhydride. Generally the reaction is carried out in an inert solvent, for example a hydrocarbon or chlorinated hydrocarbon such as benzene, toluene, xylene, chlorobenzene, dichloromethane, chloroform or dichloroethane, an ether such as THF, dioxane, dibutyl ether, diisopropyl ether or
30 DME, a ketone such as acetone or butan-2-one, an ester such as ethyl acetate or butyl acetate, or water, or a mixture of solvents, at temperatures from about $-10\text{ }^\circ\text{C}$ to about $40\text{ }^\circ\text{C}$, for example at temperatures from about $0\text{ }^\circ\text{C}$ to about $30\text{ }^\circ\text{C}$. Generally

the reaction is carried out with addition of a base, for example a tertiary amine, such as triethylamine, ethyldiisopropylamine or N-methylmorpholine, or an inorganic base such as an alkaline metal hydroxide, carbonate or hydrogencarbonate like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate. In case the group R' in the compound of the formula VI is hydroxy, the cyclization of the compound of the formula VI to the compound of the formula VII can favorably be carried out in the presence of a halogenating agent such as a phosphorus halide, like phosphorus pentachloride or phosphorus oxychloride or a mixture thereof, in an inert solvent, for example a hydrocarbon or chlorinated hydrocarbon such as benzene, toluene, xylene, chlorobenzene, dichloromethane, chloroform or dichloroethane, at temperatures from about 20 °C to about 100 °C, for example temperatures from about 50 °C to about 80 °C. In case the group R' in the compound of the formula VI is halogen such as chlorine, the cyclization of the compound of the formula VI to the compound of the formula VII can be carried out thermally, for example by heating the compound of the formula VI in an inert solvent such as a hydrocarbon or chlorinated hydrocarbon, for example toluene, xylene or chlorobenzene, or an amide, for example DMF, DMA or NMP, or a nitrile, for example acetonitrile, to temperatures from about 100 °C to about 200 °C, for example to temperatures from about 120 °C to about 180 °C, optionally under pressure, and optionally in the presence of a base, such as a tertiary amine, for example triethylamine, ethyldiisopropylamine or N-methylmorpholine, or an inorganic base, for example an alkaline metal hydroxide, carbonate or hydrogencarbonate like sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or sodium hydrogencarbonate. The thermal cyclization can favorably be performed in a microwave reactor.

The coupling of compounds of the formula VIII with compounds of the formulae VII and XVII can be carried out via reactions of various types as already indicated above, for example via an alkylation reaction. For example, if the group R² carries a hydroxy group representing FG¹, it can be alkylated using a compound of the formula VIII in which FG² is a leaving group suitable for nucleophilic substitution reactions such as a halogen atom like chlorine, bromine or iodine, or a sulfonyloxy group like

methanesulfonyloxy or toluenesulfonyloxy. The nucleophilic substitution reaction at the carbon atom in the compound of the formula VIII carrying the group FG^2 can be carried out under standard conditions for such reactions which are well known to a person skilled in the art. Generally the reaction is carried out in an inert solvent, for example a hydrocarbon or chlorinated hydrocarbon such as benzene, toluene, xylene, chlorobenzene, dichloromethane, chloroform or dichloroethane, an ether such as THF, dioxane, dibutyl ether, diisopropyl ether or DME, an alcohol such as methanol, ethanol or isopropanol, a ketone such as acetone or butan-2-one, an ester such as ethyl acetate or butyl acetate, a nitrile such as acetonitrile, an amide such as N,N-dimethylformamide or N-methylpyrrolidin-2-one, or a mixture of solvents, at temperatures from about 20 °C to about 100 °C, for example at temperatures from about 40 °C to about 80 °C, depending on the particulars of the specific case. Generally it is favorable for enhancing the nucleophilicity of the compound of the formula VII or XVII and/or binding an acid which is liberated during the reaction, to add a base, for example a base, for example a tertiary amine, such as triethylamine, ethyldiisopropylamine or N-methylmorpholine, or an inorganic base such as an alkaline metal hydride, hydroxide, carbonate or hydrogencarbonate like sodium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate or sodium hydrogencarbonate, or an alkoxide or amide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium tert-butoxide, sodium amide or lithium diisopropylamide. A compound of the formula VII or XVII in which FG^1 is hydroxy can also be treated with a base and converted into a salt separately before the reaction with the compound of the formula VIII. Besides by reaction with a compound of the formula VIII in which FG^2 is a leaving group as indicated, a compound of the formula VII or XVII in which FG^1 is hydroxy can also be converted into a compound of the formula IX or XIV by reaction with the respective alcohol, i.e. with a compound of the formula VIII in which FG^2 is hydroxy, under the conditions of the Mitsunobu reaction in the presence of an azodicarboxylate such as diethyl azodicarboxylate or diisopropyl azodicarboxylate and a phosphine such as triphenylphosphine or tributylphosphine in an inert aprotic solvent, for example an ether such as THF or dioxane (cf. O. Mitsunobu, Synthesis (1981), 1-28). The coupling of compounds of the formula VIII with compounds of the formulae VII and

XVII via a transition metal-catalyzed reaction can be performed under the conditions of palladium-catalyzed cross coupling reactions like the Heck, Stille or Suzuki coupling reaction (c. f. A. de Meijere and F. Diederich (Eds.), *Metal-Catalyzed Cross-Coupling Reactions* (Wiley-VCH, 2004)).

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The deprotection of the R"-protected carboxylic acid group in the compounds of the formulae IX and XIV to give the compounds of the formulae X and XV can be achieved by standard methods which are well known to a person skilled in the art and are summarized in the above-mentioned books by P. J. Kocienski and by T. W.

10 Greene and P. G. M. Wuts, for example under basic conditions by treatment with an alkaline metal hydroxide such as sodium hydroxide or lithium hydroxide in the case of compounds in which R" is an alkyl group such as methyl or ethyl, by treatment with trifluoroacetic acid in the case of compounds in which R" is a tert-butyl group, or by hydrogenation in the presence of a transition metal catalyst such as palladium on
15 charcoal in the case of compounds in which R" is a benzyl group.

For the introduction of the moiety R¹O-C(O)-Y-, the carboxylic acid group HO-C(O)- in the compounds of the formulae X and XV is generally activated in situ by means of a customary amide coupling reagent or converted into a reactive carboxylic acid

20 derivative which can be prepared in situ or isolated. For example, the compound of the formula X or XV can be converted into an acid halide by treatment with thionyl chloride, phosphorus pentachloride, phosphorus tribromide or oxalyl chloride, or treated with an alkyl chloroformate like ethyl chloroformate or isobutyl chloroformate to give a mixed anhydride. Customary coupling reagents which can be employed, are
25 propanephosphonic anhydride, N,N'-carbonyldiazoles like N,N'-carbonyldiimidazole (CDI), carbodiimides like 1,3-diisopropylcarbodiimide (DIC), 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), carbodiimides together with additives like 1-hydroxy-
benzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT), uronium-based
30 coupling reagents like O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) or O-(cyano(ethoxycarbonyl)methyleneamino)-

N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), and phosphonium-based coupling reagents like (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) or bromotripyrrolidinophosphonium

5 hexafluorophosphate (PyBroP).

