

CYCLIC PYRIMIDIN-4-CARBOXAMIDES AS CCR2 RECEPTOR ANTAGONISTS FOR TREATMENT OF INFLAMMATION, ASTHMA AND COPD

Field of invention

The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2) 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 cardiovascular diseases, especially atherosclerotic disease.

Background of the invention

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.

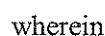
Chemokine receptors, such as CCR2 or CCR5 have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Accordingly, agents which modulate chemokine receptors such as the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

In particular it is widely accepted that numerous conditions and diseases involve 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 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 move towards an inflammation area for conversion into macrophages.

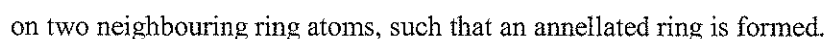
Based on the aforesaid there is a need for providing effective antagonists for CCR2, which are pharmacologically acceptable.

In a first aspect, there is provided compounds according to formula (I),



wherein L₁ if different from a bond is optionally substituted with one or more groups selected from among methyl, and ethyl.

or wherein the ring R₇ is bi-valently substituted by one or more groups selected from among



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

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

wherein R₄ and R₅ are independently selected from among an electron pair, -H, and a group selected from among -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H, and -C₁-C₆-alkyl,

and wherein R₄ and R₅ if different from an electron pair or -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}), -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),

wherein Q is selected from among -C(O)-, and -SO₂-,

wherein R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

wherein R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a -C₂-C₆-alkylene group,

wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,

and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl,

or wherein R₄ and / or R₅ are independently a group of the structure -L₂-R₁₈,

wherein L₂ is selected from among -NH- and -N(C₁-C₄-alkyl)-,

wherein R₁₈ is selected from among -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl,

wherein R₁₈ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl, -NH-C(O)-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-C(O)-C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, -NH-S(O)₂-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-S(O)₂-C₁-C₆-alkyl, and -C(O)-O-C₁-C₆-alkyl,

and wherein R₄, R₅ and R₁₈ are optionally further substituted by spiro-C₃-C₈-cycloalkyl or spiro-C₃-C₈-heterocyclyl such that together with R₄, R₅ and/or R₁₈ a spirocycle is formed, wherein said spiro-C₃-C₈-heterocyclyl optionally comprises one or more groups selected from among nitrogen, -C(O)-, -SO₂-, and -N(SO₂-C₁-C₄-alkyl)- in the ring,

or wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be 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, and halogen;

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

wherein A is selected from among a single bond, -CH₂-, -O-, -S-, and -NH-;

wherein n is 1, 2 or 3;

wherein Z is C or N,

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

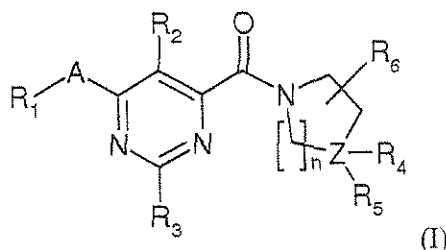
In a second aspect, there is provided a compound as defined herein for use as a medicament.

In a third aspect, there is provided the compound as defined herein for use in the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.

In a fourth aspect, there is provided the use of the compound as defined herein in the manufacture of a medicament for the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.

Description of the invention

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



wherein R₁ is -L₁-R₇,

wherein L₁ is a linker selected from a bond or a group selected from -C₁-C₂-alkylene, and -C₁-C₂-alkenylene which optionally comprises one or more groups selected from -O-, -C(O)-, and -NH- in the chain and which is optionally substituted by a group selected from among -OH, -NH₂, -C₁-C₃-alkyl, O-C₁-C₆-alkyl, and -CN,

wherein R₇ is a ring selected from among -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, and -C₅-C₁₀-heteroaryl,

wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, and -halogen,

or wherein the ring R₇ is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₁-C₆-alkenyl, and -C₁-C₆-alkynyl, optionally being further substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O,

or wherein the ring R₇ is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by 1 or 2 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;

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

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

R₄ and R₅ are independently selected from among an electron pair, -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H and -C₁-C₆-alkyl,

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wherein R₄ and R₅ if different from an electron pair or -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R₉'), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R₁₁'), -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R₁₃'), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R₁₅'), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇)

20 wherein Q is selected from among -C(O)- and -SO₂-

wherein R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

25 wherein R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₃, R₁₃', R₁₅, R₁₅' are independently selected from among -H and -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R₉', R₁₁ and R₁₁', R₁₃ and R₁₃', R₁₅ and R₁₅', together form a -C₂-C₆-alkylene group, preferably a -C₅-C₆-alkylene group,

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wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring, and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl,

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or wherein R₄ and / or R₅ are independently a group of the structure -L₂-R₁₈,

wherein L₂ is selected from among -NH-, and -N(C₁-C₄-alkyl)-,

wherein R_{18} is selected from among $-C_5-C_{10}$ -aryl, $-C_5-C_{10}$ -heteroaryl, $-C_3-C_8$ -cycloalkyl, and $-C_3-C_8$ -heterocyclyl,

