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(54) Title: NEW CCR2 RECEPTOR ANTAGONISTS, METHOD FOR PRODUCING THE SAME, AND USE THEREOF AS MEDICAMENTS

(57) Abstract: The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2) and their use for providing medicaments for treating conditions and diseases, especially pulmonary diseases like asthma and COPD and pain diseases.

New CCR2 receptor antagonists, method for producing the same, and use thereof as medicaments

Field of invention

5 The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2), the method for producing the same, and their use for providing medicaments for treating conditions and diseases where activation of CCR2 plays a causative role, especially pulmonary diseases like asthma and COPD, neurologic disease, especially of pain diseases, immune related diseases, especially diabetes mellitus including diabetes nephropathy, and
10 cardiovascular diseases, especially atherosclerotic disease.

Background of the invention

15 The chemokines are a family of small, proinflammatory cytokines, with potent chemotactic activities. Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract various cells, such as monocytes, macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation.

Chemokine receptors, such as CCR2 or CCR5 have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases as well as
20 autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Accordingly, agents which modulate chemokine receptors such as the CCR2 and CCR5 receptor would be useful in such disorders and diseases.

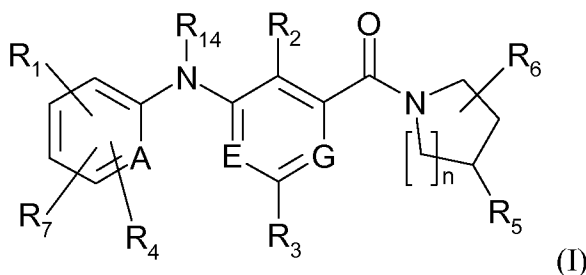
In particular it is widely accepted that numerous conditions and diseases involve
25 inflammatory processes. Such inflammations are critically triggered and / or promoted by the activity of macrophages, which are formed by differentiation out of monocytes. It has further been found that monocytes are characterized by, e.g., a high expression of membrane-resident CCR2, whereas the CCR2 expression in macrophages is lower. CCR2 is a critical regulator of monocytes trafficking, which can be described as the movement of the monocytes towards an
30 inflammation along a gradient of monocyte chemoattractant proteins (MCP-1, MCP-2, MCP-3, MCP-4).

Therefore, in order to reduce macrophage-induced inflammation, it would be desirable to block the monocyte CCR2 by an antagonist, so that the monocytes can be less triggered to
35 move towards an inflammation area for conversion into macrophages.

Based on the aforesaid there is a need for providing effective antagonists for CCR2, which are pharmacologically acceptable.

Description of the invention

It has now been found that such effective CCR2 inhibitors can be provided by compounds according to general formula (I),



5

wherein R₁ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, -C₅-C₁₀-heteroaryl, and -OCFH₂,

and wherein R₇ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

10

or wherein R₇ and R₁ on two neighbouring ring atoms together form a -C₃-C₆-alkenylene group, such that an annellated aromatic ring is formed, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O, and S, wherein the resulting annelated ring being optionally substituted by one or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and halogen;

15

wherein R₄ is a group selected from among -hydrogen, -C₁-C₃-alkyl, -CF₃, -OCF₃, -OCF₂H, -halogen, -CN, -O-C₁-C₄-alkyl, -CH=CH₂, -C≡CH, and -OCFH₂;

20

wherein A is C or N;

wherein R₁₄ is a group selected from among -hydrogen, and -C₁-C₃-alkyl;

25

wherein R₂ is selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -cyclopropyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

30

wherein n is 1, 2 or 3;

wherein G and E are N,

or wherein G is N and E is C,

35

or wherein G is C and E is N;

wherein R₅ is a group of the structure -NR₈R₉,

5 wherein R₈, R₉, are independently selected from among -H, -C₁-C₆-alkyl, and a group of the structure -C₃-C₆-cycloalkyl, wherein such ring is optionally substituted by one or more groups selected from among -F, and -OCH₃;

or wherein R₅ is a group of the structure -N(R₁₀,R_{10'}),

10 wherein R₁₀ and R_{10'}, together form a -C₂-C₆-alkylene group such that a ring is formed, wherein such ring is optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -N(C₀-C₃-alkyl)-SO₂-C₁-C₃-alkyl;

or wherein R₅ is a group of the structure -N(R₁₁,R_{11'}),

15 wherein R₁₁ and R_{11'}, together form a -C₂-C₆-alkylene group such that a ring is formed, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O, and S,

20 wherein such ring is optionally substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, =O, and halogen;

or wherein R₅ is a group of the structure -L₁-R₁₃,

25 wherein L₁ is selected from among -NH- and -N(C₁-C₄-alkyl)-, wherein R₁₃ is -C₃-C₈-heterocyclyl, wherein R₁₃ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl;

30 wherein R₆ is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen, -CN, -CF₃, and -OCF₃;

as well as in form of their acid addition salts with pharmacologically acceptable acids.

Preferred compounds of formula (I) according to the invention are compounds wherein

35 R₁ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, -C₅-C₁₀-heteroaryl, and -OCFH₂, and wherein R₇ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

or wherein R₇ and R₁ on two neighbouring ring atoms together form a -C₃-C₆-alkenylene group, such that an annellated aromatic ring is formed, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O, and S, wherein the resulting annelated ring being optionally substituted by one or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and halogen;

wherein R₄ is a group selected from among -hydrogen, -C₁-C₃-alkyl, -CF₃, -OCF₃, -OCF₂H, -halogen, -CN, -O-C₁-C₄-alkyl, -CH=CH₂, -C≡CH, and -OCFH₂;

wherein A is C or N;

wherein R₁₄ is a group selected from among -hydrogen, and -C₁-C₃-alkyl;

wherein R₂ is selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -cyclopropyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

wherein n is 1, 2 or 3;

wherein G and E are N,

or wherein G is N and E is C,

or wherein G is C and E is N;

wherein R₅ is a group of the structure -N(R₁₀,R_{10'}),

wherein R₁₀ and R_{10'}, together form a -C₂-C₆-alkylene group such that a ring is formed, wherein such ring is optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -N(C₀-C₃-alkyl)-SO₂-C₁-C₃-alkyl;

or wherein R₅ is a group of the structure -L₁-R₁₃,

wherein L₁ is selected from among -NH- and -N(C₁-C₄-alkyl)-,

wherein R₁₃ is -C₃-C₈-heterocyclyl,

wherein R₁₃ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl;

wherein R₆ is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen, -CN, -CF₃, and -OCF₃.

Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

5 wherein R₁ is a group selected from among -H, -halogen, -C₁-C₄-alkyl, -CF₃, -OCF₃, and -C₆-heteroaryl comprising a N atom; and wherein R₇ is a group selected from among -H, -halogen, -C₁-C₄-alkyl, -CF₃, -OCF₃, and -C₆-heteroaryl comprising a N atom; and wherein R₄ denotes -hydrogen.

10 Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₁ and R₇ are a group selected from -halogen, preferably selected from -Cl; and wherein R₄ denotes -hydrogen.

15 Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₇ and R₁ on two neighbouring ring atoms together form -C₃-C₆-alkenylene group, such that an annellated aromatic ring is formed, in which which one or two carbon centers may optionally be replaced by 1 or 2 hetero atoms selected from N; and wherein R₄ is a group selected from among -H, -OCH₃, and -C₁-C₃-alkyl, preferably selected from among -hydrogen, and -C₁-C₃-alkyl.

25 Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₇ and R₁ on two neighbouring ring atoms together form -C₃-C₆-alkenylene group, such that an annellated aromatic ring is formed, in which which one carbon centers may optionally be replaced by 1 hetero atoms selected from N; and wherein R₄ is a group selected from among -H, -OCH₃, and -C₁-C₃-alkyl, preferably selected from among -hydrogen, and -C₁-C₃-alkyl.

35 Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₇ and R₁ on two neighbouring ring atoms together form -C₃-C₆-alkenylene group, and wherein R₄ is a group selected from among -H, -OCH₃, and -C₁-C₃-alkyl, preferably selected from among -hydrogen, and -C₁-C₃-alkyl.

- Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₅, R₆, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,
- 5 wherein R₇ and R₁ on two neighbouring ring atoms together form a -C₄-alkenylene group, such that an annellated aromatic ring is formed, in which one or two carbon centers may optionally be replaced by 1 or 2 hetero atoms selected from N; and wherein R₄ is a group selected from among -hydrogen, and -C₁-C₃-alkyl.
- 10 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, and n as herein before or below defined,
wherein A denotes N.
- 15 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, and n as herein before or below defined,
wherein A denotes C.
- 20 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,
wherein R₂ is selected from among -H, -C₁-C₄-alkyl, -cyclopropyl, and -O-C₁-C₄-alkyl.
- 25 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,
wherein R₂ is selected from among -H, -CH₃, -cyclopropyl, and -OCH₃.
- 30 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,
wherein R₂ is selected from among -CH₃, -cyclopropyl, and -OCH₃.
- 35 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,
wherein R₂ is selected from among -Methyl and -OCH₃.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₂ denotes -Methyl.

5

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₂ denotes -OCH₃.

10

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₂ denotes -cyclopropyl.

15

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₂ denotes -H.

20

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₃ is selected from among -hydrogen, -CF₃, and -OCH₃.

25

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₃ is selected from among -CF₃, and -OCH₃.

30

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₃ denotes -hydrogen.

35

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

wherein R₃ denotes -OCH₃.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

5 wherein R₃ denotes -CF₃.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n as herein before or below defined,

10 wherein R₃ denotes -cyclopropyl.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, and A, as herein before or below defined,

15 wherein n is selected from among 1, and 2.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, and A, as herein before or below defined,

20 wherein n is 2.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, A, and n as herein before or below defined, wherein G and E are N or wherein G is N and E is C.

25

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, A, and n as herein before or below defined, wherein G and E are N.

30 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, A, and n as herein before or below defined, wherein G is N and E is C.

35 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, A, and n as herein before or below defined,

wherein G is C and E is N.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined, wherein R_5 is a group of the structure $-N(R_{10}, R_{10'})$, wherein R_{10} and $R_{10'}$, together form a $-C_4$ -alkylene group such that a ring is formed, wherein such ring is optionally substituted with one or more groups selected from among $-N(C_0-C_3\text{-alkyl})-SO_2-C_1-C_3\text{-alkyl}$;
5 or wherein R_5 is a group of the structure $-L_1-R_{13}$, wherein L_1 denotes $-NH-$, wherein R_{13} is $-C_6$ -heterocyclyl comprising an O atom, wherein R_{13} is optionally substituted by a group selected from among $-O-C_1-C_4\text{-alkyl}$.

10 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{11} , $R_{11'}$, R_{13} , R_{14} , L_1 , E, G, A, and n as herein before or below defined, wherein R_5 is a group of the structure $-N(R_{10}, R_{10'})$, wherein R_{10} and $R_{10'}$, together form a $-C_4$ -alkylene group such that a ring is formed, wherein such ring is optionally substituted with one or more
15 groups selected from among $-N(C_0-C_3\text{-alkyl})-SO_2-C_1-C_3\text{-alkyl}$.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{11} , $R_{11'}$, R_{13} , R_{14} , L_1 , E, G, A, and n as herein before or below defined, wherein
20 R_5 is a group of the structure $-N(R_{10}, R_{10'})$, wherein R_{10} and $R_{10'}$, together form a $-C_4$ -alkylene group such that a ring is formed, wherein such ring is optionally substituted with one or more groups selected from among $-N(CH_3)-SO_2-CH_3$.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
25 R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined, wherein R_5 is a group of the structure $-L_1-R_{13}$, wherein L_1 denotes $-NH-$, wherein R_{13} is $-C_6$ -heterocyclyl comprising an O atom, wherein R_{13} is optionally substituted by a group selected from among $-O-C_1-C_4\text{-alkyl}$.

30 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined, wherein R_5 is a group of the structure $-L_1-R_{13}$, wherein L_1 denotes $-NH-$, wherein R_{13} is
35 $-C_6$ -heterocyclyl comprising an O atom, wherein R_{13} is optionally substituted by a group selected from $-halogen$.

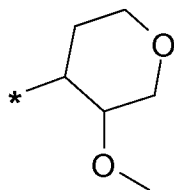
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined,

5 wherein R_5 is a group of the structure $-L_1-R_{13}$, wherein L_1 denotes $-NH-$, wherein R_{13} is $-C_6$ -heterocyclyl comprising an O atom, wherein R_{13} is optionally substituted by a group selected from $-F$.

10 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined,

wherein R_5 is a group of the structure $-L_1-R_{13}$, wherein L_1 denotes $-NH-$, wherein R_{13} is $-C_6$ -heterocyclyl comprising an O atom, wherein R_{13} is optionally substituted by a group selected from among $-OCH_3$, and $-halogen$, preferably selected from among $-OCH_3$.

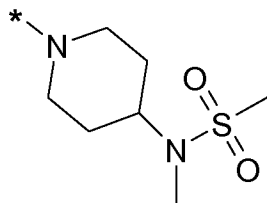
15 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{14} , E, G, A, and n as herein before or below defined, wherein R_4 denotes $-H$, and wherein R_5 denotes a group of the structure $-L_1-R_{13}$, wherein L_1 is a group selected from among $-NH-$, and $-N(CH_3)-$, wherein R_{13} is a group of the structure



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Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{11} , $R_{11'}$, R_{13} , R_{14} , L_1 , E, G, A, and n as herein before or below defined, wherein

R_5 is a group of the structure



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Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} , $R_{10'}$, R_{11} , $R_{11'}$, R_{13} , R_{14} , L_1 , E, G, A, and n as herein before or below defined,

30 wherein R_6 denotes $-H$.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, L₁, E, G, A, and n as herein before or below defined,

wherein R₁₄ denotes -H.

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All of the above embodiments under formula (I) have to be understood to optionally be present in form of their individual optical isomers, mixtures of their individual optical isomers, or racemates, as well as in form of their acid addition salts with pharmacologically acceptable acids, as well as in form of their solvates and/or hydrates.

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It has now been found that such compounds as herein before or below defined could be used as a medicament.

It has been found that such compounds as herein before or below defined could be used for making a medicament for the treatment of inflammatory diseases. It has been found that such

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compounds as herein before or below defined could be used for making a medicament for the treatment of inflammatory diseases, wherein the inflammatory diseases are selected from inflammatory diseases of the respiratory tract. It has been found that such compounds as

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herein before or below defined could be used for making a medicament for the treatment of inflammatory diseases, wherein the inflammatory diseases are selected from chronic obstructive pulmonary disease, asthma, and cystic fibrosis. It has been found that such

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compounds as herein before or below defined could be used for making a medicament for the treatment of neurologic diseases, preferably for the treatment of pain diseases especially for the treatment of inflammatory and neuropathic pain disease, especially for the treatment of chronic pain. It has been found that such compounds as herein before or below defined could

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be used for making a medicament for the treatment of immune related diseases, preferably for the treatment of diabetes mellitus. It has been found that such compounds as herein before or below defined could be used for making a medicament for the treatment of cardiovascular diseases, preferably for the treatment of peripheral atherosclerotic disease. It has been found that such compounds as herein before or below defined could be used for making a

medicament for the treatment of diabetic nephropathy.

Present invention encloses compounds as herein before or below defined as medicaments. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of inflammatory diseases. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of inflammatory diseases, wherein

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the inflammatory diseases are selected from inflammatory diseases of the respiratory tract. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of inflammatory diseases, wherein the inflammatory diseases are selected from chronic obstructive pulmonary disease, asthma, and cystic fibrosis. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of neurologic

diseases, preferably for the treatment of pain diseases especially for the treatment of inflammatory and neuropathic pain disease, especially for the treatment of chronic pain. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of immune related diseases, preferably for the treatment of diabetes mellitus.

5 Present invention encloses compounds as herein before or below defined as medicaments for the treatment of cardiovascular diseases, preferably for the treatment of peripheral atherosclerotic disease. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of diabetic nephropathy.

10 It has been found that such compounds as herein before or below defined could be used for the treatment of inflammatory diseases. It has been found that such compounds as herein before or below defined could be used for the treatment of inflammatory diseases, wherein the inflammatory diseases are selected from inflammatory diseases of the respiratory tract. It has been found that such compounds as herein before or below defined could be used for the treatment of inflammatory diseases, wherein the inflammatory diseases are selected from
15 chronic obstructive pulmonary disease, asthma, and cystic fibrosis. It has been found that such compounds as herein before or below defined could be used for the treatment of neurologic diseases, preferably for the treatment of pain diseases especially for the treatment of inflammatory and neuropathic pain disease, especially for the treatment of chronic pain. It has been found that such compounds as herein before or below defined could be used for the
20 treatment of immune related diseases, preferably for the treatment of diabetes mellitus. It has been found that such compounds as herein before or below defined could be used for the treatment of cardiovascular diseases, preferably for the treatment of peripheral atherosclerotic disease. It has been found that such compounds as herein before or below defined could be used for the treatment of diabetic nephropathy.

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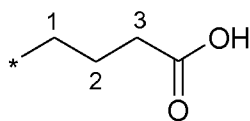
Definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning
30 indicated and the following conventions are adhered to.

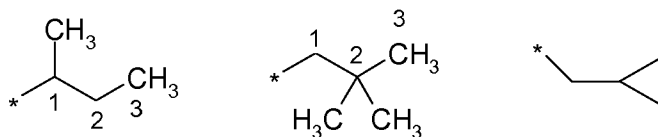
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, -C₁-C₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent
35 "aryl-C₁-C₃-alkyl-" means an aryl group which is bound to a C₁-C₃-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk is may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

5 For example, the term "3-carboxypropyl-group" represents the following substituent:



10 wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



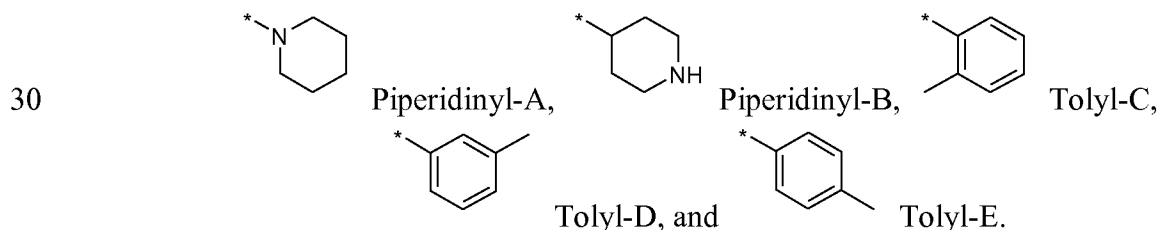
15 The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Many of the following terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

20 Unless otherwise stated, all the substituents are independent of one another. If for example there might be a plurality of C₁-C₆-alkyl groups as substituents in one group, in the case of three substituents C₁-C₆-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

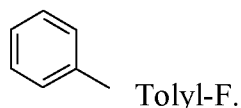
25 Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule.

Moreover, the atom of the substituent which follows the linking point is referred to as the atom in position number 1. Thus, for example, the groups *N*-piperidinyl (Piperidin-A), 4-piperidinyl (Piperidin-B), 2-tolyl (Tolyl-C), 3-tolyl (Tolyl-D), and 4-tolyl (Tolyl-E) are shown as follows:



If there is no asterisk (*) in the structural formula of the substituent, each hydrogen atom may be removed from the substituent and the valency thus freed may act as a binding site to the rest of a molecule. Thus, for example, (Tolyl-F) may represent 2-tolyl, 3-tolyl, 4-tolyl, and benzyl

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The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

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By the term "optionally substituted" is meant within the scope of the invention the above-mentioned group, optionally substituted by a lower-molecular group. Examples of lower-molecular groups regarded as chemically meaningful are groups consisting of 1-200 atoms. Preferably such groups have no negative effect on the pharmacological efficacy of the compounds. For example the groups may comprise:

20

- Straight-chain or branched carbon chains, optionally interrupted by heteroatoms, optionally substituted by rings, heteroatoms or other common functional groups.
- Aromatic or non-aromatic ring systems consisting of carbon atoms and optionally heteroatoms, which may in turn be substituted by functional groups.
- A number of aromatic or non-aromatic ring systems consisting of carbon atoms and optionally heteroatoms which may be linked by one or more carbon chains, optionally interrupted by heteroatoms, optionally substituted by heteroatoms or other common functional groups.