The reaction conditions for the preparation of the compounds of the formulae XII and I from compounds of the formulae X and XV and the compounds of the formula XI depend on the particulars of the specific case, for example the employed coupling

10 reagent, and are well known to a person skilled in the art. For example, in case of an activation of the compound of the formula X or XV via an acid chloride or acid

bromide, the coupling reaction with the cyclic amine of the formula XI is generally carried out in an inert solvent, for example a hydrocarbon or chlorinated hydrocarbon or an ether like the aforementioned ones, an ester like ethyl acetate or butyl acetate,

15 a nitrile like acetonitrile, or water, or a mixture of solvents including a mixture of water and an organic solvent which is miscible or immiscible with water, at temperatures from about -10 °C to about 100 °C, in particular at temperatures from about 0 °C to about 80 °C, for example at about room temperature. Favorably, the reaction of an

acid halide derived from the carboxylic acid of the formula X or XV with a compound 20 of the formula XI is carried out in the presence of a base such as a tertiary amine like triethylamine, ethyldiisopropylamine, N-methylmorpholine or pyridine, or an inorganic base like an alkaline metal hydroxide, carbonate or hydrogencarbonate, for example sodium hydroxide, potassium hydroxide, sodium carbonate or sodium

hydrogencarbonate. In case the carboxylic acid group in the compounds of the formula X or XV is activated by means of an amide coupling reagent such as, for 25 example, a carbodiimide or TOTU, the reaction is generally carried out under anhydrous conditions in an inert aprotic solvent, for example an ether like THF, dioxane or DME or an amide like DMF or NMP, at temperatures from about -10 °C to about 80 °C, in particular at temperatures from about 0 °C to about 60 °C in the

30 presence of a base such as a tertiary amine, like triethylamine, ethyldiisopropylamine or N-methylmorpholine. In case the compound of the formula XI is employed in the form of an acid addition salt in the reaction with the compound of the formula X or

XV, usually a sufficient amount of a base is added in order to liberate the free compound of the formula XI.

The compound of the formula XII can already be a compound of the formula II and employed in the reaction with the compound of the formula III, if it has been obtained from a compound of the formula VI in which R' is halogen, such as chlorine, and the halogen atom in the cyclization product has not been replaced in the course of the synthesis, for example with a hydroxy group during work-up, or if it has been obtained from a compound of the formula VI in which R' is hydroxy, and concomitantly with the cyclization the second hydroxy group in the compound of the formula VII is halogenated, for example replaced with a chlorine atom as may occur during the cyclization by means of a phosphorus halide. If a compound of the formula VII in which R' is hydroxy, is obtained as cyclization product, the hydroxy group in the compound of the formula XII can be converted into a leaving group under standard conditions, for example into a halogen atom such as a chlorine atom by treatment with a halogenating agent such as a phosphorus halide, or into a sulfonyloxy group as indicated above by treatment with a sulfonyl chloride or sulfonic anhydride. Depending on the particulars of the specific case, such as the reactivity of the specific compound of the formula III which is to be reacted with the compound of the formula II, it can also be advantageous to modify the group R' in a compound of the formula XII, or in a compound of the formula IX which is converted into a compound of the formula XIII, or in a compound of the formula VII which is converted into a compound of the formula XVI, even though it already is a leaving group. For example, a compound of the formula VII, IX or XII in which R' is halogen, such as chlorine, can be converted into a compound of the formula XVI, XIII and II, respectively, in which L¹ is the group -S(O)₂-Alk and which is then reacted with a compound of the formula III, by treatment with an alkanesulfinic acid of the formula Alk-S(O)-OH, wherein Alk is (C₁-C₄)-alkyl. Such a conversion is generally carried out in the presence of a base, such as an alkaline metal hydride, hydroxide, carbonate or hydrogencarbonate like sodium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate or sodium hydrogencarbonate, in an inert solvent, such as a hydrocarbon or chlorinated

hydrocarbon like benzene, toluene, xylene, chlorobenzene, dichloromethane, chloroform or dichloroethane, an ether such as THF, dioxane, dibutyl ether, diisopropyl ether or DME, an amide such as DMF or NMP, or a mixture of solvents, at temperatures from about 20 °C to about 150 °C, for example at temperatures from about 50 °C to about 120 °C. An alkanesulfinic acid can also be treated with a base and converted into a salt separately before the reaction with the compound of the formula VII, IX or XII.

The explanations given above for the reaction of the compounds of the formulae II and III and for the individual reaction steps in the synthesis of the compounds of the formula II from the compounds of the formula VII apply correspondingly to respective reaction steps in the synthesis of the compounds of the formula I from the compounds of the formula IX via the compounds of the formula XIII, XIV and XV, and to the synthesis of the compounds of the formula XIV from the compounds of the formula VII via the compounds of the formulae XVI and XVII, if not already referred to above. The sequence of steps in the preparation of the compounds of the formula I can also be changed in other ways.

Further compounds of the formula I can be obtained from suitable compounds prepared according to the above-described processes by functionalization or modification of contained functional groups according to standard procedures, for example by esterification, amidation, hydrolysis, etherification, alkylation, acylation, sulfonylation, reduction, oxidation, conversion into salts, and others. For example, a hydroxy group, which may be liberated from an ether group by ether cleavage, for example by means of boron tribromide, or from a protected hydroxy group by deprotection, can be esterified to give a carboxylic acid ester or a sulfonic acid ester, or etherified. Etherifications of hydroxy groups can favorably be performed by alkylation with the respective halogen compound, for example a bromide or iodide, in the presence of a base, for example an alkaline metal carbonate such as potassium carbonate or cesium carbonate in an inert solvent, for example an amide like DMF or NMP or a ketone like acetone or butan-2-one, or with the respective alcohol under the conditions of the Mitsunobu reaction referred to above. A hydroxy group can be

converted into a halide by treatment with a halogenating agent. A halogen atom can be replaced with a variety of groups in a substitution reaction which may also be a transition-metal catalyzed reaction. A nitro group can be reduced to an amino group, for example by catalytic hydrogenation. An amino group can be modified under
5 standard conditions for alkylation, for example by reaction with a halogen compound or by reductive amination of a carbonyl compound, or for acylation or sulfonylation, for example by reaction with a reactive carboxylic acid derivative, like an acid chloride or anhydride or a sulfonic acid chloride, or with an activated carboxylic acid which may be obtained from the carboxylic acid by treatment with a coupling agent
10 like CDI, a carbodiimide such as DCC or EDC, HATU, TOTU, TBTU, for example. A carboxylic ester group can be hydrolyzed under acidic or basic conditions to give a carboxylic acid. A carboxylic acid group can be activated or converted into a reactive derivative as mentioned afore and reacted with an alcohol or an amine or ammonia to give an ester or amide. A primary amide can be dehydrated to give a nitrile. A
15 sulfur atom, for example in an alkyl-S- group or in a heterocyclic ring, can be oxidized with a peroxide like hydrogen peroxide or a peracid to give a sulfoxide moiety S(O) or a sulfone moiety S(O)₂. A carboxylic acid group, carboxylic acid ester group and a ketone group can be reduced to an alcohol, for example by means of a complex hydride such as lithium aluminium hydride, lithium borohydride or sodium
20 borohydride. A compound of the formula I or an intermediate such as a compound of the formula II, which contains a double bond or a triple bond in the group X, which can be readily obtained via a transition metal-catalyzed coupling reaction from a compound of the formula XIV containing a double or triple bond in the group X^a and a compound of the formula XIII as outlined above, can be converted into a compound
25 in which X is a saturated group, by hydrogenation in the presence of hydrogenation catalyst such as a palladium catalyst.

All reactions used in the above-described syntheses of the compounds of the formula I are per se well known to the skilled person and can be carried out under standard
30 conditions according to, or analogously to, procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry) (Thieme-Verlag, Stuttgart), or Organic Reactions (John Wiley & Sons,

New York). If desired, the obtained compounds of the formula I, as well as any intermediate compounds, can be purified by customary purification procedures, for example by recrystallization or chromatography. As already mentioned, all starting compounds and intermediates employed in the above-described syntheses which

5 contain an acidic or basic group, can also be employed in the form of salts, and all intermediates and final target compounds can also be obtained in the form of salts. As likewise mentioned above, depending on the circumstances of the specific case, in order to avoid an unwanted course of a reaction or side reactions during the synthesis of a compound it can generally be necessary or advantageous to

10 temporarily block functional groups by introducing protective groups and deprotect them at a later stage of the synthesis, or to introduce functional groups in the form of precursor groups which later are converted into the desired functional groups. As examples of protecting groups amino-protecting groups may be mentioned which can be acyl groups or alkyloxycarbonyl groups, for example a tert-butyloxycarbonyl group

15 (= Boc) which can be removed by treatment with trifluoroacetic acid (= TFA), a benzyloxycarbonyl group which can be removed by catalytic hydrogenation, or a fluoren-9-ylmethoxycarbonyl group which can be removed by treatment with piperidine, and protecting groups of carboxylic acid groups which can be protected as ester groups, such as tert-butyl esters which can be deprotected by treatment with

20 trifluoroacetic acid, or benzyl esters which can be deprotected by catalytic hydrogenation. As an example of a precursor group the nitro group may be mentioned which can be converted into an amino group by reduction, for example by catalytic hydrogenation. Such synthesis strategies, and protective groups and precursor groups which are suitable in a specific case, are known to the skilled

25 person.