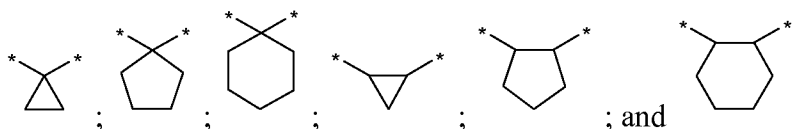
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By the term "branched or unbranched, saturated or unsaturated C₁-C₆-carbon chain" it is meant a chain of carbon atoms, which is constituted by 1 to 6 carbon atoms arranged in a row and which can optionally further comprise branches or one or more hetero atoms selected from N, O or S. Said carbon chain can be saturated or unsaturated by comprising double or triple bonds.

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If the carbon chain is to be substituted by a group which together with one or two carbon atoms of an alkylene chain forms a carbocyclic ring with 3, 5 or 6 carbon atoms, this includes the following examples of the rings:

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The term "C₁-C_n-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁-C₅-alkyl embraces the radicals H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-,

5 H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-, H₃C-C(CH₃)₂-CH₂-, H₃C-CH(CH₃)-CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-

By the term "C₁-C₆-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term

10 "C₁-C₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms.

Alkyl groups with 1 to 4 carbon atoms are preferred. By the term "C₁-C₃-alkyl" are meant branched and unbranched alkyl groups with 1 to 3 carbon atoms and by the term

"C₂-C₄-alkyl" are meant branched and unbranched alkyl groups with 2 to 4 carbon atoms.

Examples for alkyl groups with 1-6 carbon atoms include: methyl, ethyl, *n*-propyl, *iso*-propyl,

15 *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl or hexyl. Optionally the abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. may also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

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The term "C₁-C_n-alkylene" wherein n is an integer 2 to n, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical

containing from 1 to n carbon atoms. For example the term C₁-C₄-alkylene includes -CH₂-,

-CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -C(CH₃)₂-, -CH(CH₂CH₃)-, -CH(CH₃)-CH₂-,

25 -CH₂-CH(CH₃)-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH(CH₃)-, -CH(CH₃)-CH₂-CH₂-,

-CH₂-CH(CH₃)-CH₂-, -CH₂-C(CH₃)₂-, -C(CH₃)₂-CH₂-, -CH(CH₃)-CH(CH₃)-,

-CH₂-CH(CH₂CH₃)-, -CH(CH₂CH₃)-CH₂-, -CH(CH₂CH₂CH₃)-, -CH(CH(CH₃))₂- and

-C(CH₃)(CH₂CH₃)-

By the term "C₁-C₈-alkylene" (including those which are part of other groups) are meant

30 branched and unbranched alkylene groups with 1 to 8 carbon atoms. By the term

"C₁-C₆-alkylene" are meant branched and unbranched alkylene groups with 1 to 6 carbon

atoms. By the term "C₂-C₈-alkylene" are meant branched and unbranched alkylene groups

with 2 to 8 carbon atoms. By the term "C₂-C₆-alkylene" are meant branched and unbranched

alkylene groups with 2 to 6 carbon atoms. By the term "C₄-C₅-alkylene" are meant branched

35 and unbranched alkylene groups with 4 to 5 carbon atoms. By the term "C₂-C₆-alkylene" are

meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. By the term

"C₁-C₄-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon

atoms. By the term "C₁-C₂-alkylene" are meant branched and unbranched alkylene groups

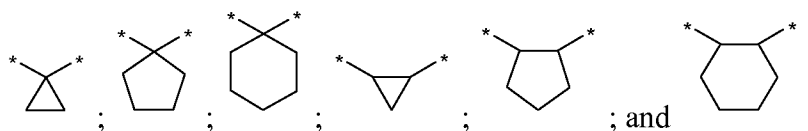
with 1 to 2 carbon atoms. By the term "C₁-alkylene" are meant an alkylene groups with 1

carbon atom. By the term "C₅-alkylene" are meant branched and unbranched alkylene groups with 5 carbon atoms. By the term "C₀-C₄-alkylene" are meant branched and unbranched alkylene groups with 0 to 4 carbon atoms, thus also a single bond is encompassed. By the term "C₀-C₃-alkylene" are meant branched and unbranched alkylene groups with 0 to 3 carbon atoms, thus also a single bond is encompassed. By the term "C₁-C₃-alkylene" are meant branched and unbranched alkylene groups with 1 to 3 carbon atoms. Examples for C₁-C₈-alkylene include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, hexylene, heptylene or octylene. Unless stated otherwise, the definitions propylene, butylene, pentylene, hexylene, heptylene and octylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

A -C₁-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₃-carbocycle. A -C₂-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₄-carbocycle. A -C₃-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₅-carbocycle. A -C₄-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₆-carbocycle. A -C₅-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₇-carbocycle. A -C₆-alkylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C₈-carbocycle.

In the definition of possible substituents, which are linked to such C₁-C₆-alkylene groups forming a C₃-C₈-carbocycle, it is to be understood that any of the atoms of the resulting C₃-C₈-carbocycles could be the linking point for such a substituent.

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



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The term "C₂-C_n-alkenyl", is used for a group as defined in the definition for "C₁-C_n-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.

By the term "C₂-C₆-alkenyl" (including those which are part of other groups) are meant
 5 branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term
 "C₂-C₄-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms,
 provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are
 preferred. Examples for C₂-C₆-alkenyls include: ethenyl or vinyl, propenyl, butenyl,
 pentenyl, or hexenyl. Unless stated otherwise, the definitions propenyl, butenyl, pentenyl and
 10 hexenyl include all the possible isomeric forms of the groups in question. Thus, for example,
 propenyl includes 1-propenyl and 2-propenyl, butenyl includes 1-, 2- and 3-butenyl,
 1-methyl-1-propenyl, 1-methyl-2-propenyl etc.

By the term "methenylene" is meant a group with 1 carbon atom, provided that it is linked by
 15 a single bond as well as on the other side by a double bond. The asterisks (*) in the structural
 formula is to be understood as being the linking points to the rest of the molecule, whereas the
 valency of the rest of the molecule be freed thus a single and a double bond can be formed by
 replacement of further hydrogens at the binding site if applicable:



The term "C₂-C_n-alkenylene" is used for a group as defined in the definition for
 "C₁-C_n-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said
 25 group are bonded to each other by a double bond.

By the term "C₂-C₈-alkenylene" (including those which are part of other groups) are meant
 branched and unbranched alkenylene groups with 2 to 8 carbon atoms and by the term
 "C₂-C₆-alkenylene" are meant branched and unbranched alkenylene groups with 2 to 6 carbon
 atoms, provided that they have at least one double bond. By the term "C₃-C₆-alkenylene" are
 30 meant branched and unbranched alkenylene groups with 3 to 6 carbon atoms, provided that
 they have at least one double bond. By the term "C₄-alkenylene" are meant branched and
 unbranched alkenylene groups with 4 carbon atoms, provided that they have at least one
 double bond. By the term "C₁-C₂-alkenylene" are meant alkenylene groups with 1 to 2 carbon
 atoms, provided that they have at least one double bond, whereas by the term "C₁-alkenylene"
 35 is meant "methenylene". Examples for C₂-C₈-alkenylenes include: ethenylene, propenylene,
 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene,
 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene,
 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene, heptenylene or octenylene.

Unless stated otherwise, the definitions propenylene, butenylene, pentenylene and hexenylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propenyl also includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene.

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A $-C_3$ -alkenylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C_5 -carbocycle. A $-C_4$ -alkenylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C_6 -carbocycle. A $-C_5$ -alkenylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C_7 -carbocycle. A $-C_6$ -alkenylene group, which is linked to a structure on two neighbouring ring atoms such that an annellated ring is formed, results to a C_8 -carbocycle.

10

In the definition of possible substituents, which are linked to such C_3 - C_6 -alkenylene groups forming a C_5 - C_8 -carbocycle, it is to be understood that any of the atoms of the resulting C_5 - C_8 -carbocycles could be the linking point for such a substituent.

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The term " C_2 - C_n -alkynyl", is used for a group as defined in the definition for " C_1 - C_n -alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.

By the term " C_2 - C_6 -alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term " C_2 - C_4 -alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples for C_2 - C_6 -alkynyls include: ethynyl, propynyl, butynyl, pentynyl or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1-, 2-, and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

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The term " C_2 - C_n -alkynylene" is used for a group as defined in the definition for " C_1 - C_n -alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.

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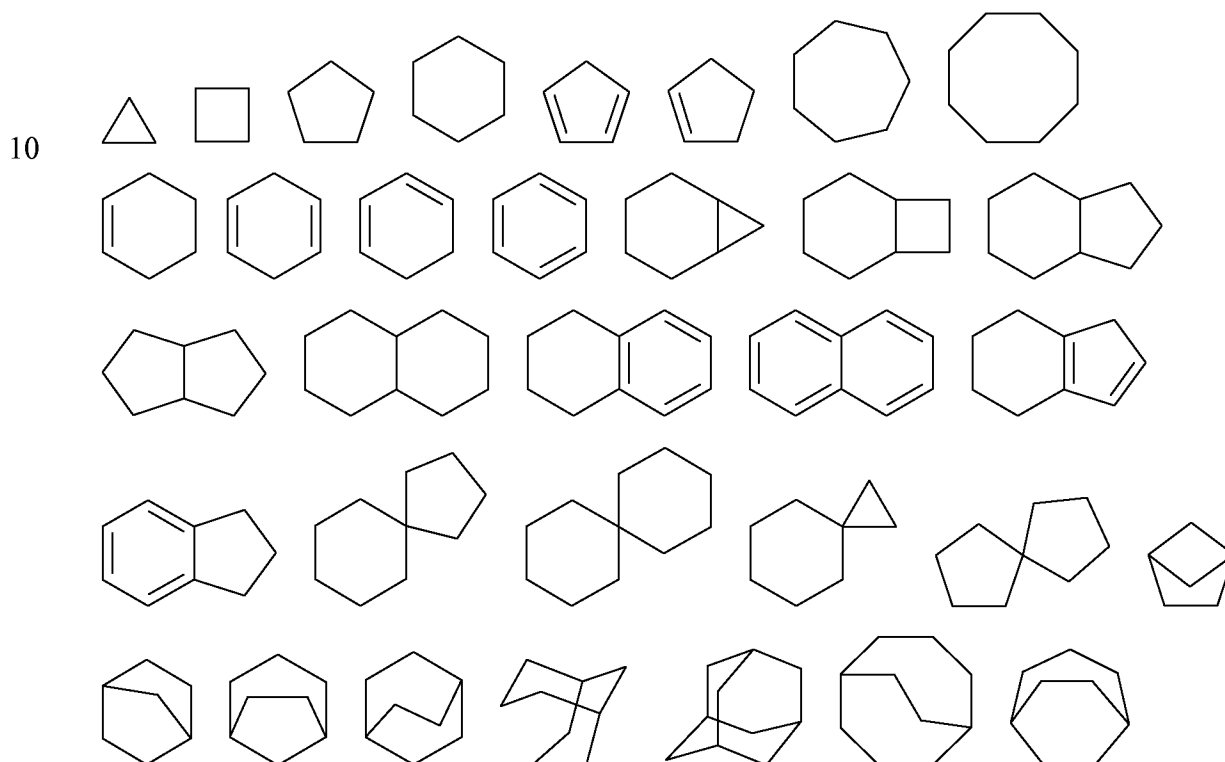
By the term " C_2 - C_8 -alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 8 carbon atoms and by the term " C_2 - C_6 -alkynylene" are meant branched and unbranched alkynylene groups with 2 to 6 carbon atoms, provided that they have at least one triple bond. Examples of C_2 - C_8 -alkynylenes include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene, heptynylene or octynylene. Unless stated otherwise, the definitions propynylene, butynylene,

35

pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1, 1-dimethylethynylene, 1, 2-dimethylethynylene.

5

The term "carbocyclyl" as used either alone or in combination with another radical, means a mono- bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The term "carbocycle" refers to fully saturated and aromatic ring systems and partially saturated ring systems. The term "carbocycle" encompasses fused, bridged and spirocyclic systems:



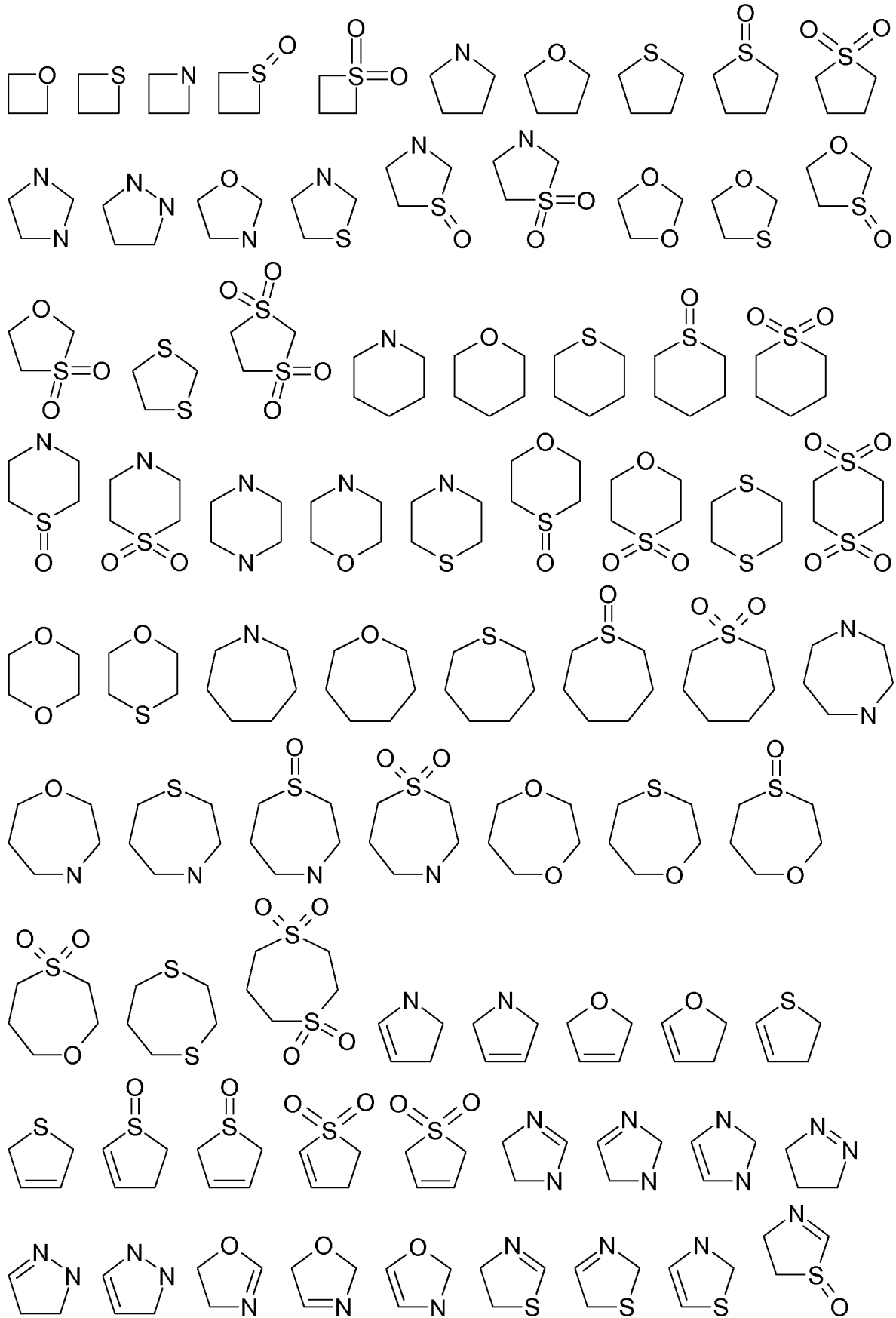
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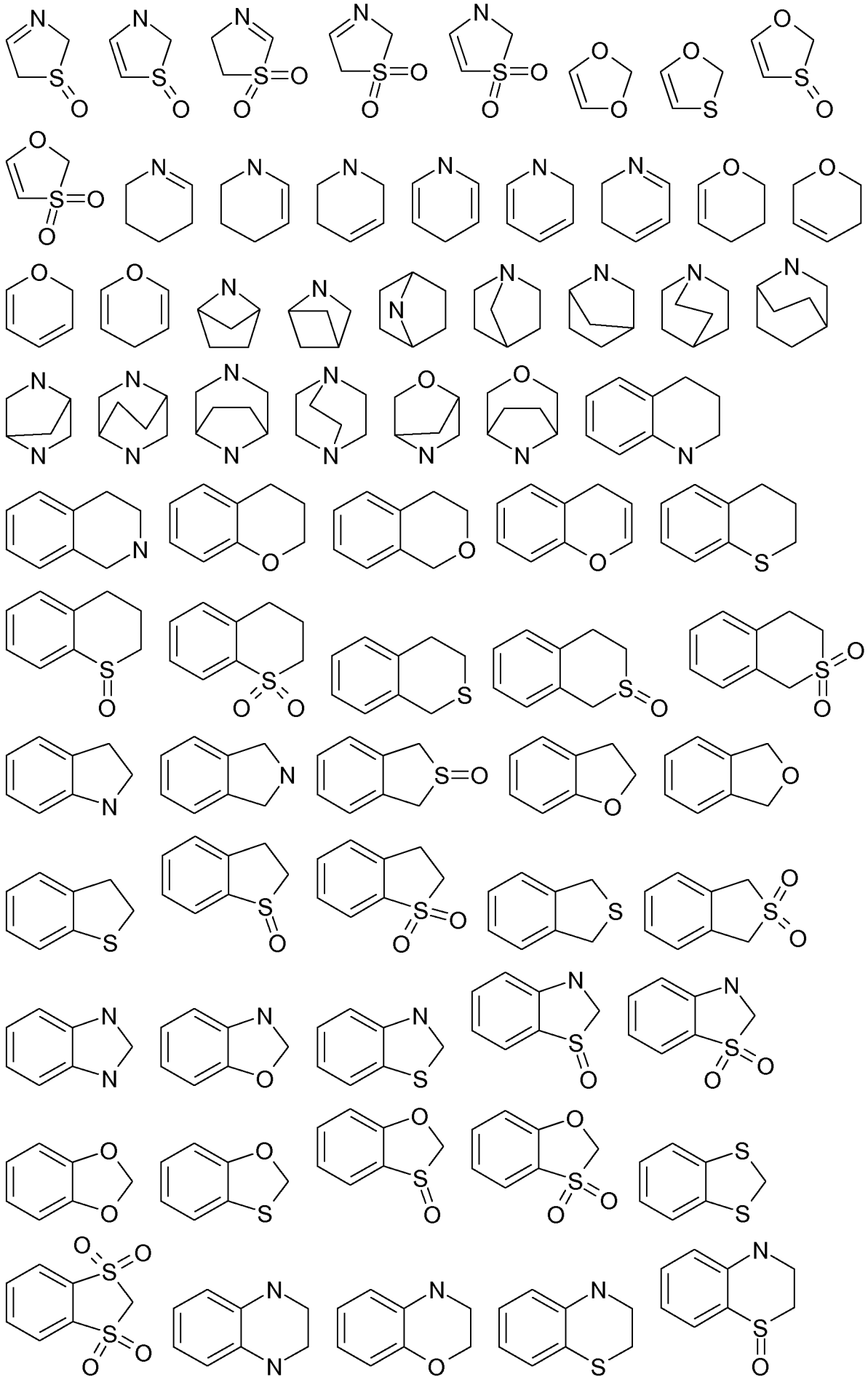
By the term "ring" are meant carbocycles, which can be saturated, unsaturated or aromatic and which optionally can comprise one or more hetero atoms selected from N, O or S.

20 The term "heterocyclyl" means a saturated or unsaturated mono- or polycyclic-ring systems including aromatic ring system containing one or more heteroatoms selected from N, O or S(O)_r, wherein r = 0, 1 or 2, consisting of 3 to 14 ring atoms wherein none of the heteroatoms is part of the aromatic ring. The term "heterocycle" is intended to include all the possible isomeric forms.

25 Thus, the term "heterocyclyl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

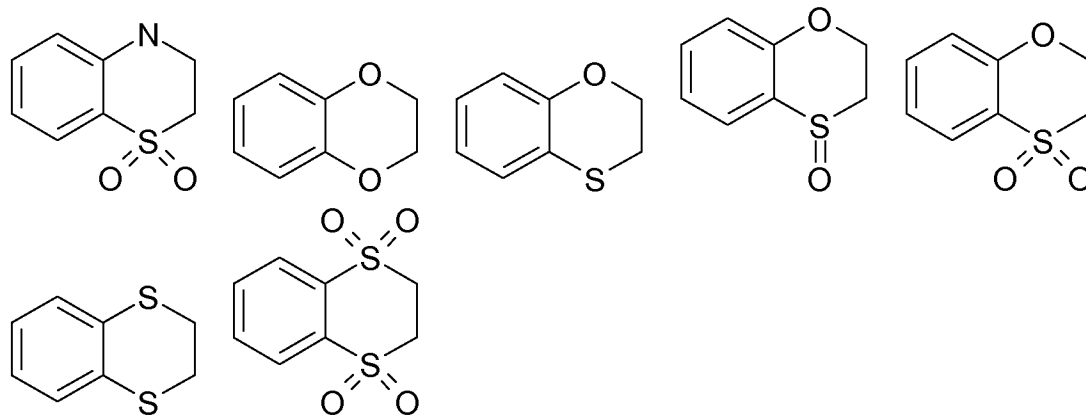
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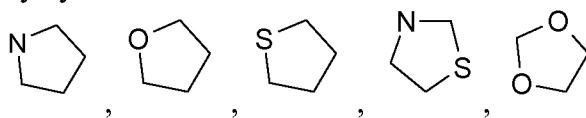
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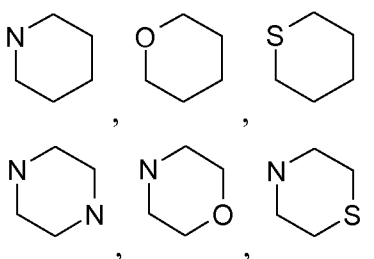


By the term “-C₃-C₈-heterocyclyl” are meant three-, four-, five-, six-, seven-, or eight-
 5 membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three
 heteroatoms, selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be
 replaced by such heteroatoms. The ring may be linked to the molecule through a carbon atom
 or through a nitrogen atom, if there is one. By the term “-C₅-C₈-heterocyclyl” are meant five-,
 six-, seven-, or eight-membered, saturated or unsaturated heterocyclic rings which may
 10 contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen,
 while the ring may be linked to the molecule through a carbon atom or through a nitrogen
 atom, if there is one. By the term “-C₅-heterocyclyl” are meant five-membered, saturated or
 unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected
 from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule
 15 through a carbon atom or through a nitrogen atom, if there is one. By the term “-C₆-
 heterocyclyl” are meant six-membered, saturated or unsaturated heterocyclic rings which may
 contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen,
 while the ring may be linked to the molecule through a carbon atom or through a nitrogen
 atom, if there is one.

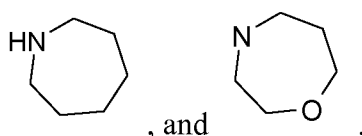
20 Examples for C₅-heterocyclyl include:



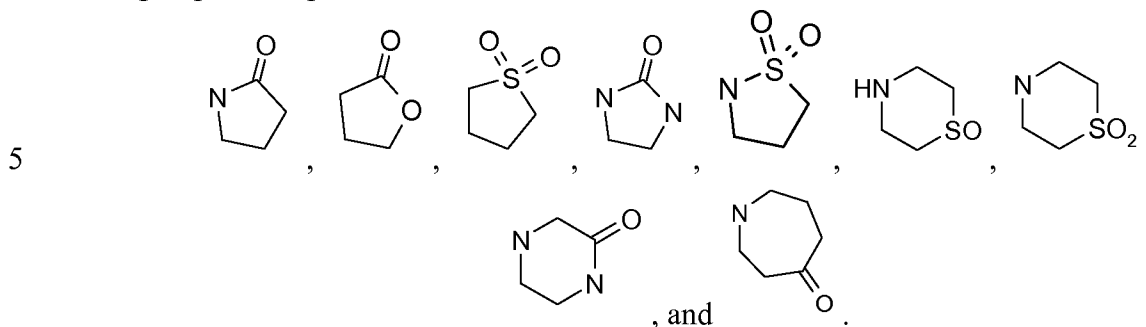
Examples for C₆-heterocyclyl include:



25 Examples for C₇-heterocyclyl include:



Unless otherwise mentioned, a heterocyclic ring (or “heterocycle”) may be provided with a keto group. Examples include:



10 The term “C₃-C_n-cycloalkyl”, wherein n is an integer from 3 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C₃-C₇-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

15 By the term “C₃-C₈-cycloalkyl” (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 8 carbon atoms. Likewise, by the term “C₃-C₆-cycloalkyl” are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples of C₃-C₈-cycloalkyls include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Unless otherwise stated, the cyclic alkyl groups may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

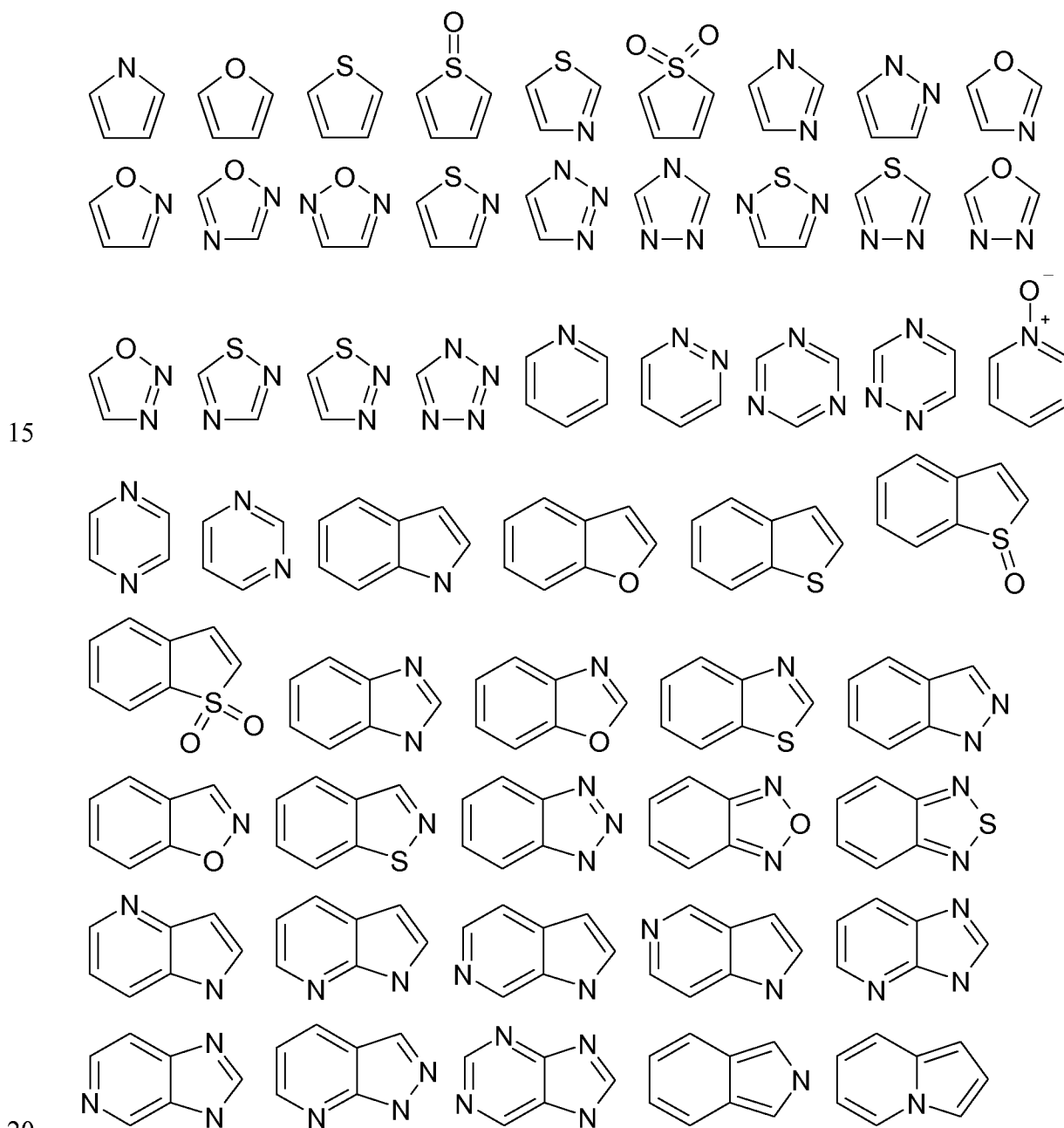
20 The term “C₃-C_n-cycloalkenyl”, wherein n is an integer from 3 to n, either alone or in combination with another radical, denotes an cyclic, unsaturated but nonaromatic, unbranched hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a double bond. For example the term C₃-C₇-cycloalkenyl includes cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl
25 cycloheptadienyl and cycloheptatrienyl.

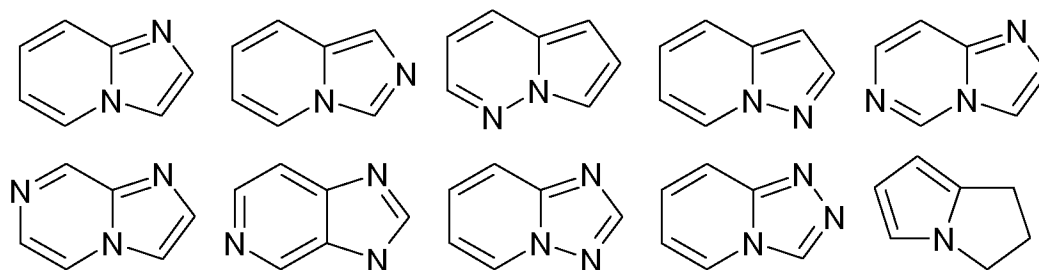
30 By the term “aryl” (including those which are part of other groups) are meant aromatic ring systems. By the term “C₅-C₁₀-aryl” (including those which are part of other groups) are meant aromatic ring systems with 5 to 10 carbon atoms. Preferred are “C₆-C₁₀-aryl” groups whereas aromatic rings are meant with 6 to 10 carbon atoms. Examples include: phenyl or naphthyl. Also preferred are “C₅-C₆-aryl” groups whereas aromatic rings are meant with 5 to 6 carbon atoms Unless otherwise stated, the aromatic ring systems may be substituted by one or more

groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

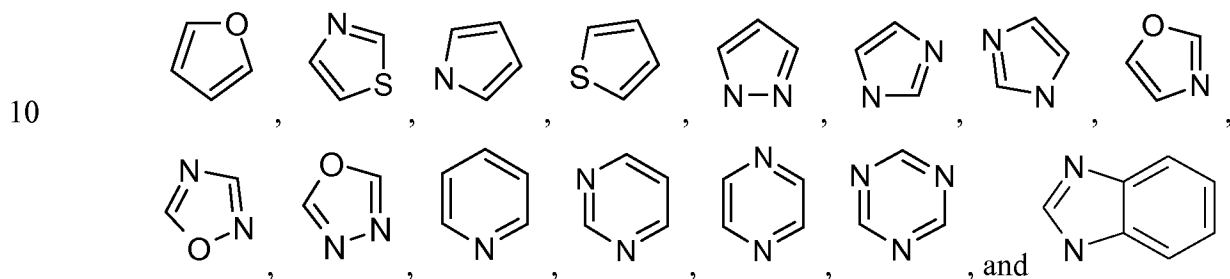
The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or S(O)_r, wherein r = 0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms.

Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:





By the term "C₅-C₁₀-heteroaryl" (including those which are part of other groups) are meant five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. The following are examples of five- or six- or nine-membered heterocyclic aromatic groups:



Preferred are "C₅-C₆-heteroaryl" groups whereas aromatic rings are meant five- or six-membered heterocyclic aromatic groups. Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

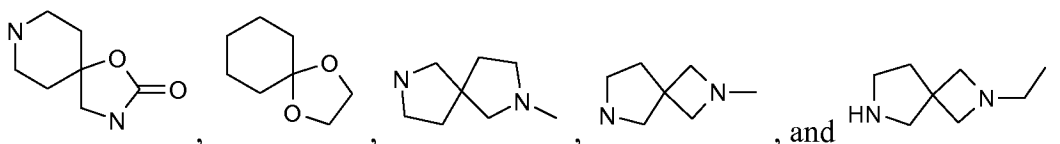
When a generic combined groups are used, for example -X-C₁-C₄-alkyl- with X being a functional group such as -CO-, -NH-, -C(OH)- and the like, the functional group X can be located at either of the ends of the -C₁-C₄-alkyl chain.

By the term "spiro-C₃-C₈-cycloalkyl" (spiro) are meant 3-8 membered, spirocyclic rings while the ring is linked to the molecule through a carbon atom, and whereas the resulting 3-8 membered carbocycle is formed by alkylene groups with 2 to 7 carbon atoms. By the term "spiro-C₅-cycloalkyl" (spiro) are meant 5 membered, spirocyclic rings while the ring is linked to the molecule through a carbon atom, whereas the resulting 5 membered carbocycle is formed by an alkylene group with 4 carbon atoms. By the term "spiro-C₃-C₈-cycloalkenyl" (spiro) are meant 3-8 membered, spirocyclic rings while the ring is linked to the molecule through a carbon atom, whereas the resulting 3-8 membered carbocycle is formed by alkenylene groups with 2 to 7 carbon atoms. By the term "spiro-C₅-cycloalkenyl" (spiro) are meant 5 membered, spirocyclic rings while the ring is linked to the molecule through a carbon

atom, whereas the resulting 5 membered carbocycle is formed by alkenylene groups with 4 carbon atoms.

By the term "spiro-C₃-C₈-heterocyclyl" (spiro) are meant 3-8 membered, saturated or unsaturated, spirocyclic rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. By the term "spiro-C₅-heterocyclyl" (spiro) are meant 5 membered, saturated or unsaturated, spirocyclic rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one.

Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl, or ethyl group. Examples include:



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

"Linker" within the scope of the present invention denominates a bivalent group or a bond.

The above listed groups and residues can be combined to form more complex structures composed from carbon chains and rings or the like.

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

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof.

Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-

arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-5 (2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2''-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-10 disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric 15 acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic 20 acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the 25 parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

30 As mentioned hereinbefore, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand the compound of formula (I) 35 may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use

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

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

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

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

The compounds according to the invention may optionally occur as racemates, but they may also be obtained as pure enantiomers / diastereomers.

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

The compounds according to formula (I) according to the invention have the meanings hereinbefore whereas in particular the preferred embodiments defined by R₁, R₂, R₃, R₄, R₅,

R₆, R₇, R₈, R₉, R₁₀, R_{10'}, R₁₁, R_{11'}, R₁₃, R₁₄, L₁, E, G, A, and n in each case are independently selected of one another.

Therapeutic applications

- 5 The above exemplary substances have been tested for binding to CCR2 using a binding assay as outlined herein below:

Cell culture:

10 THP-1 cells (human acute monocytic leukaemia cells) were cultured under standardized conditions at 37 °C and 5 % CO₂ in a humidified incubator. THP-1 cells were cultivated in RPMI 1640 medium (Gibco 21875) containing 1 % MEM-NEAA (Gibco 11140) 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES and 1.0 mM sodium pyruvate, 90 %; 10 % fetal calf serum (FCS Gibco 10500-064).

15 Membranes were prepared from THP-1 cells. THP-1 cells were centrifuged at 300xg at 4°C for 10 min. The cell pellet was resuspended in Phosphate Buffer Saline (PBS, including 10 µM Pefabloc and a protease inhibitor mix 'complete', Boehringer Mannheim (1 tablet/50 ml)), to a concentration of 80 cells/ml. The membrane preparation was performed by disrupting the cells by nitrogen decomposition (at 50 bar, for 1h) in a "Nitrogen Bombe" (Parr Instrument). Cell debris was removed by centrifugation (800xg at 4°C, 1 min). The
20 supernatant was centrifuged at 80000xg, 4°C for 30 min to sediment the cell membranes. Usually 50 mg of protein (Bradford assay) were yielded from 1x10⁹ cells. The membranes were resuspended in 25 mM HEPES, 25 mM MgCl₂, 1 mM CaCl₂, 10 % Glycerine for storage in aliquots at -80 °C in 25 mM HEPES, 25 mM MgCl₂, 1 mM CaCl₂, 10 % Glycerine and stored at -80°C.

25

Receptor membrane binding assay:

Perkin Elmer NEX 332 Jod 125 MCP-1, Stock: 2200 Ci/mmol solved in 2000 µl assay buffer, stored at -20°C. THP-1 membrane were adjusted with 25 mM HEPES, pH 7.2; 5 mM MgCl₂; 0.5 mM CaCl₂; 0.2 % BSA assay buffer to a concentration of 2.5 µg/15 µl.
30 Amersham Biosciences PVT-WGA Beads (RPNQ0001) were adjusted with assay buffer to a concentration of 0.24 mg/30 µl. For preparation of the membrane-bead-suspension membranes and beads were incubated for 30 min at RT under rotation (60 rpm) with a ratio of 1:2. Test compounds dissolved in 100 % DMSO to a concentration of 10 mM and are further diluted with 100 % DMSO to 1 mM. All additional compound dilutions were obtained
35 with assay buffer, final 1% DMSO. Compounds, membrane-bead-suspension and [125I]MCP-1 (ca. 25000 cpm/10 µl) were incubated. Bound radioactivity was determined by scintillation counter after 8h. Determination of affinity of test compounds (dissociation constant hKi) is calculated by iterative fitting of experimental data using the "easy sys"

program, which is based on law of mass action (Schittkowski K. (1994), Numerische Mathematik, Vol. 68, 129-142).

5 All of the referenced examples have been found to have an activity in this assay of 10 μ M or less.

Example	hKi [nM]
1	16
2	121
3	450
4	110
5	232
6	280
7	138
8	398
9	2
10	481
11	15
12	728

Example	hKi [nM]
13	2994
14	146
15	30
16	707
17	5178
18	6
19	49
20	26
21	23
22	14
23	17
24	854

Example	hKi [nM]
25	165
26	46
27	5
28	10
29	53
30	1482
31	5311
32	64
33	36

Example	hKi [nM]
34	1008
35	26
36	70
37	15
38	91
39	84
40	84
41	196
42	20
43	17

Example	hKi [nM]
17a	1
17b	5
33a	0.5
33b	0.7
33c	0.2
33d	0.3
33e	23
33g	8
33h	2
33i	3
33j	1
33k	5
33l	6

Example	hKi [nM]
33m	0.7
33n	1
33o	0.2
33p	0.3
33q	0.8
33r	0.9
33s	1
33t	0.3
33u	1
33v	0.4
33w	3

Based on the ability of the substances described by formula (I) to effectively bind to CCR2 a range of therapeutic applications can be envisaged. The present invention provides a method for modulating or treating at least one MCP-1 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one CCR2 antagonist of the present invention. The present invention also provides a method for modulating or treating at least one MCP-1 related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of malignant disease, metabolic disease, an immune or inflammatory related disease, a cardiovascular disease, an infectious disease, or a neurologic disease. Such conditions are selected from, but not limited to, diseases or conditions mediated by cell adhesion and/or angiogenesis. Such diseases or conditions include an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified MCP-1 related conditions. In particular, the CCR2 antagonists are useful for the treatment of diseases that involve inflammation such as COPD, angiogenesis such as disease of the eye and neoplastic disease, tissue remodeling such as restenosis, and proliferation of certain cells types particularly epithelial and squamous cell carcinomas. Particular indications include use in the treatment of atherosclerosis, restenosis, cancer metastasis, rheumatoid arthritis, diabetic retinopathy and macular degeneration. The antagonists may also be useful in the treatment of various fibrotic

diseases such as idiopathic pulmonary fibrosis, diabetic nephropathy, hepatitis, and cirrhosis. Thus, the present invention provides a method for modulating or treating at least one CCR2 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one CCR2 antagonist of the present invention. Particular indications are discussed below:

Pulmonary Diseases

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: pneumonia; lung abscess; occupational lung diseases caused by agents in the form of dusts, gases, or mists; asthma, bronchiolitis fibrosa obliterans, respiratory failure, hypersensitivity diseases of the lungs including hypersensitivity pneumonitis (extrinsic allergic alveolitis), allergic bronchopulmonary aspergillosis, and drug reactions; adult respiratory distress syndrome (ARDS), Goodpasture's Syndrome, chronic obstructive airway disorders (COPD), idiopathic interstitial lung diseases such as idiopathic pulmonary fibrosis and sarcoidosis, desquamative interstitial pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, idiopathic bronchiolitis obliterans with organizing pneumonia, lymphocytic interstitial pneumonitis, Langerhans' cell granulomatosis, idiopathic pulmonary hemosiderosis; acute bronchitis, pulmonary alveolar proteinosis, bronchiectasis, pleural disorders, atelectasis, cystic fibrosis, and tumors of the lung, and pulmonary embolism.