Another subject of the present invention are the novel starting compounds and intermediates occurring in the synthesis of the compounds of the formula I, including the compounds of the formulae II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV,

30 XVI and XVII, wherein A, X, X^a, Y, R¹, R², R³, R', R'', FG¹, FG², L¹ and L² are defined as above, in any of their stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, and their salts, and solvates of any of them, and their use as intermediates.

The invention also includes all tautomeric forms of the said intermediates and starting compounds. All explanations given above and embodiments specified above with respect to the compounds of the formula I apply correspondingly to the said intermediates and starting compounds. A subject of the invention are in particular the novel specific starting compounds and intermediates disclosed herein. Independently thereof whether they are disclosed as a free compound and/or as a specific salt, they are a subject of the invention both in the form of the free compounds and in the form of their salts, and if a specific salt is disclosed, additionally in the form of this specific salt, and in the form of solvates of any of them.

The compounds of the formula I, optionally in combination with other pharmacologically active compounds, can be administered to animals, in particular to mammals including humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. The administration can be carried out orally, for example in the form of tablets, film-coated tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, solutions including aqueous, alcoholic and oily solutions, juices, drops, syrups, emulsions or suspensions, rectally, for example in the form of suppositories, or parenterally, for example in the form of solutions for subcutaneous, intramuscular or intravenous injection or infusion, in particular aqueous solutions. The compounds of the formula I can additionally be used in modes of local drug delivery, for example in coated stents for preventing or reducing in-stent restenosis or by applying them locally by means of a catheter. The appropriate administration form depends, among others, on the disease to be treated and on its severity.

The amount of a compound of the formula I and/or its physiologically acceptable salts and/or solvates present in the pharmaceutical compositions normally ranges from about 0.2 to about 800 mg, for example from about 0.5 to about 500 mg, for example from about 1 to about 200 mg, per unit dose, but depending on the type of the pharmaceutical composition it may also be higher. The pharmaceutical compositions usually comprise from about 0.5 to about 90 percent by weight of the compound of the formula I and/or its physiologically acceptable salts and/or solvates. The

production of the pharmaceutical compositions can be carried out in a manner known per se. To this end, one or more compounds of the formula I and/or their physiologically acceptable salts and/or solvates together with one or more solid or liquid pharmaceutical carrier substances, or vehicles, and/or additives, or auxiliary substances, and, if a combination medicament is desired, other pharmacologically active compounds having therapeutic or prophylactic action are brought into a suitable form for administration and dosage which can be used in human or veterinary medicine. As carrier substances and additives, suitable organic and inorganic substances can be used which do not react in an undesired manner with the compounds of the formula I or their physiologically acceptable salts or solvates. As examples of types of additives which can be contained in the pharmaceutical compositions and medicaments, lubricants, preservatives, thickeners, stabilizers, disintegrants, wetting agents, agents for achieving a depot effect, emulsifiers, salts, for example for influencing the osmotic pressure, buffer substances, colorants, flavorings and aromatic substances may be mentioned. Examples of carrier substances and additives are water, physiological sodium chloride solution, vegetable oils, waxes, alcohols such as ethanol, isopropanol, 1,2-propanediol, benzyl alcohols or glycerol, polyols, mannitol, polyethylene glycols, polypropylene glycols, glycerol triacetate, polyvinylpyrrolidone, gelatin, cellulose, carbohydrates such as lactose, glucose, saccharose or starch like corn starch, stearic acid and its salts such as magnesium stearate, talc, lanolin, petroleum jelly, or mixtures thereof, for example mixtures of water with one or more organic solvents such as mixtures of water with alcohols. The compounds of the formula I and their physiologically acceptable salts and solvates can also be lyophilized and the obtained lyophilisates used for the production of injectable compositions, for example.

The dosage of a compound of the formula I and/or a physiologically acceptable salt and/or solvate thereof to be administered depends on the specific case and, as is usual, has to be adapted by the physician according to the customary rules and procedures to the individual circumstances in order to achieve an optimum effect. It depends, for example, on the nature and the severity of the disorder to be treated, the sex, age, weight and individual responsiveness of the human or animal patient,

on the efficacy and duration of action of the compound used, on whether the treatment is for the therapy of an acute or chronic disease or prophylactic, or on whether other active compounds are administered in addition to a compound of the formula I. In general, a daily dose from about 0.01 mg/kg to about 100 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg, or from about 0.3 mg/kg to about 5 mg/kg (in each case mg per kg of bodyweight), for example, is appropriate for administration to an adult weighing about 75 kg in order to obtain the desired results. The daily dose in this case can be administered in a single dose or, in particular when larger amounts are administered, divided into several, for example two, three or four, individual doses. The administration can also be carried out continuously, for example by continuous infusion or injection. Depending on the individual behavior in a specific case, it may be necessary to deviate upward or downward from the indicated dosages.

The following examples illustrate the invention.

When example compounds containing a basic group were purified by preparative high pressure liquid chromatography (HPLC) on reversed phase (RP) column material and, as customary, the eluent was a gradient mixture of water and acetonitrile containing trifluoroacetic acid (TFA), they were in part obtained in the form of their acid addition salt with trifluoroacetic acid, depending on the details of the workup such as evaporation or lyophilization conditions. In the names of the example compounds and their structural formulae any such contained trifluoroacetic acid is not specified.

The prepared compounds were in general characterized by spectroscopic data and chromatographic data, in particular mass spectra (MS) and HPLC retention times (R_t ; in min) which were obtained by combined analytical HPLC/MS characterization (LC/MS), and/or nuclear magnetic resonance (NMR) spectra. In the NMR characterization, the chemical shift δ (in ppm), the number of hydrogen atoms and the multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quartet, m = multiplet; br = broad) of the signals is given. In the MS

characterization, in general the mass number (m/z) of the peak of the molecular ion M , e.g. M^+ , or of a related ion such as the ion $M+1$, e.g. $[M+1]^+$, i.e. the protonated molecular ion $[M+H]^+$, which was formed depending on the ionization method used, is given. Generally, the ionization method was electrospray ionization (ESI). The LC/MS
5 conditions used were as follows.