Malignant Diseases

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, renal cell carcinoma, breast cancer, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, adenocarcinomas, squamous cell carcinomas, sarcomas, malignant melanoma, particularly metastatic melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Immune Related Diseases

The present invention also provides a method for modulating or treating at least one immune

related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis, uveitis, optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/Wegener's granulomatosis, sarcoidosis, orchitis, vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococemia, trauma, hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphylaxis, dermatitis, pernicious anemia, hemolytic diseases, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type I hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, OKT3 therapy, anti-CD3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic

salicylate intoxication, and the like.

Cardiovascular Diseases

The present invention also provides a method for modulating or treating at least one
5 cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to,
at least one of cardiac 25 stunned syndrome, myocardial infarction, congestive heart failure,
stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic
arteriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension,
10 syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary
pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial
fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass
inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS
tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias,
15 atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery
disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive
cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial
disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of
the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders,
20 occlusive arterial disorders, peripheral atherosclerotic disease, thromboangitis obliterans,
functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis,
erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula,
lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-
reperfusion injury, and the like. Such a method can optionally comprise administering an
effective amount of a composition or pharmaceutical composition comprising at least one
25 CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation,
treatment or therapy.

Neurologic Diseases

The present invention also provides a method for modulating or treating at least one
30 neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at
least one of: Inflammatory pain, chronic pain, Neuropathic pain such as low back pain, hip
pain, leg pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve
injury-induced pain, acquired immune deficiency syndrome (AIDS) related neuropathic pain,
head trauma, toxin and chemotherapy caused nerve injuries, phantom limb pain, multiple
35 sclerosis, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy, thalamic
pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, carpal
tunnel syndrome, trigeminal neuralgia, post mastectomy syndrome, postthoracotomy
syndrome, stump pain, repetitive motion pain, neuropathic pain associated hyperalgesia and
allodynia, alcoholism and other drug-induced pain; neurodegenerative diseases, multiple

sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerorden-Spatz disease; and Dementia pugilistica, and the like.

Fibrotic Conditions

In addition to the above described conditions and diseases, the present invention also provides a method for modulating or treating fibrotic conditions of various etiologies such as liver fibrosis (including but not limited to alcohol-induced cirrhosis, viral-induced cirrhosis, autoimmune-induced hepatitis); lung fibrosis (including but not limited to scleroderma, idiopathic pulmonary fibrosis); kidney fibrosis (including but not limited to scleroderma, diabetic nephritis, glomerular nephritis, lupus nephritis); dermal fibrosis (including but not limited to scleroderma, hypertrophic and keloid scarring, burns); myelofibrosis; Neurofibromatosis; fibroma; intestinal fibrosis; and fibrotic adhesions resulting from surgical procedures.

The present invention also provides a method for modulating or treating at least one wound, trauma or tissue injury or chronic condition resulting from or related thereto, in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: bodily injury or a trauma associated with surgery including thoracic, abdominal, cranial, or oral surgery; or wherein the wound is selected from the group consisting of aseptic wounds, contused wounds, incised wounds, lacerated wounds, non-penetrating wounds, open wounds, penetrating wounds, perforating wounds, puncture wounds, septic wounds, infarctions and subcutaneous wounds; or wherein the wound is selected from the group consisting of ischemic ulcers, pressure sores, fistulae, severe bites, thermal burns and donor site wounds; or wherein the wound is an aphthous wound, a traumatic wound or a herpes associated wound. Donor site wounds are wounds which e.g. occur in connection with removal of hard tissue from one part

of the body to another part of the body e.g. in connection with transplantation. The wounds resulting from such operations are very painful and an improved healing is therefore most valuable. Wound fibrosis is also amenable to CCR2 antagonist therapy as the first cells to invade the wound area are neutrophils followed by monocytes which are activated by macrophages. Macrophages are believed to be essential for efficient wound healing in that they also are responsible for phagocytosis of pathogenic organisms and a clearing up of tissue debris. Furthermore, they release numerous factors involved in subsequent events of the healing process. The macrophages attract fibroblasts which start the production of collagen. Almost all tissue repair processes include the early connective tissue formation, a stimulation of this and the subsequent processes improve tissue healing, however, overproduction of connective tissue and collagen can lead to a fibrotic tissue characterized as inelastic and hypoxic. The CCR2 antagonist of the invention can be used in methods for modulating, treating or preventing such sequelae of wound healing.

15 Other Therapeutic Uses of CCR2 antagonists

The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic bacterial infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection, HIV neuropathy, meningitis, hepatitis (A,B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis/epididymitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis/septic meningitis, and the like.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

35 Combinations

The compounds of formula (I) may be used on their own or in conjunction with other active substances of formula (I) according to the invention. If desired the compounds of formula (I) may also be used in combination with other pharmacologically active substances. It is preferable to use for this purpose active substances selected for example from among

β2-adrenoceptor-agonists (short and long-acting betamimetics), anti-cholinergics (short and long-acting), anti-inflammatory steroids (oral and topical corticosteroids), cromoglycate, methylxanthine, dissociated-glucocorticoidmimetics, PDE3 inhibitors, PDE4- inhibitors, PDE7- inhibitors, LTD4 antagonists, EGFR- inhibitors, Dopamine agonists, statins, PAF antagonists, Lipoxin A4 derivatives, FPRL1 modulators, LTB4-receptor (BLT1, BLT2) antagonists, Histamine H1 receptor antagonists, Histamine H4 receptor antagonists, dual Histamine H1/H3-receptor antagonists, PI3-kinase inhibitors, inhibitors of non-receptor tyrosine kinases as for example LYN, LCK, SYK (spleen tyrosine kinase-inhibitors), ZAP-70, FYN, BTK or ITK, inhibitors of MAP kinases as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, inhibitors of the NF-kappaB signalling pathway as for example IKK2 kinase inhibitors, iNOS inhibitors (inducible nitric oxide synthase-inhibitors), MRP4 inhibitors, leukotriene antagonists, leukotriene biosynthesis inhibitors as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 Hydrolase inhibitors or FLAP inhibitors, non-steroidal antiinflammatory drugs (NSAIDs) including COX-2 inhibitors, CRTH2 antagonists, DP1-receptor modulators, Thromboxane receptor antagonists, CCR1 antagonists, CCR4 antagonists, CCR5 antagonists, CCR6 antagonists, CCR7 antagonists, CCR8 antagonists, CCR9 antagonists, CCR10 antagonists, CCR11 antagonists, CXCR1 antagonists, CXCR2 antagonists, CXCR3 antagonists, CXCR4 antagonists, CXCR5 antagonists, CXCR6 antagonists, CX3CR1 antagonists, Neurokinin (NK1, NK2) antagonists, Sphingosine 1-Phosphate receptor modulators, Sphingosine 1 phosphate lyase inhibitors, Adenosine receptor modulators as for example A2a-agonists, modulators of purinergic receptors as for example P2X7 inhibitors, Histone Deacetylase (HDAC) activators, Bradykinin (BK1, BK2) antagonists, TACE inhibitors, PPAR gamma modulators, Rho-kinase inhibitors, interleukin 1-beta converting enzyme (ICE) inhibitors, Toll-Like receptor (TLR) modulators, HMG-CoA reductase inhibitors, VLA-4 antagonists, ICAM-1 inhibitors, SHIP agonists, GABAa receptor antagonist, ENaC-inhibitors, Melanocortin receptor (MC1R, MC2R, MC3R, MC4R, MC5R) modulators, CGRP antagonists, Endothelin antagonists, TNFalpha antagonists, anti-TNF antibodies, anti-GM-CSF antibodies, anti-CD46 antibodies, anti-IL-1 antibodies, anti-IL-2 antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IL-4/IL-13 antibodies, anti-TSLP antibodies, anti-OX40 antibodies, mucoregulators, immunotherapeutic agents, compounds against swelling of the airways, compounds against cough, antiviral drugs, opiate receptor agonists, cannabinoid agonists, sodium channel blockers, N-type calcium channel blockers, serotonergic and noradrenergic modulators, proton pump inhibitors, local anesthetics, VR1 agonists and antagonists, Nicotinic acetylcholine receptor agonists, P2X3 receptor antagonists, NGF agonists and antagonists, NMDA antagonist, potassium channel modulators, GABA modulators, serotonergic and noradrenergic modulators, anti-migraine drugs. The invention also encompasses combinations of three active substances, each selected from one of the above-mentioned categories of compounds. Said list is not considered to have a limiting character.

The betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenol, sulphonterol, tiaramide, terbutaline, tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Preferably the beta mimetics are selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol,

salmeterol, sulphonterol, terbutaline, tolubuterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-
 5 {2-[3-(2-phenylethoxy)propyl]sulphonyl}ethyl-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-
 10 hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-
 15 {1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-
 20 hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
 25 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the
 30 pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Particularly preferred betamimetics are selected from among fenoterol, formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-

butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetate ethyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

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

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

The anticholinergics used are preferably compounds selected from among the tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, -scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate -methobromide, tropenol 9-fluoro-fluorene-9-carboxylate -methobromide, scopine 9-hydroxy-fluorene-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine 2,2-diphenylpropionate methobromide, cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide, methyl -cyclopropyltropine 4,4'-difluorobenzilate methobromide, tropenol 9-hydroxy-xanthene-9-carboxylate -methobromide, scopine 9-hydroxy-xanthene-9-carboxylate methobromide, tropenol 9-methyl-xanthene-9-carboxylate methobromide, scopine 9-methyl-xanthene-9-carboxylate methobromide, tropenol 9-ethyl-xanthene-9-carboxylate methobromide, tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide, scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide, optionally in the form of the solvates or hydrates thereof.

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

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

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

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

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

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

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

The PDE4-inhibitor used are preferably compounds selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, CI-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

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

LTD4-antagonists which may be used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methyl)cyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2.3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane-acetic acid and [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

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

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

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

EGFR-inhibitors which may be used are preferably compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N,N-

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

yl} amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-
{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-
chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-
methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-
5 morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-
fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-
(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {2-[4-(2-
oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-
phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-
10 [(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-
quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-
cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-
(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-
methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-
15 {1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-
fluoro-phenyl)amino]-6- {1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-
quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-
quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-
yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-
20 yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-
yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-
yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {trans-4-
[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-
chloro-4-fluoro-phenyl)amino]-6- {trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-
25 yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {trans-4-[(morpholin-
4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-
phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-
chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-
ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {1-[(piperidin-1-yl)carbonyl]-
30 piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-
aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-
phenyl)amino]-6-(cis-4- {N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-
1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4- {N-
[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline,
35 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4- {N-[(morpholin-4-yl)sulphonyl]-N-methyl-
amino}-cyclohexan-1-yloxy)-7-methoxy- quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-
6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-
4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-
[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-

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

[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, Cetuximab, Trastuzumab, ABX-EGF and Mab ICR-62, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

Preferred EGFR inhibitors are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-diethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl}amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl}amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl}amino}-7-cyclopentyloxy-quinazoline,

4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-
 7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-
 {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-
 5 quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-
 chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-
 quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-
 d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(N,N-dimethylamino)-1-
 oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4- {[3-chloro-4-(3-fluoro-benzyloxy)-
 phenyl]amino}-6-(5- {[2-methanesulphonyl-ethyl]amino]methyl}-furan-2-yl)quinazoline, 4-
 10 [(R)-(1-phenyl-ethyl)amino]-6- {[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-
 yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(morpholin-4-
 yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-
 4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-
 yl]amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-
 15 {[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-
 chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-
 methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-
 morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-
 fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-
 20 (tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {2-[4-(2-
 oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-
 phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-
 [(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-
 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-
 25 cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-
 (tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-
 methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-
 {1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-
 fluoro-phenyl)amino]-6- {1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-
 30 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-
 quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-
 yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-
 yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-
 yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-
 35 yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {trans-4-
 [(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-
 chloro-4-fluoro-phenyl)amino]-6- {trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-
 yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {trans-4-[(morpholin-
 4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

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

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

25 Preferable the EGFR-inhibitors are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6- {[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-

pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenylethyl)amino]-6- {[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6- {[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynylphenyl)amino]-6- {[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- (trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4- {N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4- {N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6- {1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6- {1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-

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

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

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

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

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

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

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

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

MRP4-inhibitors are preferably selected from among N-acetyl-dinitrophenyl-cysteine, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-S-glutathione, estradiol 3,17-disulphate, flurbiprofen, glycocholate, glycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, lithocholic acid sulphate, MK571, PSC833, sildenafil, taurochenodeoxycholate, taurocholate, tauroolithocholate, tauroolithocholic acid sulphate, trequinsin and zaprinast, dipyridamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

Particularly preferred MRP4-inhibitors are selected from among dehydroepiandrosterone 3-sulphate, estradiol 3,17-disulphate, flurbiprofen, indomethacin, indoprofen, MK571, taurocholate, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof. The separation of enantiomers from the racemates can be carried out using methods known from the art (e.g. chromatography on chiral phases, etc.) .

By acid addition salts with pharmacologically acceptable acids are meant, for example, salts selected from among the hydrochlorides, hydrobromides, hydroiodides, hydrosulphates, hydrophosphates, hydromethanesulphonates, hydronitrates, hydromaleates, hydroacetates,

hydrobenzoates, hydrocitrates, hydrofumarates, hydrotartrates, hydrooxalates, hydrosuccinates, hydrobenzoates and hydro-*p*-toluenesulphonates, preferably the hydrochlorides, hydrobromides, hydrosulphates, hydrophosphates, hydrofumarates and hydromethanesulphonates.

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The invention further relates to pharmaceutical preparations which contain a triple combination of the CCR2 inhibitors, MRP4-inhibitors and another active substance according to the invention, such as, for example, an anticholinergic, a steroid, an LTD4-antagonist or a betamimetic, and the preparation thereof and the use thereof for treating respiratory

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The iNOS-inhibitors used are preferably compounds selected from among: S-(2-aminoethyl)isothiourea, aminoguanidine, 2-aminomethylpyridine, AMT, L-canavanine, 2-iminopiperidine, S-isopropylisothiourea, S-methylisothiourea, S-ethylisothiourea, S-methyltiocitrulline, S-ethylthiocitrulline, L-NA (N^o-nitro-L-arginine), L-NAME (N^o-nitro-L-arginine methylester), L-NMMA (N^G-monomethyl-L-arginine), L-NIO (N^o-iminoethyl-L-ornithine), L-NIL (N^o-iminoethyl-lysine), (S)-6-acetimidoylamino-2-amino-hexanoic acid (1*H*-tetrazol-5-yl)-amide (SC-51) (*J. Med. Chem.* 2002, 45, 1686-1689), 1400W, (S)-4-(2-acetimidoylamino-ethylsulphanyl)-2-amino-butyric acid (GW274150) (*Bioorg. Med. Chem. Lett.* 2000, 10, 597-600), 2-[2-(4-methoxy-pyridin-2-yl)-ethyl]-3*H*-imidazo[4,5-*b*]pyridine (BYK191023) (*Mol. Pharmacol.* 2006, 69, 328-337), 2-((R)-3-amino-1-phenyl-propoxy)-4-chloro-5-fluorobenzonitrile (WO 01/62704), 2-((1R,3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-6-trifluoromethyl-nicotinonitrile (WO 2004/041794), 2-((1R,3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-4-chloro-benzonitrile (WO 2004/041794), 2-((1R,3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-benzonitrile (WO 2004/041794), (2S,4R)-2-amino-4-(2-chloro-5-trifluoromethyl-phenylsulphanyl)-4-thiazol-5-yl-butan-1-ol (WO 2004/041794), 2-((1R,3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-nicotinonitrile (WO 2004/041794), 4-((S)-3-amino-4-hydroxy-1-phenyl-butylsulphanyl)-6-methoxy-nicotinonitrile (WO 02/090332), substituted 3-phenyl-3,4-dihydro-1-isoquinolinamines such as e.g. AR-C102222 (*J. Med. Chem.* 2003, 46, 913-916), (1S,5S,6R)-7-chloro-5-methyl-2-aza-bicyclo[4.1.0]hept-2-en-3-ylamine (ONO-1714) (*Biochem. Biophys. Res. Commun.* 2000, 270, 663-667), (4R,5R)-5-ethyl-4-methyl-thiazolidin-2-ylideneamine (*Bioorg. Med. Chem.* 2004, 12, 4101), (4R,5R)-5-ethyl-4-methyl-selenazolidin-2-ylideneamine (*Bioorg. Med. Chem. Lett.* 2005, 15, 1361), 4-aminotetrahydrobiopterine (*Curr. Drug Metabol.* 2002, 3, 119-121), (E)-3-(4-chloro-phenyl)-*N*-(1-{2-oxo-2-[4-(6-trifluoromethyl-pyrimidin-4-yloxy)-piperidin-1-yl]-ethylcarbonyl}-2-pyridin-2-yl-ethyl)-acrylamide (FR260330) (*Eur. J. Pharmacol.* 2005, 509, 71-76), 3-(2,4-difluoro-phenyl)-6-[2-(4-imidazol-1-ylmethyl-phenoxy)-ethoxy]-2-phenyl-pyridine (PPA250) (*J. Pharmacol. Exp. Ther.* 2002, 303, 52-57), methyl 3-[[benzo[1.3]dioxol-5-ylmethyl]-

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carbamoyl]-methyl}-4-(2-imidazol-1-yl-pyrimidin-4-yl)-piperazin-1-carboxylate (BBS-1) (*Drugs Future* 2004, 29, 45-52), (R)-1-(2-imidazol-1-yl-6-methyl-pyrimidin-4-yl)-pyrrolidine-2-carboxylic acid (2-benzo[1.3]dioxol-5-yl-ethyl)-amide (BBS-2) (*Drugs Future* 2004, 29, 45-52) and the pharmaceutical salts, prodrugs or solvates thereof.

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Compounds which may be used as SYK-inhibitors are preferably compounds selected from among: R343 or R788.

Examples of preferred MAP kinase inhibitors, as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, which may be mentioned include SCIO-323, SX-011, SD-282, SD-169, NPC-037282, SX-004, VX-702, GSK-681323, GSK-856553, ARRY-614, ARRY-797, ARRY-438162, ARRY-p38-002, ARRY-371797, AS-602801, AS-601245, AS-602183, CEP-1347, KC706, TA-5493, RO-6226, Ro-1487, SC-409, CBS-3595, VGX-1027, PH-797804, BMS-582949, TA-5493 and BIRB-796 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

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Examples of preferred inhibitors of the NF- κ B signalling pathway including IKK2 kinase inhibitors which may be mentioned include: MD-1041, MLN-041 und AVE-0547 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

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Examples of preferred Leukotriene biosynthesis inhibitors, as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 hydrolase inhibitors oder FLAP inhibitors, which may be mentioned include zileuton, tiplelukast, licofelone, darapladib, TA-270, IDEA-033, IDEA-070, NIK-639, ABT-761, fenleuton, tepoxalin, AM-103, AM-803, Abbott-79175, Abbott-85761, PLT-3514, CMI-903, PEP-03, CMI-977, MLN-977, CMI-947, LDP-977, efipradib, PLA-695, veliflapon, MK-591, MK-886 und BAYx1005 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

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Examples of preferred non-steroidal anti-inflammatory agents (NSAIDs) which may be mentioned include COX-2 inhibitors :propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenhufen, fenoprofen, flubiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (meclofenamic acid, mefenamic acid, and tolfenamic acid), biphenyl- carboxylic acid derivatives, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam and tenoxicam),

35

salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoxib, rofecoxib and etoricoxib) optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

5

Examples of preferred CCR1 antagonists which may be mentioned include AZD-4818, CCX-354, MLN-3701, MLN-3897, optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

10 Examples of preferred CCR5 antagonists which may be mentioned include maraviroc, INCB-15050, CCR5mAb004, GSK-706769, PRO-140, SCH-532706, vicriviroc and nifeviroc optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

15 Examples of preferred CXCR1 or CXCR2 antagonists which may be mentioned include SCH-527123 and SB-656933 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

20 Examples of preferred Neurokinin (NK1 or NK2) antagonists which may be mentioned include Saredutant, Nepadutant, PRX-96026 und Figopitant optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

25 Examples of preferred purinergic receptor modulators, including P2X7 inhibitors, which may be mentioned include AZD-9056 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

30 Examples of preferred PPAR gamma modulators which may be mentioned include Rosiglitazone, Ciglitazone, Pioglitazone and SMP-028 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

35 Examples of preferred Interleukin 1-beta converting enzyme (ICE) inhibitors which may be mentioned include Pralnacasan, VRT-18858, RU-36384, VX-765 and VRT-43198 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

Examples of preferred Toll-like receptor (TLR) modulators which may be mentioned include Resiquimod, PF-3512676, AVE-0675, Heplisav, IMO-2055, CpG-28, TAK-242, SAR-21609, RC-52743198 and 852A optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

Examples of preferred VLA4 antagonists which may be mentioned include Natalizumab, Valategrast, TBC-4746, CDP-323 and TL-1102 optionally in racemic form, as enantiomers, diastereomers or as pharmacologically acceptable salts, solvates or hydrates.

5

Examples of preferred ICAM-1 inhibitors which may be mentioned include BIRT-2584 optionally in racemic form, as enantiomers, diastereomers or as pharmacologically acceptable salts, solvates or hydrates.

10 Examples of preferred anti-TNF antibodies which may be mentioned include Infliximab, Adalimumab, Golimumab, CytoFab and Etanercept.

Examples of preferred mucoregulators which may be mentioned include MSI-2216, Erdosteine, Fluorovent, Talniflumate, INO-4995, BIO-11006, VR-496 and fudosteine
15 optionally in racemic form, as enantiomers, diastereomers or as pharmacologically acceptable salts, solvates or hydrates.

Examples of preferred Antiviral drugs which may be mentioned include acyclovir, tenovir, pleconaril, peramivir, pocosanol.

20

Examples of preferred Antibiotic drugs like gentamicin, streptomycin, geldanamycin, doripenem, cephalixin, cefaclor, ceftazichine, cefepime, erythromycin, vancomycin, aztreonam, amoxicillin, bacitracin, enoxacin, mafenide, doxycycline, chloramphenicol.

25 Examples of preferred opiate receptor agonists are selected from among morphine, propoxyphene (Darvon), tramadol, buprenorphin.

Examples of preferred anti-TNF antibodies or TNF-receptor antagonists such as but not limited to Etanercept, Infliximab, Adalimumab (D2E7), CDP 571, and Ro 45-2081
30 (Lenercept), or biologic agents directed against targets such as but not limited to CD-4, CTLA-4, LFA-1, IL-6, ICAM-1, C5 and Natalizumab.

Examples of preferred IL-1 receptor antagonists such as but not limited to Kineret;
Sodium channel blockers: carbamazepine, mexiletine, lamotrigine, tectin, lacosamide

35

Examples of preferred N-type calcium channel blockers are selected from among Ziconotide.

Examples of preferred Serotonergic and noradrenergic modulators such as but not limited to paroxetine, duloxetine, clonidine, amitriptyline, citalopram;

Examples of preferred Histamine H1 receptor antagonists such as but not limited to bromophthiramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine,
5 promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine.

Examples of preferred Histamine H2 receptor antagonists such as but not limited to cimetidine, famotidine and ranitidine.

10

Examples of preferred proton pump inhibitors such as but not limited to omeprazole, pantoprazole and esomeprazole.

Examples of preferred Leukotriene antagonists and 5-lipoxygenase inhibitors such as but not
15 limited to zafirlukast, montelukast, pranlukast and zileuton.

Examples of preferred local anesthetics such as but not limited to ambroxol, lidocaine.

Examples of preferred potassium channel modulators such as but not limited to retigabine.

20

Examples of preferred GABA modulators such as but not limited to lacosamide, pregabalin, gabapentin.

Examples of preferred anti-migraine drugs such as but not limited to sumatriptan,
25 zolmitriptan, naratriptan, eletriptan, telcegepant.

Examples of preferred NGF antibodies such as but not limited to RI-724.

Combination therapy is also possible with new principles for the treatment of pain e.g. P2X3
30 antagonists, VR1 antagonists, NK1 and NK2 antagonists, NMDA antagonists, mGluR antagonists and the like.

Pharmaceutical formulations

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

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

Preferably, therefore, pharmaceutical formulations are characterised in that they contain one or more compounds of formula (I) according to the preferred embodiments above.

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

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

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

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

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

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

5

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

15

It is also preferred if the compounds of formula (I) are administered by inhalation, particularly preferably if they are administered once or twice a day. For this purpose, the compounds of formula (I) have to be made available in forms suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions, which are optionally present in admixture with conventional physiologically acceptable excipients.

20

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

Inhalable powders

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

35

Methods of preparing the inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

Propellant-containing inhalable aerosols

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

Propellant-free inhalable solutions

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

glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body. Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. For the treatment forms described above, ready-to-use packs of a medicament for the treatment of respiratory complaints are provided, containing an enclosed description including for example the words respiratory disease, COPD or asthma, a pteridine and one or more combination partners selected from those described above.

25 Experimental procedures and synthetic examples

LIST of ABBREVIATIONS

	<i>ACN</i>	<i>acetonitrile</i>
	<i>APCI</i>	<i>atmospheric pressure chemical ionization (in MS)</i>
30	<i>Ctrl</i>	<i>control</i>
	<i>DAD</i>	<i>diode array detector</i>
	<i>DMA</i>	<i>N,N-dimethylacetamide'</i>
	<i>DMF</i>	<i>N,N-dimethylformamide</i>
	<i>DMSO</i>	<i>dimethyl sulfoxide</i>
35	<i>EI</i>	<i>electron impact (in MS)</i>
	<i>ESI</i>	<i>electrospray ionization (in MS)</i>
	<i>ex</i>	<i>example</i>
	<i>GC/MS</i>	<i>gas chromatography with mass spectrometric detection</i>
	<i>h</i>	<i>hour(s)</i>

	<i>HATU</i>	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluoro-phosphate
	<i>HPLC</i>	high performance liquid chromatography
	<i>HPLC/MS</i>	coupled high performance liquid chromatography-mass spectrometry
5	<i>min</i>	minutes
	<i>MS</i>	mass spectrometry
	<i>NMR</i>	nuclear magnetic resonance
	<i>NMP</i>	<i>N</i> -Methyl-2-pyrrolidinone
	<i>R_t</i>	retention time (in HPLC)
10	<i>sec</i>	secondary
	<i>TBTU</i>	<i>O</i> -(1 <i>H</i> -benzo-1,2,3-triazol-1-yl)- <i>N,N,N',N'</i> - tetramethyluronium tetrafluoroborate
	<i>tert</i>	tertiary
	<i>TFA</i>	trifluoroacetic acid
15	<i>THF</i>	tetrahydrofurane
	<i>TLC</i>	thin-layer chromatography
	<i>UV</i>	ultraviolet absorption

20 ANALYTICAL METHODS

HPLC methods

Method:

- 1E (Hydro)

	Column:	Synergy Hydro RP80A, 4 μm, 4.6 x 100 mm
25	Mobile phase:	A = (10 mM aqueous solution of NH ₄ COOH) + 10% ACN; B = ACN + 10% (10 mM aqueous solution of NH ₄ COOH).
	Flow rate:	1200 μL/min
	Gradient:	A (100 %) for 1.5 min then to B (100 %) in 10 min for 3 min

30 Equipment:

	Instrument:	HPLC/MS ThermoFinnigan HPLC Surveyor DAD,
	Detection:	UV @ 254nm
	Detection:	Finnigan MSQ, quadrupole
	Ion source:	APCI

35

Method:

- 2FF

	Column:	Symmetry Shield RP8, 5μm, 4.6 x 150 mm
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Mobile phase: A = (H₂O + HCOOH 0.1%) + 10% ACN
 B = ACN + 10% (H₂O + 0.1% HCOOH)
Flow rate: 1000 µL/min
Gradient: A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min

5

Equipment:

Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD, LCQFLEET Ion Trap
Detection: UV λ 254 nm
Detection: Finnigan LCQDuo Ion Trap
Ion source: ESI

10

Method:

• **2G**

Column: BEH C18, 1.7µm, 2.1 x 100 mm
Mobile phase: A = (NH₄COOH 5mM) + 10% ACN
 B = ACN + 10% (NH₄COOH 5mM)
Flow rate: 450 µL/min
Gradient: A/B (100/0 %) for 0.67 min, then to A/B (0/100 %) in 3.70 min, then A/B (0/100 %) for 0.47 min

15

20

Equipment:

Instrument: Acquity UPLC/MS WATERS
Detection: Waters PDA (total scan)
Detection: Waters ELSD
Detection: Waters SQD
Ion source: ESI

25

Method:

• **2Ha**

Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm
Mobile phase: A = Water + 0.1%HCOOH; B = ACN + 0.1% HCOOH
Flow rate: 1.6 µL/min
Gradient:

30

% B	Minutes
10	0.00
90	2.70
90	3.00
10	3.30

Equipment:

Instrument: Agilent Technology; 1100 Series , DAD

35

Detection: UV 190 - 400 nm
Detection: Agilent Technology; 1100 MSD
Ion source: ESI +

5 **Method:**• **2Hb**

Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm, at 60°C

Mobile: A = water + 0.1% HCOOH; B = MeOH

Flow rate: 2.5 ml/min

10 **Gradient:**

A %	B %	Time [min]
90	10	0.00
0	100	1.61
0	100	2.25

Equipment:

15 **Instrument:** Agilent Technology; 1200 Series , DAD

Detection: UV 190 - 400 nm

Detection: Agilent Technology; 1200 MSD

Ion source: ESI +

20 **Method:**• **2Hc**

Column: Waters; XBridge C18, 3 x 30 mm, 2.5 µm, at 60°C

Mobile: A = water + 0.2% TFA; B = MeOH

Flow rate: 2.2 ml/min

25 **Gradient:**

A %	B %	Time [min]
95	5	0.00
95	5	0.05
0	100	1.40
0	100	1.80

30

Equipment:

Instrument: Agilent Technology; 1200 Series , DAD

Detection: UV 210 - 400 nm

Detection: Agilent Technology; 1200 MSD

35 **Ion source:** ESI +

Method:• **2Hd**

Column: Waters; XBridge C18, 3 x 30 mm, 2.5 µm, at 60°C

Mobile: A = water + 0.1% TFA; B = MeOH

Gradient:

A %	B %	Time [min]	Flow rate [ml/min]
95	5	0.00	1.9
95	5	0.20	1.9
0	100	1.55	1.9
0	100	1.60	2.4
0	100	1.80	2.4

5

Equipment:

10 **Instrument:** Agilent Technology; 1200 Series , DAD

Detection: UV 210 - 400 nm

Detection: Agilent Technology; 1200 MSD

Ion source: ESI +

15 **Method:**

- **2He**

Column: Waters; XBridge C18, 3 x 30 mm, 2.5 µm, at 60°C

Mobile: A = water + 0.2% NH4OH; B = MeOH

Flow rate: 2.2 ml/min

20

Gradient:

A %	B %	Time [min]
95	5	0.00
95	5	0.05
0	100	1.40
0	100	1.80

25

Equipment:

Instrument: Agilent Technology; 1200 Series , DAD

Detection: UV 210 - 400 nm

Detection: Agilent Technology; 1200 MSD

30 **Ion source:** ESI +

Method:

- **2Ja (isocratic)**

Column: DAICEL Chiralpack AD-H 5 µm, 4.6x250 mm

35

Mobile phase: A = Hexane; B = Isopropanol
A/B = 80/20%

Flow rate: 1 ml/min

Equipment

Instrument: LC Agilent Technologies. HPLC 1100 Serie, DAD Version A.

Detection: UV 220 - 300nm

GC-MS methods:

5 **Method:**

• **3B**

Column: Agilent DB-5MS, 25m x 0.25mm x 0.25 μ m

Carrier gas: Helium, 1 ml/min constant flow

Oven Program: 80°C to 110°C in 10°C / min (hold 40 min), to 280°C in
10 30°C / min

Equipment

Instrument: GC/MS Finnigan TRACE GC, TRACE MS quadrupole

Detection: TRACE MS quadrupole

Ion source: EI

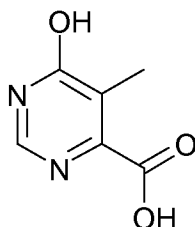
15

MICROWAVE HEATING:

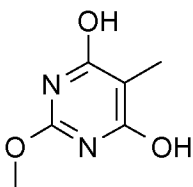
- Discover® CEM instruments, equipped with 10 and 35 mL vessels.

SYNTHESIS OF INTERMEDIATES

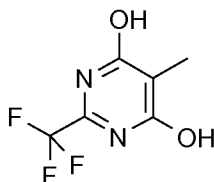
20 **Intermediate 1**



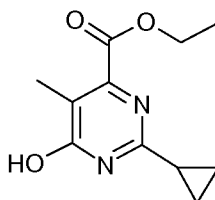
Potassium hydroxide (37.9 g, 0.67 mol) was suspended in 200 ml of dry ethanol, formamidine acetate (28.1 g, 0.27 mol) and diethyl oxalpropionate (50 ml, 0.27 mol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to room
25 temperature and the precipitate formed was filtered, washed with ethanol and diethyl ether, dissolved in 200 ml of water and the solution obtained acidified by a 37% aqueous solution of hydrochloric acid until pH=2. The acidic aqueous solution was concentrated under vacuum and the residue obtained was suspended and stirred in 100 ml of methanol. The insoluble inorganic salts were filtered off. The solution was concentrated. 15 g (97.4 mmol) of the
30 desired compound were obtained.

Intermediate 1b

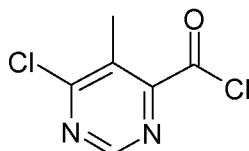
Diethylmethyl malonate (17 ml, 107 mmol) was added to sodium methoxide (30% in methanol, 101 ml, 547 mmol) and stirred for 15 min at 0°C. A solution of commercially available *O*-methylisourea hydrochloride (14.5 g, 131 mmol) in 20 ml MeOH was added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at 0°C. Then, the reaction was heated for 2 h at 65°C. The solvent was removed under vacuum. Water was added to the residue and heated for 10 min at 50°C. The mixture was acidified by addition of acetic acid until pH 4 and then cooled in an ice bath. The formed precipitate was filtered and washed with ice water to give the desired product (13.8 g).

Intermediate 1c

was synthesized in analogy to intermediate 1b starting from commercially available 2,2,2,-trifluoro-acetamide.

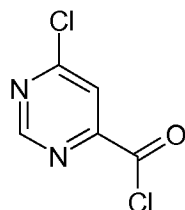
Intermediate 1d

Commercially available cyclopropanecarboxyamidine (10 g, 83 mmol), diethylmalonate (15.63 ml, 83 mmol) and potassium carbonate (26.6 g, 207 mmol) were suspended in 160 ml of ethanol and the reaction mixture was stirred under reflux for 4h. The reaction mixture was filtered over a celite pad and the filtrate solution was evaporated. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: SNAP 100g; eluent: dichloromethane) to give the desired compound (4.6 g, 18.6 mmol).

Intermediate 2a

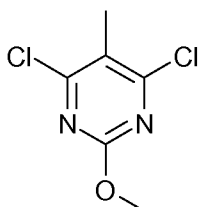
Intermediate 1 (7.0 g, 45.4 mmol) was suspended in 35 ml of thionyl chloride (0.45 mol), 0.10 ml of DMF was added and the reaction mixture was refluxed for 1h. The reaction mixture was concentrated in vacuum. 8.6 g (45 mmol) of the desired product were obtained and used in the next steps without further purification.

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Intermediate 2b

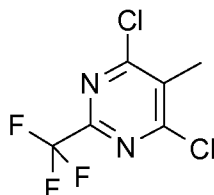
was synthesized in analogy to intermediate 2a starting from commercially available 6-hydroxypyrimidine-4-carboxylic acid.

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Intermediate 2c

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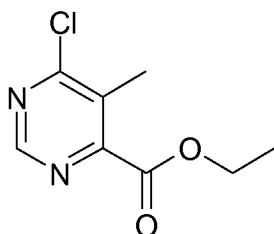
Intermediate 1b (1.9 g, 12.2 mmol) was added to phosphoryl chloride (17 ml) and the reaction mixture was stirred overnight at 60°C. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane. The combined organic layers were concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product.

Intermediate 2d

20

Thionylchloride (11.2 ml, 155 mmol) and DMF (250 µl) were added to a solution of intermediate 1c (3.0 g, 15.5 mmol) in 9 ml of dichloromethane and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane. The combined organic layers were concentrated under vacuum to give the desired product (2.7 g).

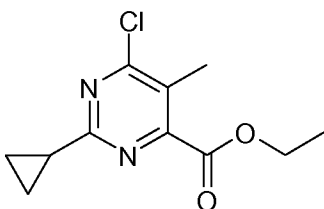
25

Intermediate 3

Potassium carbonate (43.34 g, 0.31 mol) was suspended in 350 ml of dry ethanol. A solution of intermediate 2a (20 g, 0.10 mol) in 10 ml of dichloromethane was added slowly at 0°C.

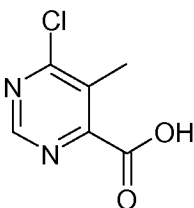
- 5 The reaction mixture was allowed to reach room temperature and stirred for 1h. Potassium carbonate was filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/ethyl acetate=95/5%). 5.3 g (26 mmol) of the desired compound were obtained.

10

Intermediate 3a

Intermediate 1d (4.6 g, 18.63 mmol) and phosphorus oxychloride (16.8 ml, 180 mmol) was refluxed at 130°C for 18h. The reaction mixture was concentrated under vacuum, the crude product was diluted with toluene and the organic phase was concentrated under vacuum. The residue was diluted with 100 ml of ethyl acetate and the organic phase was washed with 100 ml of a cooled sodium carbonate saturated water solution. The organic phase was concentrated under vacuum to yield the desired product (4.1 g) which was used in the next step without further purification.

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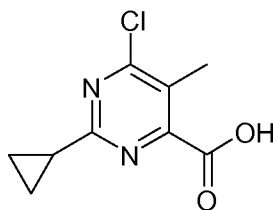
Intermediate 3b

- Intermediate 3 (1 g, 5 mmol) was diluted in 5 ml of tetrahydrofurane and 5 ml of water, lithium hydroxide (313 mg, 7.5 mmol) was added and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was concentrated under vacuum The crude product was dissolved in 10 ml of a 4 M solution of hydrochloric acid in 1,4-dioxane, the solution was stirred at room temperature for 10 minutes and then concentrated under vacuum. The crude product was dissolved in dichlorometane, the formed precipitate was filtered off

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and the filtrate was concentrated under vacuum giving the desired product (880 mg, 5.1 mmol).

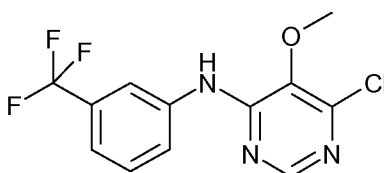
Intermediate 3c



5

was prepared in analogy to Intermediate 3b starting from Intermediate 3a.

Intermediate 4



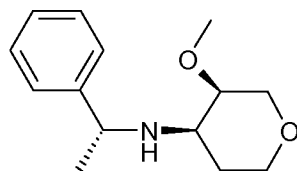
10 Commercially available 3-trifluoromethyl-aniline (322 μ l, 2.6 mmol) and commercially available 4,6-dichloro-5-methoxypyrimidine (358 mg, 2.0 mmol) were added to a mixture of 0.2 ml 32% aqueous hydrochloric acid and 2 ml water. The reaction mixture was refluxed over night. The resulting precipitate was filtered, washed with water and dried at 50°C to give the desired product (501 mg, 1.47 mmol).

15

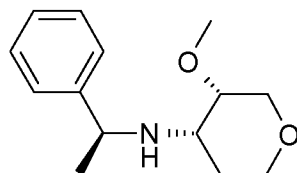
The following intermediates were synthesized in analogy to Intermediate 4.