Method LC1

Column: UPLC BEH C18, 50 x 2.1 mm, 1.7 μ m; flow: 0.9 ml/min; eluent A: acetonitrile + 0.08 % formic acid; eluent B: water + 0.1 % formic acid; gradient: from
10 5 % A + 95 % B to 95 % A + 5 % B in 1.1 min, then 95 % A + 5 % B for 0.6 min; MS ionization method: ESI⁺

Method LC2

Column: Merck Chromolith FastGrad. RP-18e, 50 x 2 mm; flow: 2 ml/min; eluent A: acetonitrile + 0.05 % TFA; eluent B: water + 0.05 % TFA; gradient: 2 % A + 98 % B
15 for 0.2 min, then from 2 % A + 98 % B to 98 % A + 2 % B in 2.2 min, then 98 % A + 2 % B for 0.8 min; MS ionization method: ESI⁺

Method LC3

Column: YMC-Pack J'sphere H80, 33 x 2.1 mm, 4 μ m; flow: 1.0 ml/min; eluent A: acetonitrile + 0.05 % TFA; eluent B: water + 0.05 % TFA; gradient: from 2 % A + 98 % B to 95 % A + 5 % B in 5 min, then 95 % A + 5 % B for 1.25 min; MS ionization
20 method: ESI⁺

Method LC4

Column: Waters XBridge C18, 50 x 4.6 mm, 2.5 μ m; flow: 1.3 ml/min; eluent A: acetonitrile + 0.05 % TFA; eluent B: water + 0.05 % TFA; gradient: 5 % A + 95 % B for 0.3 min, then from 5 % A + 95 % B to 95 % A + 5 % B in 3.2 min, then 95 % A + 5 % B for 0.5 min; MS ionization method: ESI⁺

Method LC5

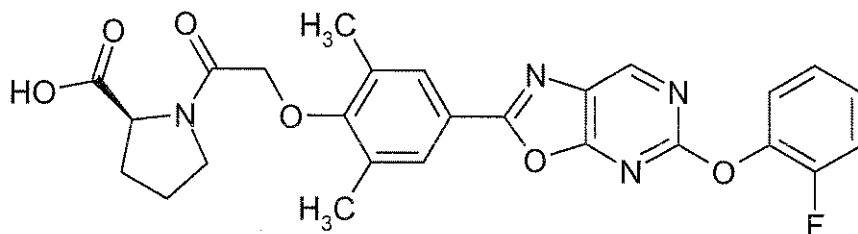
Column: UPLC BEH C18, 50 x 2.1 mm, 1.7 μ m; flow: 0.9 ml/min; eluent A: acetonitrile + 0.035% formic acid; eluent B: water + 0.05% formic acid; gradient: from 5% A + 95% B to 95% A + 5% B in 1.1 min, then 95% A + 5% B for 0.6 min; MS ionization method: ESI⁺

Method LC6

Column: Waters Xbridge C18, 50 x 4.6 mm, 2.5 μ m; flow: 1.3 ml/min; eluent A: acetonitrile + 0.1% formic acid; eluent B: water + 0.1% formic acid; gradient: from 3% A + 97% B to 60% A + 40% B in 3.5 min, from 60% A + 40% B to 98% A + 2% B in 0.5 min, then up to 98% A + 2% B for 1 min; MS ionization method: ESI⁺

Example 1

(S)-1-(2-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid



(a) N-(2,4-Dichloro-pyrimidin-5-yl)-4-methoxy-3,5-dimethyl-benzamide

A solution of 3.2 g of 5-amino-2,4-dichloropyrimidine in 50 ml of ethyl acetate was added to a mixture of 25 ml of a saturated aqueous solution of sodium hydrogencarbonate and 25 ml of water. A solution of 4.9 g of 3,5-dimethyl-4-methoxybenzoyl chloride was added at room temperature over a period of 15 min, and the mixture was mixed intensively for 4 h. Then the layers were separated and the aqueous layer was extracted twice with ethyl acetate. After drying over sodium sulfate and filtration the solvent was removed in vacuo to give 7.54 g of raw product. The raw product was triturated with 25 ml of isopropanol. After filtration and washing with 10 ml of isopropanol 2.74 g of the title compound were obtained as a white solid.

(b) 5-Chloro-2-(4-methoxy-3,5-dimethyl-phenyl)-oxazolo[5,4-d]pyrimidine

A solution of 2.74 g of N-(2,4-dichloro-pyrimidin-5-yl)-4-methoxy-3,5-dimethyl-benzamide and 3.2 ml of N,N-diisopropylethylamine in 17 ml of acetonitrile was split
5 into two batches which were each heated for 1 h to 160 °C in a microwave reactor. The batches were then recombined and the precipitate was isolated by filtration to give 600 mg of the title compound as a dark but quite pure solid (600 mg). The solvents of the mother liquor were removed in vacuo and the residue was subjected to silica gel chromatography (heptane/ethyl acetate gradient) to give another 600 mg
10 of the title compound as a pale yellow solid.

(c) 5-(2-Fluoro-phenoxy)-2-(4-methoxy-3,5-dimethyl-phenyl)-oxazolo[5,4-d]pyrimidine

149 mg of sodium hydride were added under an argon atmosphere to a solution of 418 mg of 2-fluoro-phenol in 15 ml dimethylacetamide. After stirring for 30 min at
15 room temperature a solution of 900 mg of 5-chloro-2-(4-methoxy-3,5-dimethyl-phenyl)-oxazolo[5,4-d]pyrimidine in 20 ml dimethylacetamide was added slowly. The mixture was allowed to stir for 1.5 h at room temperature. Upon consumption of the starting oxazolo[5,4-d]pyrimidine an aqueous solution of citric acid (100 g/l) was added until the pH was neutral. The aqueous layer was extracted twice with 15 ml of
20 ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and the solvents were removed in vacuo. The title compound was isolated by silica gel chromatography (heptane/ethyl acetate gradient) as a white solid. Yield: 820 mg. LC/MS (method LC4): Rt = 3.56 min; m/z = 366.0 [M+H]⁺

25 (d) 4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenol

A solution of 510 mg of 5-(2-fluoro-phenoxy)-2-(4-methoxy-3,5-dimethyl-phenyl)-oxazolo[5,4-d]pyrimidine in 20 ml dichloromethane was cooled to 0 °C, and over a period of 10 min 4.2 ml of a 1 M solution of boron tribromide in dichloromethane was added. The mixture was stirred at 0 °C for 1 h, and then another 2 ml of a 1 M
30 solution of boron tribromide in dichloromethane were added. After stirring for another 1 h, 10 ml of a saturated aqueous solution of sodium hydrogencarbonate were added slowly. The aqueous layer was extracted twice with 15 ml of dichloromethane. The

combined organic layers were dried over sodium sulfate, filtered and the solvents were removed in vacuo to give 445 mg of the title compound as a white solid.

LC/MS (method LC3): $R_t = 3.62$ min; $m/z = 352.13$ $[M+H]^+$

- 5 (e) {4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetic acid

A suspension of 430 mg of 4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenol, 0.2 ml of tert-butyl bromoacetate and 423 mg of potassium carbonate in 5 ml of dimethylformamide was stirred at 60 °C for 2 h. After cooling, the
10 solids were removed by filtration and the solvent was distilled off in vacuo. 1.3 ml of trifluoroacetic acid were added to the residue, and the solution was stirred at room temperature for 1 h. Then 10 ml of toluene were added and the solvents were removed in vacuo. The title compound was isolated by silica gel chromatography (heptane/ethyl acetate gradient) as a white solid (135 mg).

- 15 LC/MS (method LC1): $R_t = 1.26$ min; $m/z = 410.21$ $[M+H]^+$

- (f) {4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl chloride

3 ml of thionyl chloride were slowly added to 336 mg of {4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetic acid. The mixture was
20 allowed to react for 2 days. Then toluene was added and the solvents were removed in vacuo. The addition and removal of toluene was repeated to give 350 mg of the title compound as a brown oil.

- 25 (g) (S)-1-(2-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid

A solution of 175 mg of {4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl chloride in 2 ml of dichloromethane was added slowly to a suspension of 102 mg of proline tert-butyl ester hydrochloride and 170 μ l of
30 triethylamine in 5 ml of dichloromethane. After stirring for 2 h, the solvent was removed in vacuo. 1.6 ml of trifluoroacetic acid were added and the mixture was stirred for 2 h at room temperature. Then 10 ml water were added and the aqueous

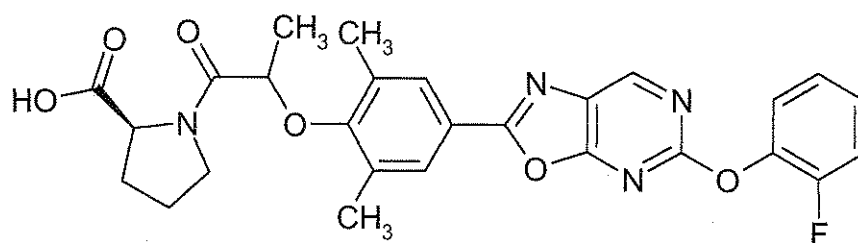
layer was extracted three times with 15 ml of a dichloromethane/isopropanol mixture (3:1). After drying with sodium sulfate and filtration, the solvents were removed in vacuo and the title compound was isolated via preparative HPLC. Yield: 56 mg of a white solid.