Starting aniline (commercially available)	Starting pyrimidine	Chloro-Intermediate	STRUCTURE
3-Trifluoromethyl-aniline	4,6-dichloro-2-trifluoromethyl-pyrimidine (commercially available)	4b	

3,4-dichloro - aniline	2d	4c	
3-Trifluoromethyl- aniline	2c	4d	
3,4-dichloro - aniline	2c	4e	

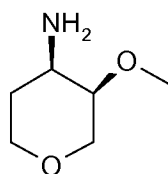
Intermediate 5a

- Commercially available 3-Methoxy-tetrahydro-pyran-4-one (1 g, 7.68 mmol), commercially available (R)-(+)-1-phenylethylamine (0.99 ml, 7.68 mmol) and Raney-Nickel (200 mg) in 10 ml of dry ethanol were stirred under a hydrogen atmosphere (5 bar) for 15 days. The reaction mixture was diluted with 20 ml of methanol and 20 ml of tetrahydrofuran, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50g). The cartridge was washed with methanol and the desired product was eluted with a 7 M solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and the crude product was purified by flash chromatography (dichloromethane/methanol= 98/2%) to obtain 710 mg (3.02 mmol) of the desired product as single stereoisomer (diastereoisomeric purity confirmed and relative cis stereochemistry assigned by NMR).
- GC/MS (method 3B) $R_t = 35.04$ min

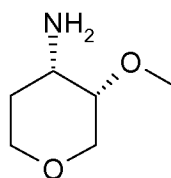
Intermediate 5b

was synthesised in analogy to Intermediate 5a, starting from 3-Methoxy-tetrahydro-pyran-4-one and commercially available (S)-(-)-1-phenylethylamine (diastereoisomeric purity confirmed and relative cis configuration assigned by NMR).

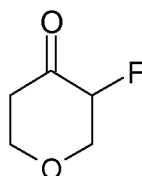
GC/MS (method 3B) $R_t = 35.04$ min

Intermediate 6a

Intermediate 5a (1.18 g, 5.01 mmol), Pd/C 10% (200 mg) and acetic acid (0.3 ml, 5.01 mmol) in 20 ml of methanol were stirred under a hydrogen atmosphere (5 bar) for 18h. The reaction mixture was diluted with 20 ml of methanol, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50g). The cartridge was washed with methanol and the desired product was eluted with a 7 M solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and 513 mg (3.91 mmol) of the desired product were obtained as single stereoisomer

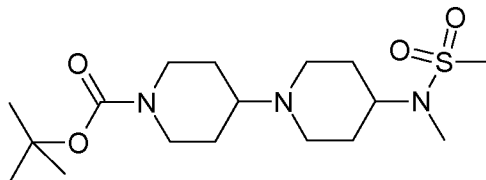
Intermediate 6b

was synthesised in analogy to Intermediate 6a, starting from Intermediate 5b.

Intermediate 6c

Commercially available 5,6-dihydro-4-methoxy-2H-pyran (5 g, 43.8 mmol) was dissolved in 70 ml acetonitrile and 70 ml water. Commercially available selectfluor(TM)-fluorinating reagent (17 g, 48.2 mmol) was added and the reaction mixture was stirred at room temperature for 2h. NaCl (2 g) was added and the reaction mixture was extracted with diethyl ether. The organic phase was dried over sodium sulfate and concentrated under vacuum to give the desired product (4 g). The crude product was used in the next step without purification.

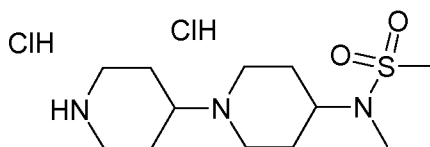
Intermediate 7a



Commercially available N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (11 g, 47.91 mmol) was suspended in 200 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (17.12 ml, 96.17 mmol) and 1-(tert-butoxycarbonyl)-piperidin-4-one (9.58 g, 48.08 mmol) were added and the reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (12.23 g, 57.50 mmol) was added and the reaction mixture was stirred at room temperature for 72h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1; silica gel cartridge: 65i; eluent: ethyl acetate/methanol=50/50%) to obtain 7.2 g (19.2 mmol) of the desired compound.

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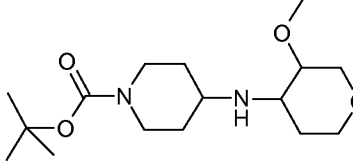
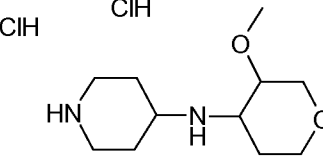
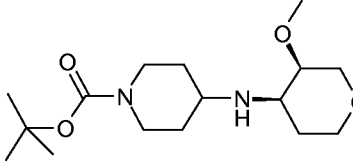
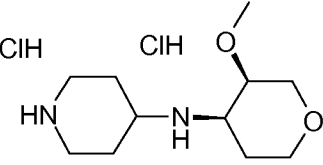
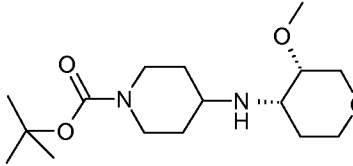
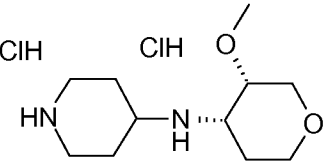
Intermediate 8a



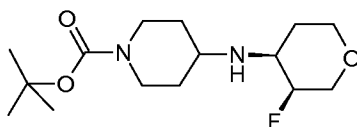
Intermediate 7a (7.2 g, 19.2 mmol) was suspended in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (48 ml, 192 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 6.3 g (18 mmol) of the desired compound were obtained.

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The following intermediates were synthesized in analogy to Intermediates 7a and 8a.

Starting ketone	Starting amine	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
3-Methoxy-tetrahydro-pyran-4-one (commercially available)	4-amino-piperidine-1-carboxylic acid tert-butyl-ester (commercially available)	7b		8b	
1-(tert-butoxycarbonyl)-4-oxopiperidine (commercially available)	6a	7c		8c	
1-(tert-butoxycarbonyl)-4-oxopiperidine (commercially available)	6b	7d		8d	

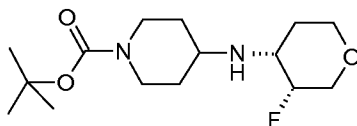
6c	4-amino-piperidine-1-carboxylic acid tert-butyl-ester (commercially available)	7e		8e	
	protocol see below	7f		8f	
	protocol see below	7g		8g	
Tetrahydro-pyran-4-one (commercially available)	4-amino-piperidine-1-carboxylic acid tert-butyl-ester (commercially available)	7h		8h	

Intermediate 7f

Preparative Chiral HPLC Separation of Intermediate 7e (360 mg, 1.19 mmol) gave 163 mg (0.54 mmol) of the isomerically pure *cis*-intermediate (first eluted *cis*-enantiomer, relative stereochemistry assigned by NMR).

Chiral HPLC (method 2Ja isocratic): $R_t = 5.197$ min

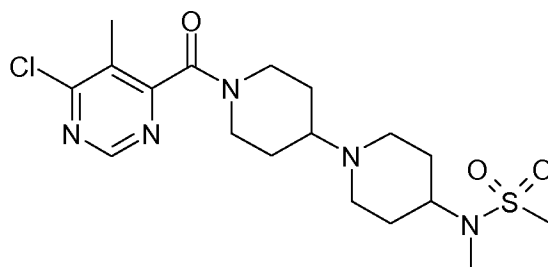
Intermediate 7g



- 5 Further elution of the column gave 164 mg (0.54 mmol) of the second eluted cis-enantiomer (relative stereochemistry assigned by NMR) .

Chiral HPLC (method 2Ja isocratic): $R_t = 6.012$ min

Intermediate 9a

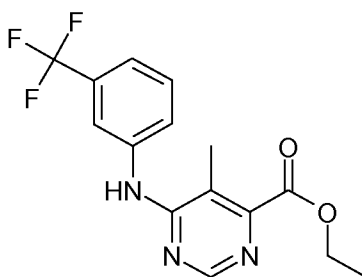


- 10 The intermediate 8a (3.95 g, 14.34 mmol) was suspended in 30 ml of dry dichloromethane, triethylamine (8 ml, 57.38 mmol) was added and the reaction mixture was stirred under nitrogen atmosphere and cooled to 0°C. Intermediate 2a (2.74 g, 14.34 mmol) in 40 ml of dry dichloromethane was added dropwise and the reaction mixture was allowed to warm to room
- 15 temperature and stirred for 18h; the reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge: 50g; eluent: ethyl acetate/methanol=8/2%). 1.27 g (2.96 mmol) of the desired compound were obtained.

- 20 The following intermediates were synthesized in analogy to Intermediate 9a.

Piperidine Intermediate	Chloro-pyrimidine Intermediate	Core Intermediate	STRUCTURE
8a	2b	9b	

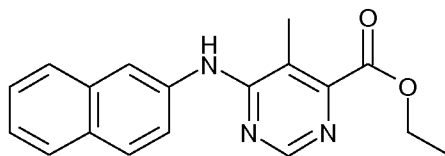
8b	2a	9c	
8d	2b	9d	
8c	2b	9e	
8d	2a	9f	
8c	2a	9g	

Intermediate 10a

Intermediate 3 (400 mg, 1.99 mmol), commercially available 3-trifluoromethyl-phenylamine (2.49 ml, 19.94 mmol) and N,N-diisopropyl-ethyl amine (0.41 ml, 2.39 mmol) were mixed in a microwave vial and reacted in the following conditions: Power 100, Ramp 5 min, Hold 2h, Temperature 150°C, Pressure 250 psi, Stirring. The reaction mixture was concentrated under vacuum and diluted with dichloromethane. The organic phase was washed with an aqueous

saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. 450 mg of the desired compound were obtained as a crude product.

Intermediate 10b



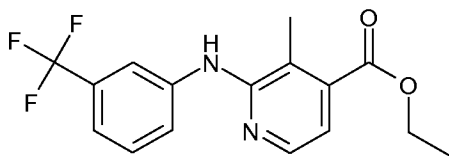
5

Commercially available 2-naphthylamine (200 mg, 1.4 mmol) and intermediate 3 (280 mg, 1.4 mmol) were added to a mixture of 0.2 ml 32% aqueous hydrochloric acid and 2 ml water. The reaction mixture was stirred for 15 min at 100°C. The resulting precipitate was filtered, washed with water and dried under vacuum to give the corresponding ester (410 mg, 1.2

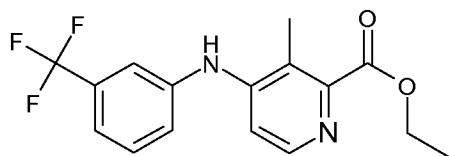
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The following intermediates were synthesised in analogy to Intermediate 10b, starting from commercially available naphthyl-amine.

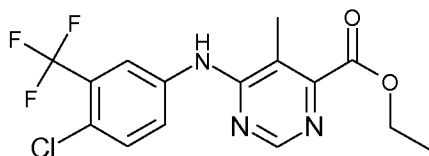
Starting Naphthyl-amine	Chloro-pyrimidine Intermediate	Core Intermediate	STRUCTURE
6-methoxy-2-naphthylamine	3	10c	
7-methoxy-2-naphthylamine	3	10d	
4-methoxy-2-naphthylamine	3	10e	
6-bromo-2-naphthylamine	3	10ea	

Intermediate 10f

Commercially available 2-chloro-3-methyl-pyridine-4-carboxylic acid ethyl ester (500mg, 2.5 mmol), commercially available 3-trifluoromethyl-phenylamine (312.8 mg, 2.5 mmol) and cesium carbonate (1.22g, 3.76 mmol) was suspended in 25 ml of toluene, then, under nitrogen atmosphere, tris(dibenzylideneacetone)dipalladium (0) (229 mg, 0.25 mmol) and (2-biphenyl)dicyclohexylphosphine (350 mg, 1 mmol) were added. The reaction mixture was stirred at 110°C for 12h. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichlorometane. The organic solution was washed with water, dried over sodium sulfate and concentrated under vacuum. The crude product was loaded on a SCX cartridge (20g) and, after washing with methanol, the product was eluted with a 7M solution of ammonia in methanol. 70 mg of the desired product were obtained and used in the further step without any other purifications.

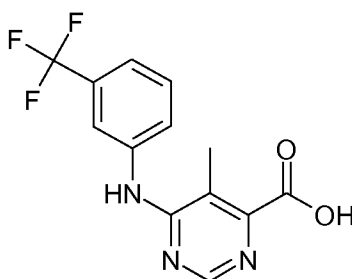
Intermediate 10g

Commercially available 4-chloro-3-methyl-picolinate (420 mg, 2.10 mmol), acetic acid (0.001 ml) and commercially available 3-trifluoromethyl-phenylamine (0.52 ml, 4.21 mmol) were mixed in a microwave vial and reacted in the following conditions: Power 200, Ramp 2 min, Hold 25 min, Temperature 120°C, Pressure 200 psi, Stirring. The reaction mixture was diluted with dichlorometane, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge: 10g; eluent: dichloromethane/methanol=9/1%). 520 mg (1.6 mmol) of the desired compound were obtained.

Intermediate 10h

Commercially available 4-chloro-3-trifluoromethyl-phenylamine (487 mg, 2.49 mmol) and sodium hydride (200 mg of a 60% suspension on mineral oil, 4.98 mmol) were suspended in 10 ml of 1,4-dioxane and stirred at 100°C for 1h. Intermediate 3 (500 mg, 2.49 mmol) was added and the reaction mixture was heated at 100°C for 2h. The reaction mixture was concentrated under vacuum, the residue was dissolved in dichloromethane, the organic phase was washed with a saturated aqueous sodium bicarbonate solution, separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge: 10g; eluent: dichloromethane=100%). 750 mg (2.08 mmol) of the desired compound were obtained.

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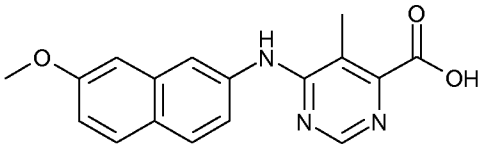
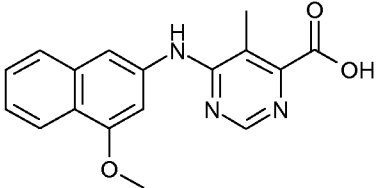
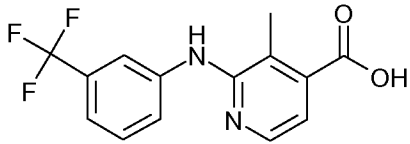
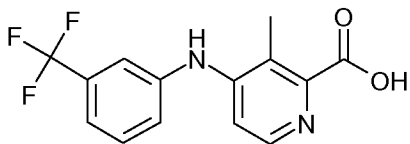
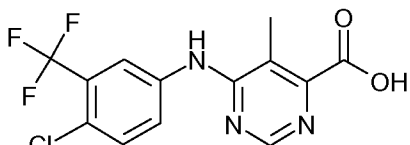
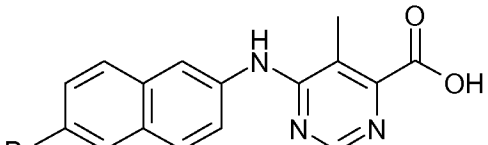
Intermediate 11a

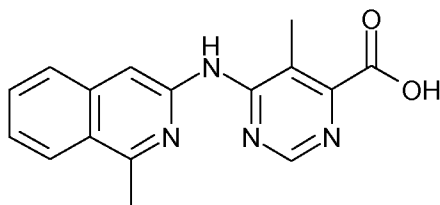
The crude intermediate 10a (450 mg) was dissolved in 3 ml of tetrahydrofuran and a solution of LiOH (81.85 mg, 1.95 mmol) in 3 ml of water was added. The reaction mixture was stirred at room temperature for 2 h and then concentrated under vacuum. 20 ml of water was added and the reaction mixture was acidified with 5 ml of a 4M solution of hydrochloric acid in water. The aqueous phase was extracted with dichloromethane (2x20ml). The organic phase was dried over sodium sulfate and concentrated under vacuum. 110 mg (0.35 mmol) of the desired product were obtained.

20

The following intermediate was synthesized in analogy to intermediate 11a.

Ester intermediate	Acid intermediate	STRUCTURE
10b	11b	
10c	11ba	

10d	11bb	
10e	11bc	
10f	11bd	
10g	11be	
10h	11bf	
10ea	11bg	

Intermediate 11c

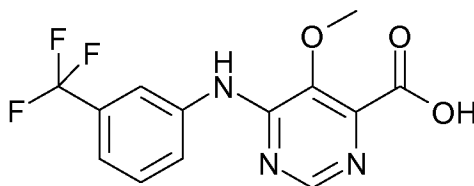
5

Sodium *tert*-butylate (273 mg, 2.85 mmol) was added to a solution of commercially available 1-methyl-isoquinolin-3-ylamine (150 mg, 950 μ mol) and intermediate 3 (190 mg, 950 μ mol) in 2 ml toluene under argon atmosphere. Then, xantphos (22 mg, 38 μ mol) and tris(dibenzylideneacetone)dipalladium(0) (17 mg, 19 μ mol) were added and the mixture was stirred over night at 100°C. The reaction mixture was diluted with ethyl acetate and extracted with 1 M aqueous sodium hydroxide (2x). The combined aqueous layers were concentrated in

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vacuum and the residue was purified by reversed phase HPLC to give the desired product (50 mg, 170 μ mol).

5 Intermediate 11d

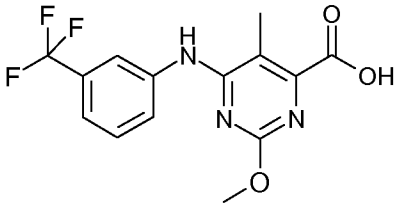
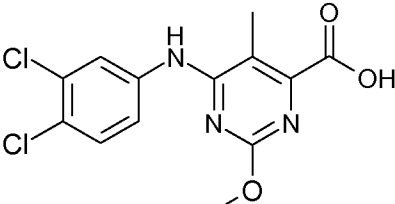


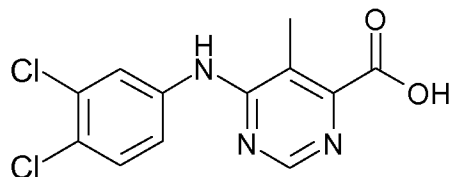
A mixture of intermediate 4 (501 mg, 1.47 mmol), palladium acetate (33 mg, 147 μ mol), 1,1'-bis(diphenylphosphino)-ferrocene (81 mg, 147 μ mol), sodium acetate (362 mg, 4.4 mmol) in 15 ml methanol and 15 ml DMF was stirred under a carbon monoxide atmosphere (5 bar) for 23 h at 70°C. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase HPLC to give the corresponding ester (554 mg, 1.26 mmol).

A 1 M aqueous solution of sodium hydroxide (2.5 ml) was added to a solution of the ester (554 mg, 1.26 mmol) in 10 ml methanol. The reaction mixture was stirred for 3 h at room temperature. Then, the reaction mixture was acidified with trifluoroacetic acid. The resulting precipitate was filtered, washed with methanol and dried at 50°C to give the desired product (301 mg, 704 μ mol).

The following intermediates were synthesized in analogy to 11d:

Starting Chloro-Intermediate	Carboxylic Acid Intermediate	STRUCTURE
4b	11e	
4c	11f	

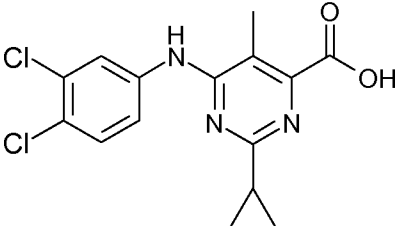
4d	11g	
4e	11h	

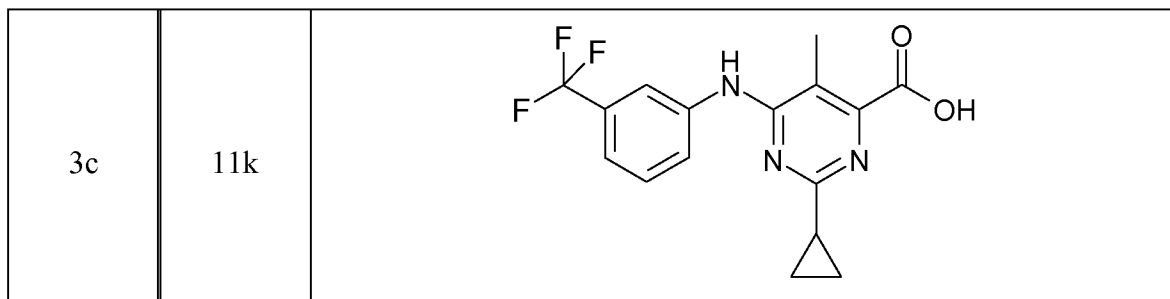
Intermediate 11i

Intermediate 3b (880 mg, 5.1 mmol) was dissolved in 10 ml of 1,4-dioxane. 2.7 ml (10.8 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane and commercially available 3,4-dichloroaniline were added and the reaction mixture was reacted in a microwave vial in the following conditions: Power 150, Ramp 2 min, Hold 30 min, Temperature 110°C, Pressure 250 psi, Stirring. The mixture was treated with water. The precipitate was filtered and dried under vacuum to yield the desired product (550 mg, 1.85 mmol).