- 5 LC/MS (method LC2): $R_t = 1.64$ min; $m/z = 507.16$ $[M+H]^+$

Example 2

(S)-1-(2-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid

10



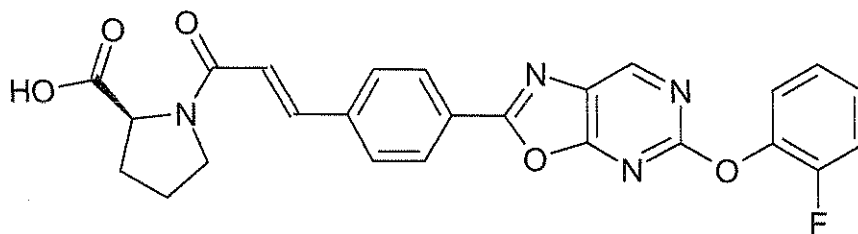
The title compound was obtained analogously as described in example 1, using 2-bromopropionic acid tert-butyl ester instead of tert-butyl bromoacetate in step (e).

- 15 LC/MS (method LC1): $R_t = 1.24$ min; $m/z = 521.37$ $[M+H]^+$

Example 3

(S)-1-((E)-3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid

20



(a) 2-(4-Bromo-phenyl)-5-chloro-oxazolo[5,4-d]pyrimidine

The title compound was prepared analogously as described in example 1, steps (a) and (b), using 4-bromo benzoyl chloride in step (a).

(b) 2-(4-Bromo-phenyl)-5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidine

70 mg of sodium hydride were added under an argon atmosphere to a solution of 162 μ l of 2-fluoro-phenol in 10 ml of dimethylacetamide. After stirring for 30 min at room temperature a suspension of 450 mg of 2-(4-bromo-phenyl)-5-chloro-oxazolo[5,4-d]pyrimidine in 5 ml of dimethylacetamide was added slowly. The mixture was allowed to stir for 2 h at room temperature. Upon consumption of the starting oxazolo[5,4-d]pyrimidine an aqueous solution of citric acid (100 g/l) was added until the pH was neutral. The precipitate formed during addition of the citric acid solution was filtered off and washed with water to give 472 mg of the title compound.

LC/MS (method LC1): R_t = 1.38 min; m/z = 386.1 $[M+H]^+$

(c) (E)-3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acrylic acid tert-butyl ester

300 mg of 2-(4-bromo-phenyl)-5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidine, 36 mg of tris(dibenzylidenacetone)dipalladium(0) and 23 mg of tri-tert-butylphosphonium tetrafluoroborate were placed into a reaction vial which was closed with a septum and evacuated and filled with argon three times. The solids were dissolved in 5.5 ml of degassed 1,4-dioxane which was added with a syringe. Subsequently, 0.124 ml of tert-butyl acrylate and 0.181 ml of N,N-dicyclohexylmethylamine were added with a syringe, and the mixture was heated to 120°C in a microwave reactor for 6 h. After cooling, the mixture was diluted with 100 ml of ethyl acetate, filtrated over silica gel and concentrated in vacuo. The residue was purified by preparative HPLC. 147 mg of the title compound were obtained.

LC/MS (method LC1): R_t = 1.44 min; m/z = 434.14 $[M+H]^+$

(d) (E)-3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acetic acid

A solution of 145 mg (E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acrylic acid tert-butyl ester in 2 ml of dichloromethane and 1 ml of trifluoroacetic acid was stirred at room temperature for 1.5 h. Then the mixture was concentrated in vacuo and freeze-dried. 154 mg of the title compound were obtained.

LC/MS (method LC1): R_t = 1.25 min; m/z = 378.08 $[M+H]^+$

(e) (S)-1-((E)-3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid tert-butyl ester

140 mg of {(E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acrylic acid were dissolved in 2 ml of N,N-dimethylformamide, and 98 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 19 mg of 1-hydroxy-7-azabenzotriazole and 397 μ l of N,N-diisopropylethylamine were added, followed by the addition of 49 mg of L-proline tert-butyl ester after 5 min. After 16 h at room temperature, 10 ml of water were added, and the mixture was brought to pH 3 by addition of 2 M aqueous hydrochloric acid and extracted twice with ethyl acetate. The combined organic layers were washed with a saturated sodium hydrogencarbonate solution and brine, dried and concentrated in vacuo. The residue was purified by preparative HPLC. 60 mg of the title compound were obtained.

LC/MS (method LC1): R_t = 1.36 min; m/z = 531.20 $[M+H]^+$

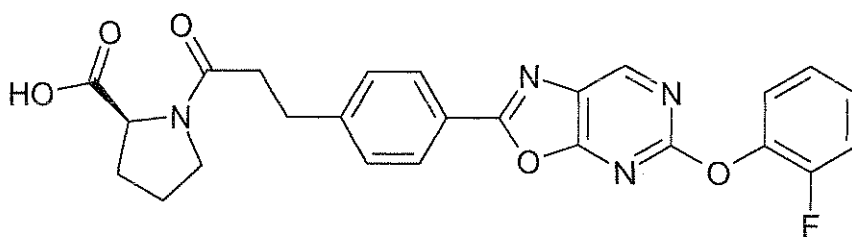
(f) (S)-1-((E)-3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid

A solution of 55 mg (S)-1-((E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid tert-butyl ester in 2 ml of dichloromethane and 1 ml trifluoroacetic acid was stirred at room temperature for 1 h. Then the mixture was concentrated in vacuo and freeze-dried. 37 mg of the title compound were obtained.

LC/MS (method LC1): R_t = 1.23 min; m/z = 475.3 $[M+H]^+$

Example 4

(S)-1-(3-{4-[5-(2-Fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-propionyl)-pyrrolidine-2-carboxylic acid



30 mg of (S)-1-((E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid were dissolved in 2 ml of ethyl acetate and
 5 hydrogenated in the presence of 30 mg of palladium on charcoal (10 %) at 5 bar for 16 h. The mixture was filtrated over Celite and concentrated in vacuo. 25 mg of the title compound were obtained.

LC/MS (method LC1): Rt = 1.11 min; m/z = 477.11 [M+H]⁺

- 10 Analogously to the preparation of the example compounds described above, the following compounds of the formula I were prepared.

Exam- ple	Name	LC/M S	m/z [M+H] ⁺	Rt [min]
5	(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	493.21	1.24
6	(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	479.15	1.20
7	1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-piperidine-4-carboxylic acid	LC1	493.18	1.20
8	(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid	LC1	493.16	1.23

Example	Name	LC/MS	m/z [M+H] ⁺	Rt [min]
9	(S)-1-(2-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-trifluoromethylphenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	547.13	1.27
10	1-(2-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-trifluoromethylphenoxy}-acetyl)-piperidine-4-carboxylic acid	LC1	561.16	1.27
11	(S)-1-(2-{4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC5	523.15	1.29
12	1-(2-{4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-piperidine-4-carboxylic acid	LC5	537.15	1.29
13	(S)-1-((E)-3-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methylphenyl}-acryloyl)-pyrrolidine-2-carboxylic acid	LC5	489.15	1.25
14	(S)-1-(3-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methylphenyl}-propionyl)-pyrrolidine-2-carboxylic acid	LC6	491.15	4.35
15	(S)-1-(2-{2,6-dimethyl-4-[5-(thiazol-2-ylsulfanyl)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	512.12	1.21
16	(S)-1-(2-{2-fluoro-4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	497.09	1.22
17	(S)-1-(3-{4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methylphenyl}-propionyl)-pyrrolidine-2-carboxylic acid	LC1	507.17	1.29

Example	Name	LC/MS	m/z [M+H] ⁺	Rt [min]
18	(S)-1-(2-(2-chloro-4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC6	529.02	4.59
19	1-(2-(2-chloro-4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-piperidine-4-carboxylic acid	LC5	543.06	1.29
20	(S)-1-(2-(4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-2-methylpropionyl)-pyrrolidine-2-carboxylic acid	LC1	535.29	1.33
21	(S)-1-(2-(4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-2-methylpropionyl)-pyrrolidine-2-carboxylic acid	LC1	551.25	1.38
22	1-(2-(4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-2-methylpropionyl)-piperidine-4-carboxylic acid	LC1	565.27	1.36
23	1-(2-(4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-piperidine-4-carboxylic acid	LC1	521.27	1.24
24	(S)-1-(2-(3-fluoro-4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC1	497.21	1.2
25	1-(2-(3-fluoro-4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-piperidine-4-carboxylic acid	LC1	511.21	1.2
26	1-(2-(2,6-dimethyl-4-(5-(2-methylphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl)-phenoxy]-acetyl)-piperidine-4-carboxylic acid	LC1	517.32	1.26

Example	Name	LC/MS	m/z [M+H] ⁺	Rt [min]
27	(S)-1-{2-[2,6-dimethyl-4-(5-{2-methylphenoxy}-oxazolo[5,4-d]pyrimidin-2-yl)-phenoxy]-acetyl}-pyrrolidine-2-carboxylic acid	LC1	503.32	1.27
28	(S)-1-(2-{4-[5-(3-methoxyphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-pyrrolidine-2-carboxylic acid	LC5	519.24	1.11
29	1-(2-{4-[5-(3-methoxyphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-piperidine-4-carboxylic acid	LC5	533.37	1.11
30	1-(2-{4-[5-(2-fluoro-4-methylphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-piperidine-4-carboxylic acid	LC5	535.39	1.15
31	1-(2-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-azetidine-3-carboxylic acid	LC1	493.34	1.21
32	1-(2-{4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-azetidine-3-carboxylic acid	LC1	509.33	1.26
33	1-(2-{4-[5-(2-fluoro-4-methylphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-azetidine-3-carboxylic acid	LC1	507.19	1.25
34	1-{2-[2,6-dimethyl-4-(5-{2-methylphenoxy}-oxazolo[5,4-d]pyrimidin-2-yl)-phenoxy]-acetyl}-azetidine-3-carboxylic acid	LC1	489.2	1.23
35	1-(2-{4-[5-(3-methoxyphenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-azetidine-3-carboxylic acid	LC1	505.19	1.2

Example	Name	LC/MS	m/z [M+H] ⁺	Rt [min]
36	1-(2-{4-[5-(2-fluorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-pyrrolidine-3-carboxylic acid	LC1	507.21	1.22
37	1-(2-{4-[5-(3-chlorophenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethylphenoxy}-acetyl)-pyrrolidine-3-carboxylic acid	LC1	523.15	1.25

Determination of the pharmacological activity

5 A) GTP- γ -S assay using human Edg-1 receptors

In order to determine the Edg-1 receptor activation by the compounds of the invention, a GTP- γ -S (guanosine 5'-[thio]triphosphate) assay for G-protein coupled receptor binding based on the scintillation proximity assay principle was used, employing a cell membrane preparation from a CHO Flp-In cell line which constitutively overexpresses the human Edg-1 receptor.

(a) Cell line generation

The Flp-In™ expression system (Invitrogen, cat. no. K6010-01) allows the generation of stable mammalian cell lines into which the gene of interest has been integrated through homologous recombination at a specific genomic location called Flp Recombination Target (FRT) site by means of a Flp recombinase encoded by the pOG44 expression plasmid. The integration of the pcDNA5/FRT expression construct into the Flp-In host cell line genome results in the transcription of the gene of interest. The stably transfected cells become hygromycin-resistant.

One day prior to transfection, 200 000 Flp-In-CHO cells were seeded in Ham F-12 medium (Invitrogen, cat. no. 31765) supplemented with 10 % fetal calf serum (FCS;

Perbio Science, cat. no. SH30068.03) in a 6-well plate and incubated at 37 °C / 5 % CO₂ overnight. Using the FuGENE[®] 6 transfection reagent (Roche, cat. no. 11988387001), cells were cotransfected with the Flp recombinase expression plasmid pOG44 and a modified plasmid additionally containing the *edg-1* gene (accession no. NM_001400) termed as pcDNA5-FRT-TO_nFLAG_DEST-EDG-1 with a 9:1 ratio. To obtain the modified pcDNA5-FRT-TO_nFLAG_DEST plasmid, the Invitrogen plasmid pcDNA5/FRT/TO (Invitrogen, cat. no. V6520-20) was adapted to the Gateway[®] (Invitrogen) cloning system by inserting a Gateway cassette containing attR recombination sites flanking a *ccdB* gene and a chloramphenicol-resistance gene (Gateway conversion system, Invitrogen, cat. no. 11828-029). In addition a FLAG tag epitope was added before the 5' att recombination site to allow recombinant expression of N-terminally FLAG-tagged proteins.

For the transfection of one well, 1.08 µg of pOG44 and 0.12 µg of pcDNA5-FRT-TO_nFLAG_DEST-EDG-1 were mixed to 100 µl of serum-free Ham F-12 medium containing 6 µl of FuGENE[®] 6 transfection reagent. After 20 min of incubation, the transfection reagent/DNA complex was distributed dropwise on the cells. The cells were incubated for 24 h at 37 °C. Then the cells from 3 wells were transferred to a T75 flask (Greiner Cellstar[®], cat. no. 658175) containing Ham F-12 medium supplemented with 10% of FCS but without antibiotic and were incubated another 24 h. 48 h after transfection, the medium was replaced by selection medium (Ham F-12 supplemented with 10 % of FCS and 300 µg/ml of hygromycin B (Invitrogen, cat. no. 10687-010)). The medium was exchanged every 2 to 3 days until a resistant population of cells had grown. Cells were several times splitted and seeded into a new flask so that the cells did not reach more than 25 % of confluency. After 2 weeks of selection, the cells were transferred into T175 flasks (Greiner Cellstar[®], cat. no. 660175) and cultivated for batch production. Cells were harvested from the culture flasks by short treatment (2 to 5 min) with Accutase (PAA, cat. no. L11-007), resuspended in selection medium (see above) and centrifuged at 200 x g for 5 min. Cells were resuspended in a mixture of 90 % of FCS and 10 % of dimethylsulfoxide and stored frozen in liquid nitrogen.

(b) Membrane preparation

A membrane preparation was obtained by standard methods from the afore-described CHO Flp-In cell line constitutively overexpressing the human Edg-1 receptor. Briefly, the cryopreserved cells were taken in culture and grown until
5 confluency in T175 cell culture flasks (Becton Dickinson, cat. no. 35 5001). Cell culture was stopped by washing with calcium-free phosphate-buffered saline (PBS; Gibco, cat. no. 14190), and cells were harvested with a rubber-policeman in 4 °C cold and calcium-free PBS supplemented with a protease inhibitor cocktail (complete protease inhibitor; Roche, cat. no. 1697498; 1 tablet per 50 ml) and subsequently
10 centrifuged at 4 °C for 15 min at 1100 x g (Heraeus Minifuge T). For cell lysis, the pellet was resuspended in a 4 °C cold hypotonic buffer consisting of 5 mM HEPES (Sigma-Aldrich, cat. no. H-0981), 1 mM EDTA (disodium salt; Merck, cat. No. 8418) supplemented with protease inhibitor cocktail (as above) in which cells were stored for another 15 min on ice. After lysis, cells were centrifuged at 4 °C for 10 min at 400
15 x g (Heraeus Minifuge T). The pellet was disrupted in a Dounce homogenizer, diluted with the supernatant of the previous centrifugation and subsequently centrifuged at 4 °C for 10 min at 500 x g (Heraeus Minifuge T) in order to separate nuclei and still intact cells from the membranes mainly present in the supernatant. The supernatant was then diluted in hypotonic buffer and centrifuged (Beckmann, Avanti J251) at
20 approximately 18600 x g for 2 h at 4 °C. After centrifugation, the membrane pellet was resuspended in a storing buffer consisting of 20 mM HEPES; 150 mM NaCl (Merck, cat. no. 6400), 1 mM EDTA (as above) supplemented with protease inhibitor cocktail (as above). The membrane preparation was aliquoted and stored at -80 °C. Protein concentration of the membrane preparation was determined in a sample by
25 means of a commercial protein assay (Bio-Rad, DC Protein Assay, cat. nos. 500-0113, 500-0114, 500-0115).