10

The following intermediates were prepared in analogy to Intermediate 11i

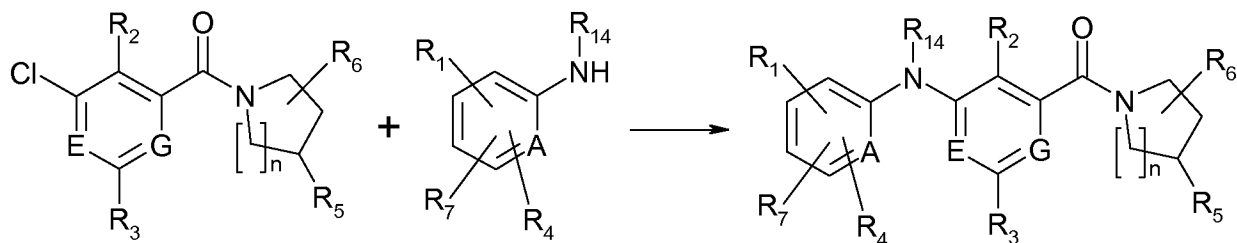
Starting Chloro-Intermediate	Carboxylic Acid Intermediate	STRUCTURE
3c	11j	



SYNTHESIS OF EXAMPLES

- 5 The examples of this invention are synthesized according to the following general synthetic procedures:

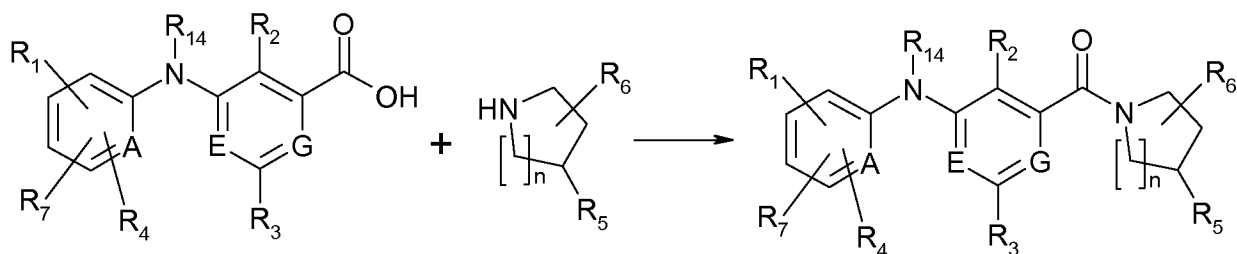
Synthetic Procedure A:



Examples: 1-17, 17a-17b

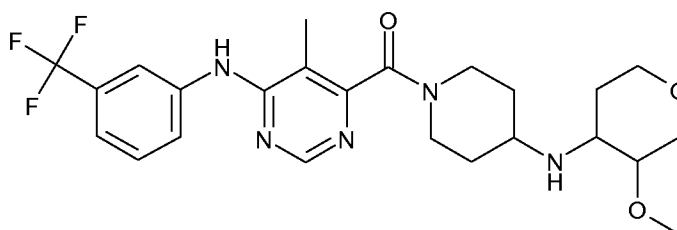
10

Synthetic Procedure B:



Examples: 18-43, 33a-33w

15 Example 1

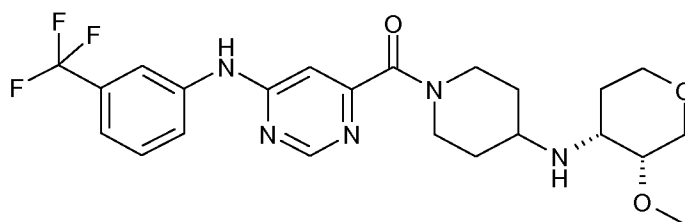


Intermediate 9c (70 mg, 0.19 mmol) and commercially available 3-trifluoromethyl-phenylamine (0.28 ml, 2.28 mmol) were mixed in a microwave vial and reacted in the following conditions: Power 200, Ramp 5 min, Hold 2h, Temperature 150°C, Pressure 250 psi, Stirring. The reaction mixture was diluted with DMF and purified by reverse phase preparative HPLC. 10 mg (0.02 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): Rt. (min) = 8.07; [M+H]⁺ = 494

The following examples were synthesized in analogy to the preparation of Example 1

Ex #	MOLSTRUCTURE	Intermediate	Amine (commercially available)	[M+H] ⁺	HPLC R _t (min)	Method
2		9c	3,5-bis-trifluoromethyl-phenylamine	562	3.51	2G
3		9c	Phenylamine	426	2.41	2G
4		9c	6-trifluoromethyl-pyridin-2-ylamine	495	7.69	1E (Hydro)
5		9c	3-methyl-phenylamine	440	7.23	1E (Hydro)

Example 6

Commercially available 3-trifluoromethyl-phenylamine (0.05 ml, 0.42 mmol) and intermediate 9e (150 mg, 0.42 mmol) were added to a mixture of 0.2 ml 32% aqueous hydrochloric acid and 2 ml water. The reaction mixture was stirred for 15 min at 100°C. The residue was purified by reversed phase HPLC to give 130 mg (0.26 mmol) of the desired product.

HPLC (2Ha): R_t (min) = 1.65

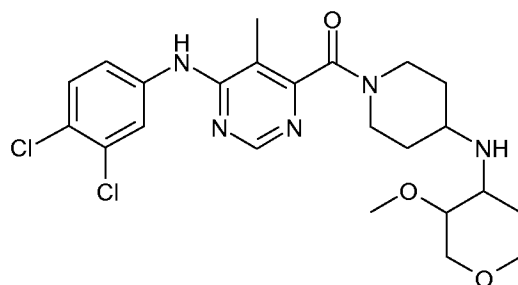
$[M+H]^+ = 480$

10

The following examples were synthesized in analogy to the preparation of Example 6:

Ex #	MOLSTRUCTURE	Intermediate	Amine (commercially available)	$[M+H]^+$	HPLC R_t (min)	Method
7		9d	3-Trifluoromethyl-phenylamine	480	1.66	2Ha
8		9b	3-Trifluoromethyl-phenylamine	541	1.73	2Ha

15

Example 9

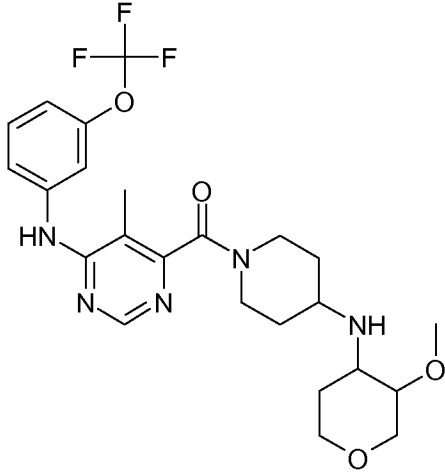
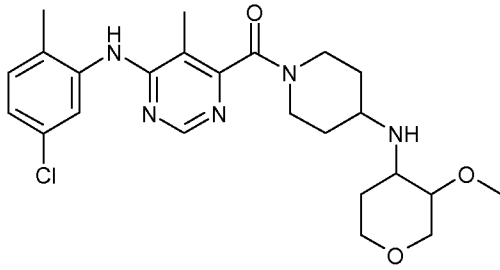
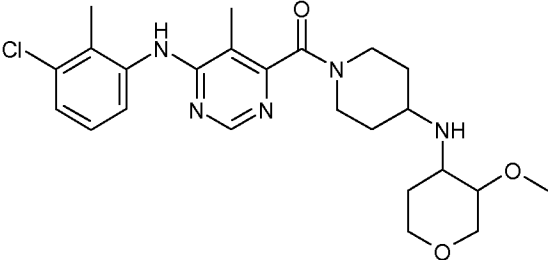
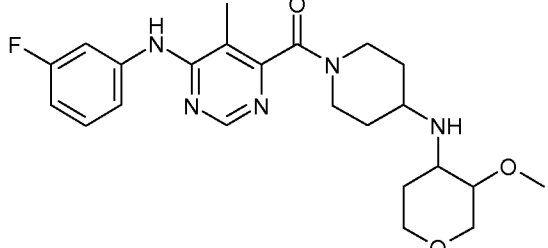
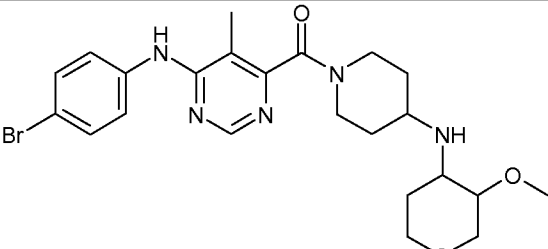
Commercially available 3,4-dichloroaniline (87 mg, 0.54 mmol) was dissolved in 1 ml of dry 1,4-dioxane, sodium hydride (22.7 mg, 0.57 mmol, 60% in mineral oil) was added and the reaction mixture was stirred at 90°C for 1h. A solution of Intermediate 9c (100 mg, 0.27 mmol) in 1 ml of dry 1,4-dioxane was added and the reaction mixture was refluxed for 3 h. The reaction mixture was concentrated, the crude product suspended in dichloromethane and the mixture washed with water. The organic phase was separated and concentrated under vacuum. The crude product was purified by reversed phase HPLC. 26 mg (0.05 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t (min) = 8.65

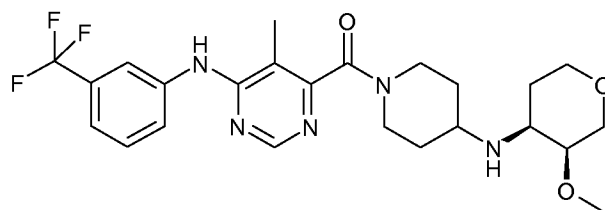
$[M+H]^+ = 494$

The following examples were synthesized in analogy to the preparation of Example 9

Ex #	MOLSTRUCTURE	Intermediate	Amine (commercially available)	$[M+H]^+$	HPLC R_t (min)	Method
10		9c	Methyl-(3-Trifluoromethyl-phenyl)-amine	508	8.55	1E (Hydro)

11		9c	3-Trifluoromethoxy-phenylamine	510	8.57	1E (Hydro)
12		9c	5-chloro-2-methyl-phenylamine	474	7.65	1E (Hydro)
13		9c	3-chloro-2-methyl-phenylamine	474	7.60	1E (Hydro)
14		9c	3-fluoro-phenylamine	444	7.22	1E (Hydro)
15		9c	4-bromo-phenylamine	504	8.07	1E (Hydro)

16		9c	3-pyridin-4-yl-phenylamine	503	7.18	1E (Hydro)
17		9c	2-chloro-phenylamine	460	7.2	1E (Hydro)
17a		9f	3,4-Dichloroaniline	494	7.92	1E (Hydro)
17b		9g	3,4-Dichloroaniline	494	7.92	1E (Hydro)

Example 18

5 Intermediate 11a (40 mg, 0.13 mmol), TBTU (43 mg, 0.13 mmol) and N,N-diisopropylethylamine (0.081 ml, 0.471 mmol) in 2 ml DMF were stirred at room temperature for 5 min. Intermediate 8d (51 mg, 0.13 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified by reversed phase HPLC. 25 mg (0.05 mmol) of the desired product were obtained.

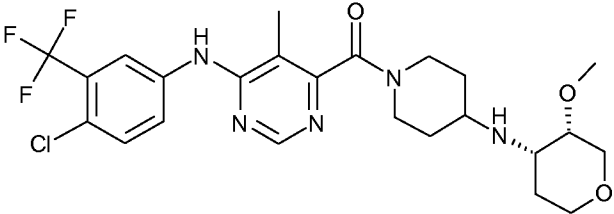
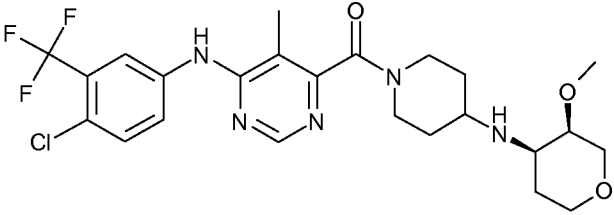
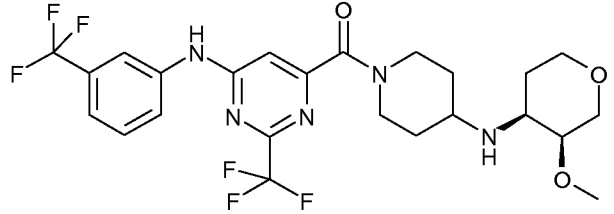
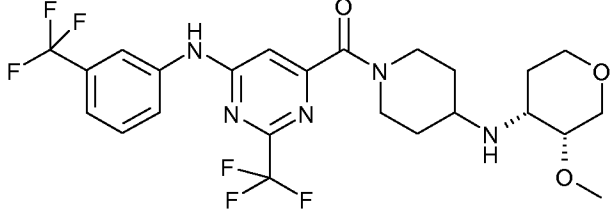
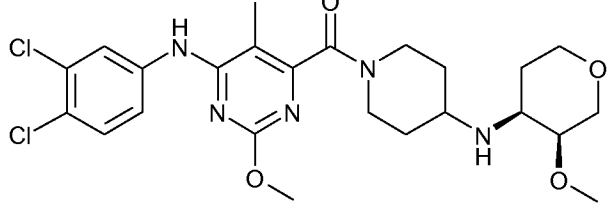
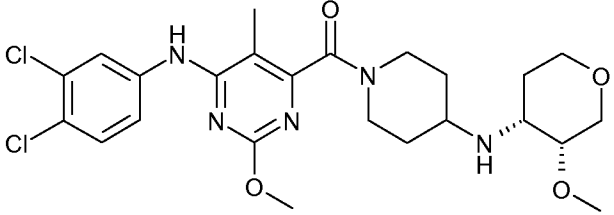
HPLC (1E Hydro): R_t (min) = 8.28

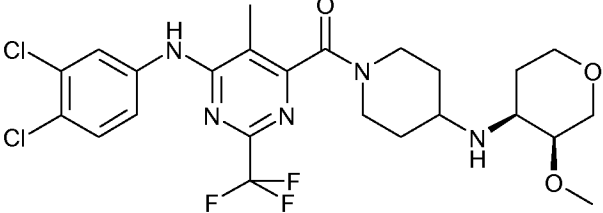
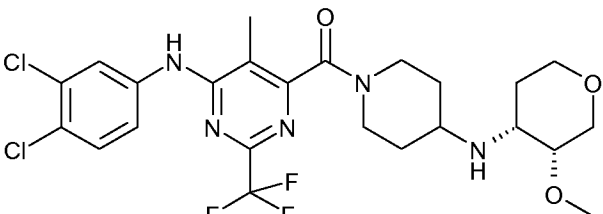
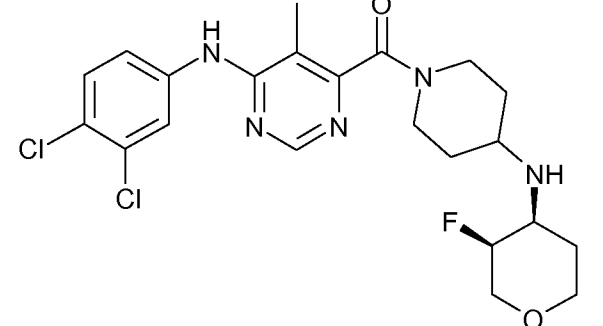
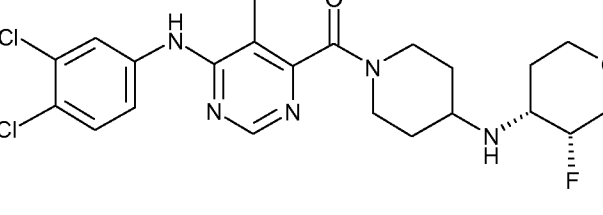
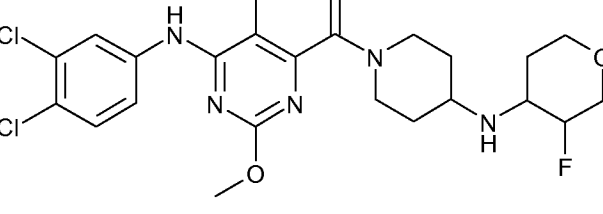
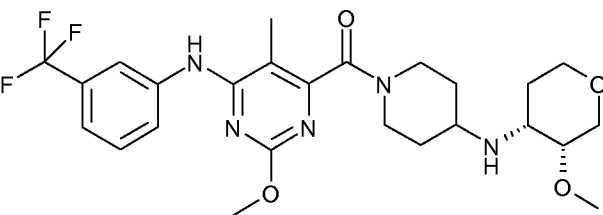
[M+H]⁺ = 494

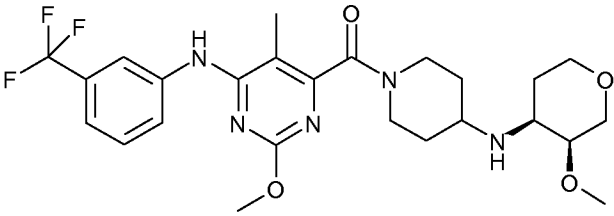
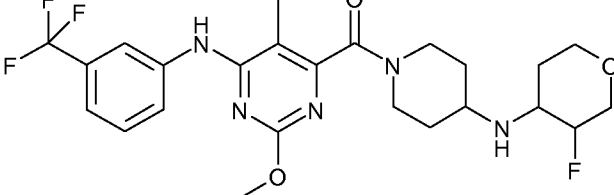
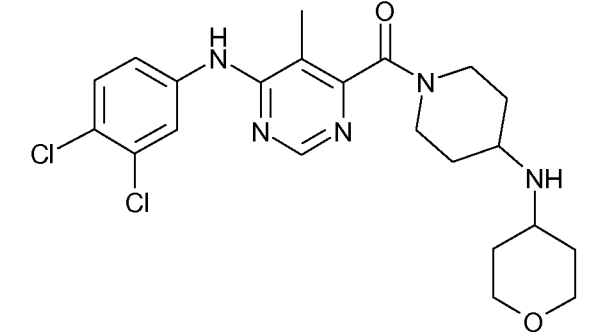
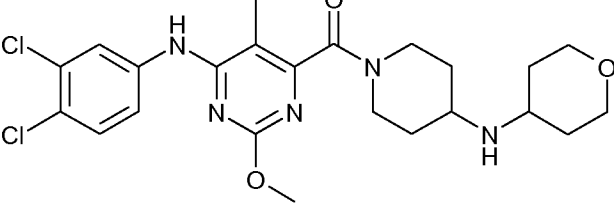
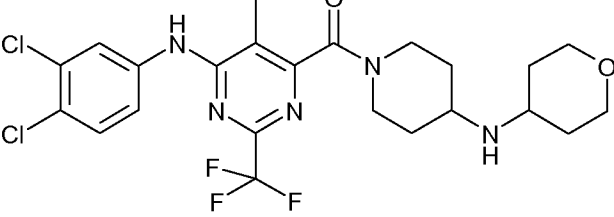
The following examples were synthesized in analogy to the preparation of Example 18.