(c) GTP- γ -S Assay

The Edg-1 membrane preparation obtained in (b) was employed in a commercially
30 available scintillation proximity assay (SPA) kit for G-protein coupled receptor binding from Amersham Biosciences/GE Healthcare (code RPNQ0210), in which ligand-induced binding of 35 S-radiolabeled GTP- γ -S to the receptor-containing membrane,

which is bound to scintillation beads, stimulates the emission of light and allows to quantify the in vitro activity of the Edg-1 agonistic compound. The assay was performed on a 96-well plate substantially according to the manufacturer's instructions. Before start of the experiments, scintillation beads were suspended in a reconstitution buffer consisting of Tris-HCl (pH 7.4) supplemented with 0.1 % (w/v) sodium azide and subsequently diluted on ice with assay buffer (consisting of 20 mM HEPES, 100 mM NaCl, 1 mM EDTA (as above), 1 mM dithiothreitol (DTT), adjusted to pH 7.4) to a final bead concentration of 30 mg/ml.

- 10 Wells were charged with 10 μ l of the specified assay buffer, 10 μ l of a 100 μ M guanosine diphosphate (GDP) solution, and 10 μ l of a solution of the test compound in assay buffer/dimethylsulfoxide resulting in a final concentration of the test compound of 10 μ M. For the high controls, 10 μ l of a solution of sphingosine-1-phosphate (S1P; Sigma, cat. no. S-9666), resulting in a final S1P concentration of
- 15 10 μ M, and for the low controls 10 μ l of assay buffer, was added into respective wells instead of the solution of the test compound. All wells contained equivalent amounts of dimethylsulfoxide. Then 10 μ l of a [35 S]GTP- γ -S solution (4 nM) and the Edg-1 membrane preparation obtained in (b) (15 μ g membrane proteins in 100 μ l of assay buffer) was added to each well. After incubation of the plates at room temperature for
- 20 5 min, 50 μ l of the specified scintillation bead suspension (30 mg/ml) was added. After a further incubation period of 45 min at room temperature, plates were centrifuged for 10 min at 500 x g. Quantification of [35 S]GTP- γ -S binding and thus receptor activation was measured by means of a beta counter (MicroBeta, Wallac) over 1 min. Values were background-corrected by subtraction of the respective low
- 25 control. All measurements were made in triplicate. The receptor activation by the test compound is expressed in percent of the respective high control (10 μ M S1P; regarded as 100 % activation). In Table 2 activations observed with example compounds at 10 μ M are listed.

Table 2. Edg-1 receptor activation by example compounds at 10 μ M in percent of the activation by 10 μ M S1P

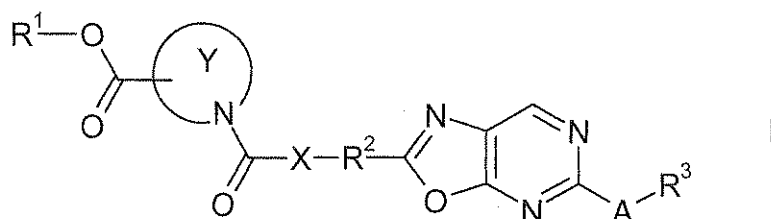
Example	% Activation
1	115
2	93
3	82
4	103
5	85
6	44
7	59
8	60
9	96
10	78
11	86
12	109
13	86
14	109
15	78
16	85
17	106
18	58
19	47
20	107
21	39
22	69
23	111
24	94
25	49
26	128
27	77

Example	% Activation
28	84
29	43
30	88
31	83
32	82
33	178
34	184
35	110
36	112
37	113

It can be seen from the measurement data that the compounds are quite suitable for wound healing and in particular for treating wound healing disorders of patients with diabetes.

Claims

1. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a
 5 physiologically acceptable solvate of any of them,



wherein

10

A is chosen from NH, O and S;

15

X is chosen from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl, (C₂-C₆)-alkynediyl, (C₃-C₇)-cycloalkanediyl and (C₁-C₆)-alkanediyl-oxy, which all are optionally substituted by one or more identical or different substituents chosen from fluorine and hydroxy, wherein the oxygen atom of the (C₁-C₆)-alkanediyl-oxy group is bonded to the group R²;

20

Y is 4-membered to 7-membered, saturated or partially unsaturated, monocyclic or bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0, 1, 2 or 3 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the additional ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring
 25 carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

R¹ is chosen from hydrogen, (C₁-C₄)-alkyl and (C₃-C₇)-cycloalkyl-C_zH_{2z-}, wherein z is chosen from 0, 1 and 2;

R^2 is chosen from phenylene and a divalent residue of an aromatic, 5-membered to 6-membered monocyclic heterocycle which comprises 1, 2 or 3 identical or different ring heteroatoms chosen from N, O and S, wherein one of the ring nitrogen atoms
5 can carry a hydrogen atom or a substituent R^{21} , and wherein the phenylene and divalent residue of an aromatic heterocycle are optionally substituted on one or more ring carbon atoms by identical or different substituents R^{22} ;

R^3 is chosen from (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, (C_3-C_7) -cycloalkyl-
10 C_uH_{2u-} and Het- C_vH_{2v-} , wherein u and v are chosen from 1 and 2, or R^3 is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1, 2, 3 or 4 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C_1-C_4) -alkyl substituent and one or two of the ring sulfur atoms can carry
15 one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R^{31} ;

R^{21} is chosen from (C_1-C_4) -alkyl, (C_3-C_7) -cycloalkyl- C_wH_{2w-} and oxy, wherein w is chosen from 0, 1 and 2;

R^{22} is chosen from halogen, hydroxy, (C_1-C_4) -alkyl-, (C_1-C_4) -alkyloxy, (C_1-C_4) -alkyl-
S(O) $_m$ -, amino, nitro, cyano, hydroxycarbonyl, (C_1-C_4) -alkyloxycarbonyl, aminocarbonyl and aminosulfonyl;

R^{31} is chosen from halogen, (C_1-C_4) -alkyl, (C_3-C_7) -cycloalkyl, hydroxy, (C_1-C_4) -
25 alkyloxy, oxo, (C_1-C_4) -alkyl-S(O) $_m$ -, amino, (C_1-C_4) -alkylamino, di $((C_1-C_4)$ -alkyl)amino, (C_1-C_4) -alkylcarbonylamino, (C_1-C_4) -alkylsulfonylamino, nitro, cyano, (C_1-C_4) -alkylcarbonyl, aminosulfonyl, (C_1-C_4) -alkylaminosulfonyl and di $((C_1-C_4)$ -alkyl)aminosulfonyl;

Het is a residue of a saturated, 4-membered to 7-membered, monocyclic heterocycle which comprises 1 or 2 identical or different ring heteroatoms chosen from N, O and

S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl;

5 m is chosen from 0, 1 and 2, wherein all numbers m are independent of each other;

wherein all cycloalkyl and cycloalkanediyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl;

10

wherein all alkyl, alkanediyl, C_uH_{2u}, C_vH_{2v}, C_wH_{2w}, C_zH_{2z}, alkenyl, alkenediyl, alkynyl and alkynediyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

15 2. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in claim 1, wherein A is chosen from O and S.

20 3. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 and 2, wherein X is chosen from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl and (C₁-C₆)-alkanediyl-oxy.

25

4. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 3, wherein Y is a 4-membered to 7-membered, saturated, monocyclic or
30 bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0 or 1 ring heteroatoms chosen from N, O and S, wherein an additional ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and a

ring sulfur atom can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents.

5 5. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 4, wherein R² is chosen from phenylene and pyridinediyl, wherein the phenylene and the pyridinediyl are optionally substituted on one or more ring carbon
10 atoms by identical or different substituents R²².

6. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of
15 claims 1 to 5, wherein
R³ is chosen from (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of
20 the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle
25 which comprises 1 ring heteroatom chosen from N, O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl.

7. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of
30 stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 6, wherein

A is chosen from O and S;

X is chosen from (C₁-C₆)-alkanediyl, (C₂-C₆)-alkenediyl and (C₁-C₆)-alkanediyl-oxy;

Y is a 4-membered to 7-membered, saturated, monocyclic or bicyclic heterocycle which, in addition to the ring nitrogen atom depicted in formula I, comprises 0 or 1

5 ring heteroatoms chosen from N, O and S, wherein an additional ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and a ring sulfur atom can carry one or two oxo groups, and wherein the heterocycle is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

10 R² is chosen from phenylene and pyridinediyl, wherein the phenylene and the pyridinediyl are optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

R³ is chosen from (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to 10-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2
15 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

20 Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle which comprises 1 ring heteroatom chosen from N, O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl.

25 8. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 7, wherein

A is O;

30 X is chosen from (C₁-C₆)-alkanediyl and (C₁-C₆)-alkanediyl-oxy;

Y is a 4-membered to 6-membered, saturated, monocyclic heterocycle which does not comprise further ring heteroatoms in addition to the ring nitrogen atom depicted in

formula I, wherein the ring is optionally substituted on one or more ring carbon atoms by identical or different (C₁-C₄)-alkyl substituents;

R¹ is chosen from hydrogen and (C₁-C₄)-alkyl;

5 R² is phenylene which is optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

R³ is chosen from (C₃-C₇)-cycloalkyl-C_uH_{2u}- and Het-C_vH_{2v}-, wherein u and v are chosen from 1 and 2, or R³ is a residue of a saturated or unsaturated, 3-membered to 7-membered, monocyclic or bicyclic ring which comprises 0, 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein one or two of the ring
10 nitrogen atoms can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and one of the ring sulfur atoms can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

R²² is chosen from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy;

15 R³¹ is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy;

Het is a residue of a saturated, 4-membered to 6-membered, monocyclic heterocycle which comprises 1 ring heteroatom chosen from O and S and which is bonded via a ring carbon atom, wherein the residue of a heterocycle is optionally substituted by
20 one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl; wherein all cycloalkyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more identical or different substituents chosen from fluorine and (C₁-C₄)-alkyl;

25 wherein all alkyl, alkanediyl, C_uH_{2u} and C_vH_{2v} groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

9. A compound of the formula I, in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a
30 physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 8, wherein

A is O;

X is chosen from (C₁-C₆)-alkanediyl and (C₁-C₆)-alkanediyl-oxy;

Y is a 4-membered to 6-membered, saturated, monocyclic heterocycle which does not comprise further ring heteroatoms in addition to the ring nitrogen atom depicted in formula I, wherein the ring is optionally substituted on one or more ring carbon atoms
5 by identical or different (C₁-C₄)-alkyl substituents;

R¹ is chosen from hydrogen and (C₁-C₄)-alkyl;

R² is phenylene which is optionally substituted on one or more ring carbon atoms by identical or different substituents R²²;

R³ is a residue of a saturated or unsaturated, 3-membered to 7-membered,
10 monocyclic ring which comprises 0 or 1 ring heteroatom chosen from N, O and S, wherein a ring nitrogen atom can carry a hydrogen atom or a (C₁-C₄)-alkyl substituent and a ring sulfur atom can carry one or two oxo groups, and wherein the residue of a ring is optionally substituted on one or more ring carbon atoms by identical or different substituents R³¹;

15 R²² is chosen from halogen, hydroxy, (C₁-C₄)-alkyl- and (C₁-C₄)-alkyloxy;

R³¹ is chosen from halogen, (C₁-C₄)-alkyl, (C₃-C₇)-cycloalkyl, hydroxy and (C₁-C₄)-alkyloxy;

wherein all cycloalkyl groups, independently of each other and independently of any other substituents, are optionally substituted by one or more identical or different

20 substituents chosen from fluorine and (C₁-C₄)-alkyl;

wherein all alkyl, alkanediyl, C_uH_{2u} and C_vH_{2v} groups, independently of each other and independently of any other substituents, are optionally substituted by one or more fluorine substituents.

25 10. A compound of the formula I, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, as claimed in one or more of claims 1 to 9, chosen from

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

30 (S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid,

(S)-1-((E)-3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-acryloyl)-pyrrolidine-2-carboxylic acid,

(S)-1-(3-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenyl}-propionyl)-pyrrolidine-2-carboxylic acid,

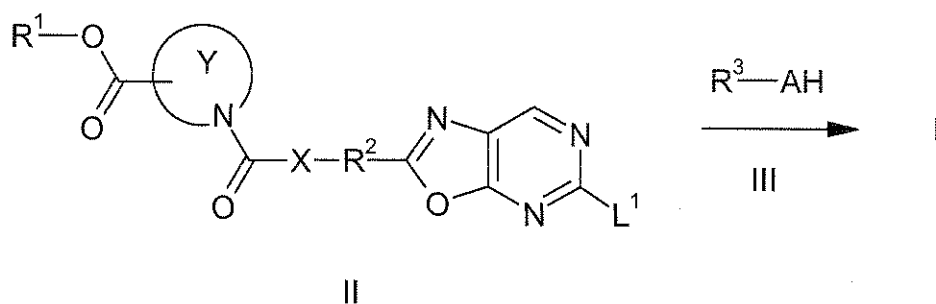
5 (S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2-methyl-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-pyrrolidine-2-carboxylic acid,

10 1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-acetyl)-piperidine-4-carboxylic acid, and

(S)-1-(2-{4-[5-(2-fluoro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-phenoxy}-propionyl)-pyrrolidine-2-carboxylic acid.

11. A process for the preparation of a compound of the formula I as claimed in any of
15 claims 1 to 10, comprising reacting a compound of the formula II with a compound of the formula III,



20 wherein the groups A, X, Y, R¹, R² and R³ in the compounds of the formulae II and III are defined as in the compounds of the formula I and additionally functional groups can be present in protected form or in the form of a precursor group, and L¹ is a halogen atom or a group of the formula -S(O)-Alk or -S(O)₂-Alk wherein Alk is a (C₁-C₄)-alkyl.

25

12. A pharmaceutical composition, comprising at least one compound of the formula I as claimed in any of claims 1 to 10 or a physiologically acceptable salt thereof, or a

physiologically acceptable solvate of any of them, and a pharmaceutically acceptable carrier.

13. A compound of the formula I as claimed in any of claims 1 to 10 or a
5 physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, for use as a pharmaceutical.
14. A compound of the formula I as claimed in any of claims 1 to 10 or a
10 physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, for the treatment of wound healing disorders.
15. A compound of the formula I as claimed in any of claims 1 to 10 or a
physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for wound healing.
- 15 16. A compound of the formula I as claimed in any of claims 1 to 10 or a
physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for wound healing in diabetics.
- 20 17. A compound of the formula I as claimed in any of claims 1 to 10 or a
physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, for the treatment of diabetic foot syndrome.