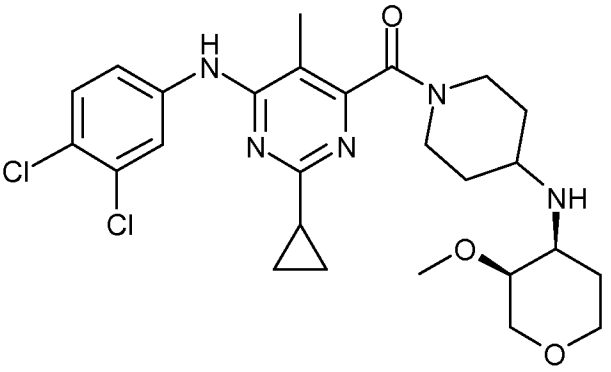
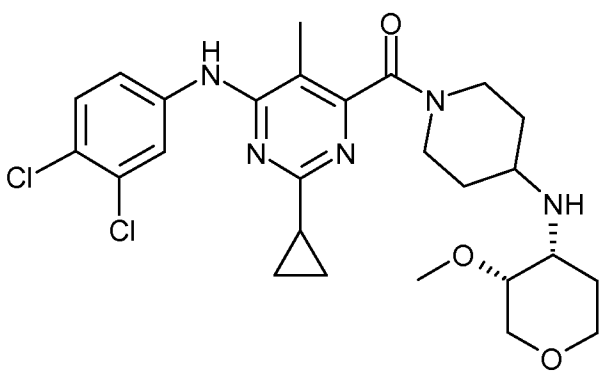
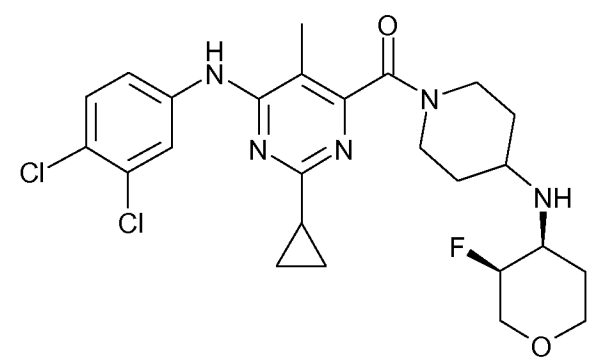
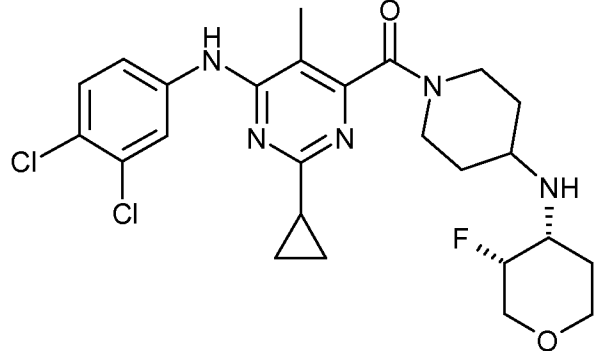
Ex #	STRUCTURE	Intermediate	Amine	[M+H] ⁺	HPLC R _c (min)	Method
19		11d	8c	510	1.75	2Ha
20		11d	8d	510	1.75	2Ha
21		11d	8a	571	1.82	2Ha
22		11b	8a	537	1.67	2Ha
23		11b	8b	476	1.54	2Ha

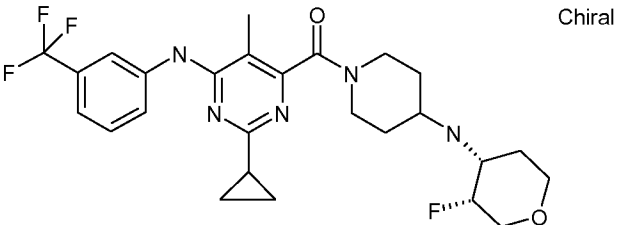
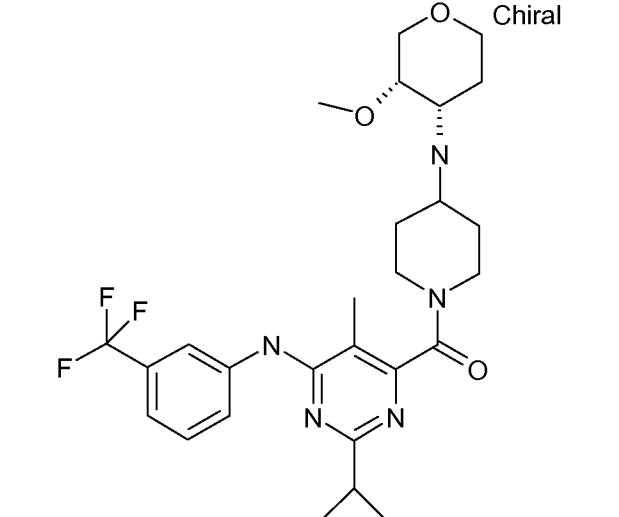
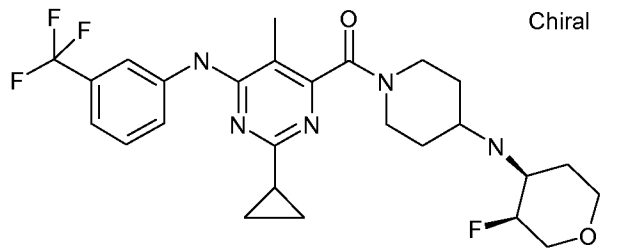
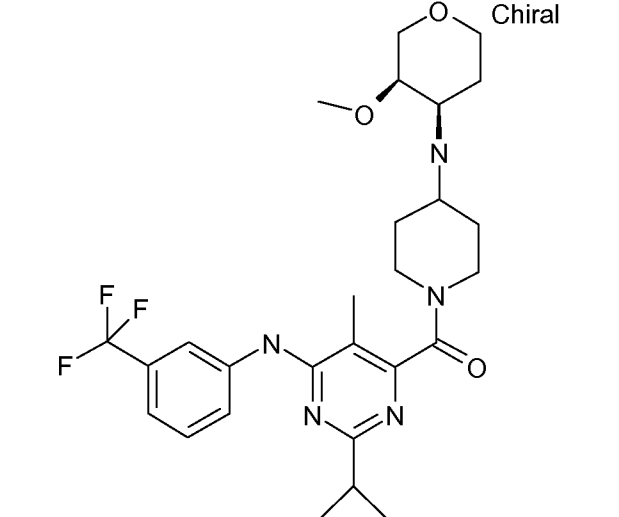
24		11c	8a	552	1.43	2Ha
25		11 bd	8d	493	8.9	1E (Hydro)
26		11 bd	8c	493	8.10	1E (Hydro)
27		11 be	8d	493	8.11	1E (Hydro)
28		11 be	8c	493	8.12	1E (Hydro)
29		11a	4-piperidin-4-yl- morpholine (commercially available)	450	1.60	2Ha

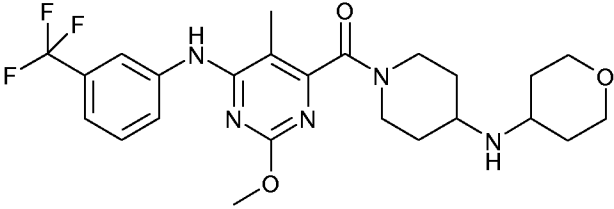
30		11 bf	8d	528	7.69	2F
31		11 bf	8c	528	7.69	2F
32		11e	8d	548	1.97	2Ha
33		11e	8c	548	2.03	2Ha
33a		11h	8d	524	1.817	2Ha
33b		11h	8c	524	1.836	2Ha

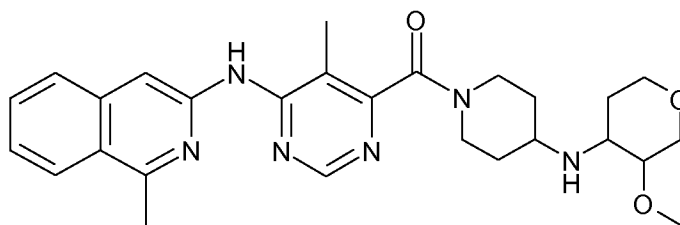
33c		11f	8d	562	2.022	2Ha
33d		11f	8c	562	2.008	2Ha
33e		11i	8f	482	8.2	1E (Hydro)
33g		11i	8g	482	8.03	1E (Hydro)
33h		11h	8e	512	1.062	2Hc
33i		11g	8c	524	1.22	2He

33j		11g	8d	524	1.212	2He
33k		11g	8e	512	1.189	2He
33l		11i	8h	464	6.81	2FF
33m		11h	8h	494	1.139	2Hd
33n		11f	8h	532	1.195	2Hc

33o		11j	8d	534	9.5	1E (Hydro)
33p		11j	8c	534	9.62	1E (Hydro)
33q		11j	8f	522	9.35	1E (Hydro)
33r		11j	8g	522	9.31	1E (Hydro)

33s	 <p>Chiral</p>	11k	8g	522	8.75	1E (Hydro)
33t	 <p>Chiral</p>	11k	8d	534	8.87	1E (Hydro)
33u	 <p>Chiral</p>	11k	8f	522	8.48	1E (Hydro)
33v	 <p>Chiral</p>	11k	8c	534	8.88	1E (Hydro)

33w		11g	8h	494	1.041	2Hc
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Example 34

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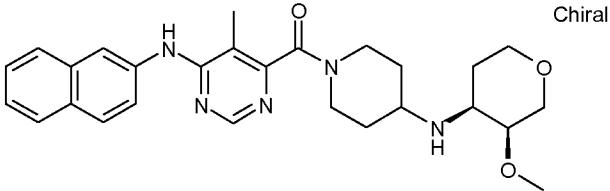
N,N-diisopropylamine (120 μ l, 680 μ mol) and HATU (35 mg, 93 μ mol) were added to a solution of intermediate 11c (25 mg, 85 μ mol) in 2 ml DMF. Then, a solution of intermediate 8b (37 mg, 127 μ mol) in 1 ml DMF was added and the reaction mixture was stirred over night. The reaction mixture was diluted with 20 ml of a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated in vacuum. The residue was purified by reversed phase HPLC to give the desired product (15 mg, 31 μ mol).

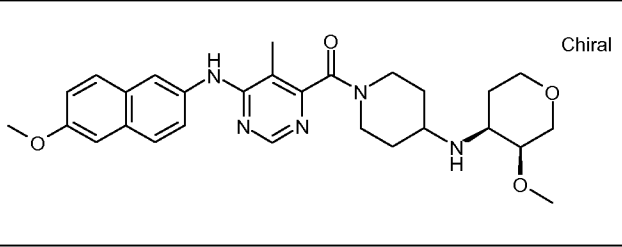
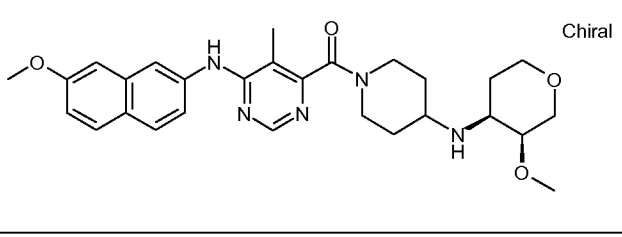
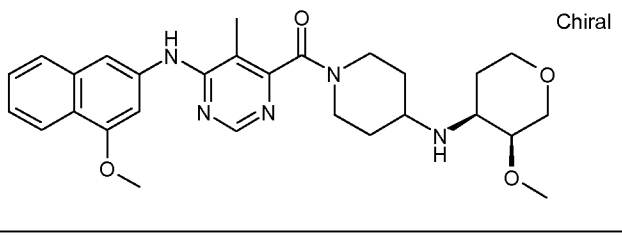
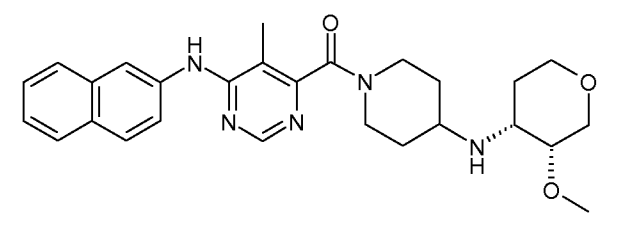
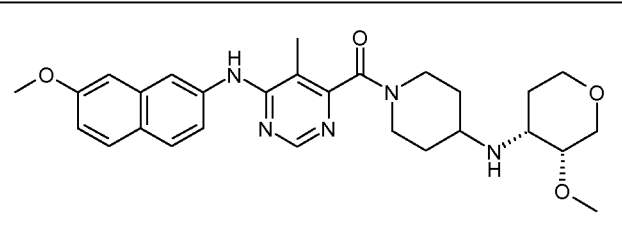
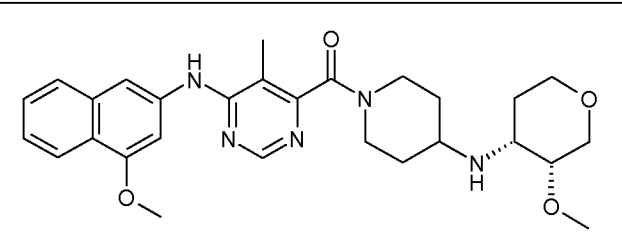
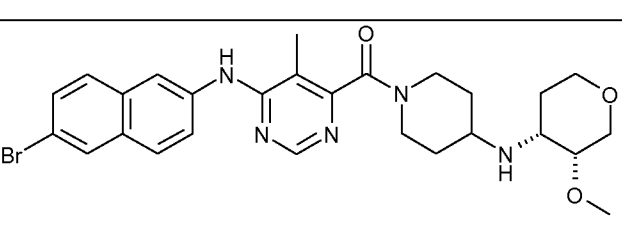
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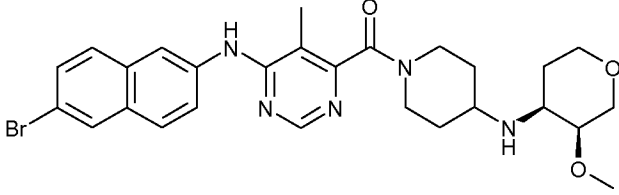
HPLC (2Ha): R_t (min) = 1.33

15 $[M+H]^+ = 491$

The following examples were synthesised in analogy to the preparation of Example 34.

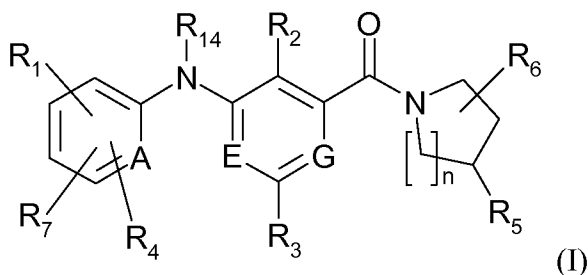
Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
35		11b	8d	476	1.60	2Ha

36		11ba	8d	506	1.59	2Ha
37		11bb	8d	506	1.59	2Ha
38		11bc	8d	506	1.70	2Ha
39		11b	8c	476	0.97	2Hb
40		11bb	8c	506	0.98	2Hb
41		11bc	8c	506	1.72	2Ha
42		11bg	8c	554	1.86	2Ha

43		11bg	8d	554	1.85	2Ha
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Claims

1. Compounds according to formula (I),



wherein R₁ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, -C₅-C₁₀-heteroaryl, and -OCFH₂,

and wherein R₇ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

or wherein R₇ and R₁ on two neighbouring ring atoms together form a -C₃-C₆-alkenylene group, such that an annelated aromatic ring is formed, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O, and S,

wherein the resulting annelated ring being optionally substituted by one or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and halogen;

wherein R₄ is a group selected from among -hydrogen, -C₁-C₃-alkyl, -CF₃, -OCF₃, -OCF₂H, -halogen, -CN, -O-C₁-C₄-alkyl, -CH=CH₂, -C≡CH, and -OCFH₂;

wherein A is C or N;

wherein R₁₄ is a group selected from among -hydrogen, and -C₁-C₃-alkyl;

wherein R₂ is selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -cyclopropyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

wherein n is 1, 2 or 3;

wherein G and E are N,
 or wherein G is N and E is C,
 or wherein G is C and E is N;

5 wherein R₅ is a group of the structure -NR₈R₉,
 wherein R₈, R₉, are independently selected from among -H, -C₁-C₆-alkyl, and a group
 of the structure -C₃-C₆-cycloalkyl, wherein such ring is optionally substituted by one
 or more groups selected from among -F, and -OCH₃;

10 or wherein R₅ is a group of the structure -N(R₁₀,R_{10'}),
 wherein R₁₀ and R_{10'}, together form a -C₂-C₆-alkylene group such that a ring is
 formed, wherein such ring is optionally substituted with one or more groups selected
 from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and
 -N(C₀-C₃-alkyl)-SO₂-C₁-C₃-alkyl;

15 or wherein R₅ is a group of the structure -N(R₁₁,R_{11'}),
 wherein R₁₁ and R_{11'}, together form a -C₂-C₆-alkylene group such that a ring is
 formed, in which one or two carbon centers may optionally be replaced by one or two
 hetero atoms selected from among N, O, and S,

20 wherein such ring is optionally substituted by one or more groups on one ring atom or
 on two neighbouring ring atoms selected from among -OH, -NH₂, -C₁-C₃-alkyl,
 -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, =O, and halogen;

or wherein R₅ is a group of the structure -L₁-R₁₃,
 25 wherein L₁ is selected from among -NH- and -N(C₁-C₄-alkyl)-,
 wherein R₁₃ is -C₃-C₈-heterocyclyl,
 wherein R₁₃ is optionally substituted by one or more groups selected from among
 halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl;

30 wherein R₆ is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen,
 -CN, -CF₃, and -OCF₃;

as well as in form of their acid addition salts with pharmacologically acceptable acids.

35 2. The compounds of claim 1,
 wherein R₁ is a group selected from among -H, -halogen, -C₁-C₄-alkyl, -CF₃, -OCF₃,
 and -C₆-heteroaryl comprising a N atom;

wherein R₇ is a group selected from among -H, -halogen, -C₁-C₄-alkyl, -CF₃, -OCF₃, and -C₆-heteroaryl comprising a N atom;

wherein R₄ denotes -hydrogen.

- 5 3. The compounds of claim 1,
wherein R₇ and R₁ on two neighbouring ring atoms together form a -C₄-alkenylene group, such that an annellated aromatic ring is formed, in which one or two carbon centers may optionally be replaced by 1 or 2 hetero atoms selected from N;
wherein R₄ is a group selected from among -hydrogen, and -C₁-C₃-alkyl.
- 10 4. The compounds of any of the preceding claims,
wherein A denotes N.
5. The compounds of any of the preceding claims,
15 wherein A denotes C.
6. The compounds of any of the preceding claims, wherein R₂ is selected from among -H, -C₁-C₄-alkyl, and -O-C₁-C₄-alkyl.
- 20 7. The compounds of any of the preceding claims,
wherein R₂ is selected from among -Methyl, and -OCH₃.
8. The compounds of any of the preceding claims,
wherein R₃ denotes -hydrogen.
- 25 9. The compounds of any of the preceding claims,
wherein n is 2.
10. The compounds of any of the preceding claims,
30 wherein G and E are N.
11. The compounds of any of the preceding claims,
wherein R₅ is a group of the structure -N(R₁₀,R_{10'}),
wherein R₁₀ and R_{10'}, together form a -C₄-alkylene group such that a ring is formed,
35 wherein such ring is optionally substituted with one or more groups selected from among -N(C₀-C₃-alkyl)-SO₂-C₁-C₃-alkyl;
- or wherein R₅ is a group of the structure -L₁-R₁₃,
wherein L₁ denotes -NH-,

wherein R₁₃ is -C₆-heterocyclyl comprising an O atom,
wherein R₁₃ is optionally substituted by a group selected from among -O-C₁-C₄-alkyl.

- 5
12. The compounds of any of the preceding claims, wherein R₆ is -H.
13. The compounds of any of the preceding claims, wherein R₁₄ is -H.
14. Use of a compound according to any of the preceding claims as a medicament.
- 10 15. Use of a compound of any of claims 1-13 for making a medicament for the treatment of inflammatory diseases.
16. Use according to claim 15, wherein the inflammatory diseases are selected from inflammatory diseases of the respiratory tract.
- 15
17. Use according to claim 16, wherein the diseases are selected from chronic obstructive pulmonary disease, asthma, and cystic fibrosis.
18. Use of a compound of any of claims 1-13 for making a medicament for the treatment of neurologic diseases, preferably for the treatment of pain diseases especially for the treatment of inflammatory and neuropathic pain disease.
- 20
19. Use of a compound of any of claims 1-13 for making a medicament for the treatment of immune related diseases, preferably for the treatment of diabetes mellitus.
- 25
20. Use of a compound of any of claims 1-13 for making a medicament for the treatment of cardiovascular diseases, preferably for the treatment of peripheral atherosclerotic disease.
- 30 21. Use of a compound of any of claims 1-13 for making a medicament for the treatment of diabetic nephropathy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/057550

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D401/06 C07D401/14 C07D405/14 A61P29/00
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
 EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/318467 A1 (ADAM JEAN-MICHEL [FR] ET AL) 24 December 2009 (2009-12-24) the whole document	1-21
A	CARTER P H ET AL: "Advances in the Discovery of CC Chemokine Receptor 2 Antagonists", ANNUAL REPORTS IN MEDICINAL CHEMISTRY, ELSEVIER INC LNKD- DOI:10.1016/S0065-7743(07)42014-0, vol. 42, 1 January 2007 (2007-01-01), pages 211-228, XP008106396, ISBN: 978-0-12-373912-4 [retrieved on 2007-11-07] the whole document	1-21

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 10 June 2011	Date of mailing of the international search report 28/06/2011
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Stroeter, Thomas
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/057550

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