- 5 wherein R_{18} is optionally substituted by one or more groups selected from among halogen, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-C_1-C_4$ -alkyl, $-C_1-C_6$ -alkyl, $-NH-C(O)-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -alkyl)- $C(O)-C_1-C_6$ -alkyl, $-C(O)-C_1-C_6$ -alkyl, $-S(O)_2-C_1-C_6$ -alkyl, $-NH-S(O)_2-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -alkyl)- $S(O)_2-C_1-C_6$ -alkyl, and $-C(O)-O-C_1-C_6$ -alkyl,
- 10 and wherein R_4 , R_5 and R_{18} are optionally further substituted by spiro- C_3-C_8 -cycloalkyl or spiro- C_3-C_8 -heterocyclyl such that together with R_4 , R_5 and/or R_{18} a spirocycle is formed, wherein said spiro- C_3-C_8 -heterocyclyl optionally comprises one or more groups selected from among nitrogen, $-C(O)-$, $-SO_2-$, and $-N(SO_2-C_1-C_4$ -alkyl)- in the ring, or wherein R_4 , R_5 and R_{18} are optionally further bi-valently substituted by one or more
- 15 spirocyclic or annellated ring forming groups selected from among $-C_1-C_6$ -alkylene, $-C_2-C_6$ -alkenylene, and $-C_4-C_6$ -alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among $-OH$, $-NH_2$, $-C_1-C_3$ -alkyl, $O-C_1-C_6$ -alkyl, $-CN$, $-CF_3$, $-OCF_3$, and
- 20 halogen;

R_6 is selected from among $-H$, $-C_1-C_4$ -alkyl, $-OH$, $-O-C_1-C_4$ -alkyl, $-halogen$, $-CN$, $-CF_3$, and $-OCF_3$;

- 25 A is selected from among a single bond, $=CH-$, $-CH_2-$, $-O-$, $-S-$, and $-NH-$;

n is 1, 2 or 3;

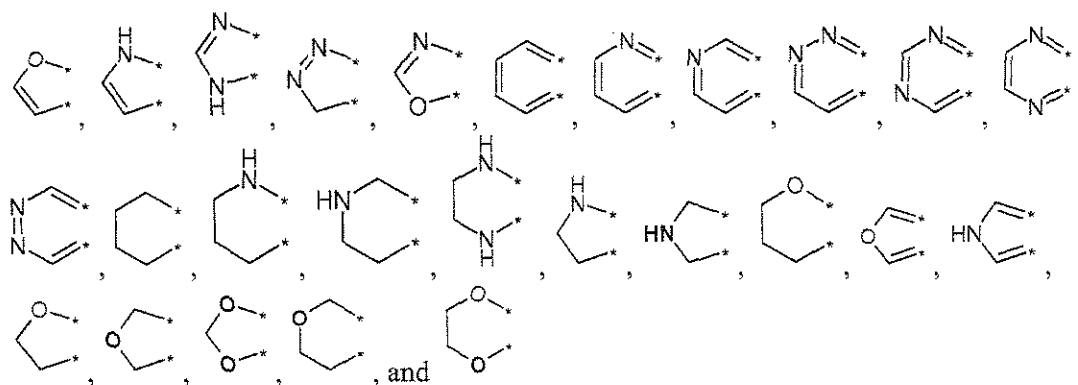
Z is C or N,

- 30 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.

- Preferred compounds of formula (I) according to the invention are compounds with R_2 , R_3 ,
 35 R_4 , R_5 , R_6 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A, L₂, Z, Q, and n as herein before or below defined, wherein R_1 is $-L_1-R_7$,

with L_1 being a linker selected from a bond or a group selected from among $-C_1-C_2$ -alkylene, and $-C_1-C_2$ -alkenylene optionally comprising one or more groups selected from among $-O-$, -

- C(O)-, and, -NH- in the chain and optionally being substituted by a group selected from among -OH, -NH₂, -C₁-C₃-alkyl, O-C₁-C₆-alkyl, and -CN, wherein R₇ is a ring selected from among -C₃-C₈-cycloalkyl, -C₅-C₁₀-aryl, -C₃-C₈-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O, and -C₅-C₁₀-heteroaryl comprising 1 or 2 hetero atoms selected from among N, and O,
- wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, and -halogen,
- or wherein the ring R₇ is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₁-C₆-alkenyl, and -C₁-C₆-alkynyl, optionally being substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O,
- or wherein the ring R₇ is optionally further bi-valently substituted by one or more annellated ring forming groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by 1 or 2 hetero atoms selected from N, and O, wherein the bivalent group is optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;
- Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, A, L₂, Z, Q, and n as herein before or below defined, wherein R₁ is -L₁-R₇,
- wherein L₁ is a linker selected from among a bond, methylene, ethylene, methenylene, and ethenylene,
- wherein L₁, if different from a bond, is optionally substituted with one or more groups selected from among methyl, and ethyl,
- wherein R₇ is a ring selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, pyrrolidinyl, piperidinyl, azepanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, phenyl, pyridyl, and furanyl,
- wherein the ring R₇ is optionally substituted with one or more groups selected from among -F, -Cl, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -t-butyl, -CF₃, -O-CF₃, -CN, -O-methyl, -furanyl and -phenyl, wherein said furanyl and said phenyl are optionally independently substituted by one or more groups selected from among -C₁-C₆-alkyl, or halogen, -OCH₃, -CF₃, and -OCF₃.
- or wherein R₇ is bi-valently substituted by one or more groups selected from among



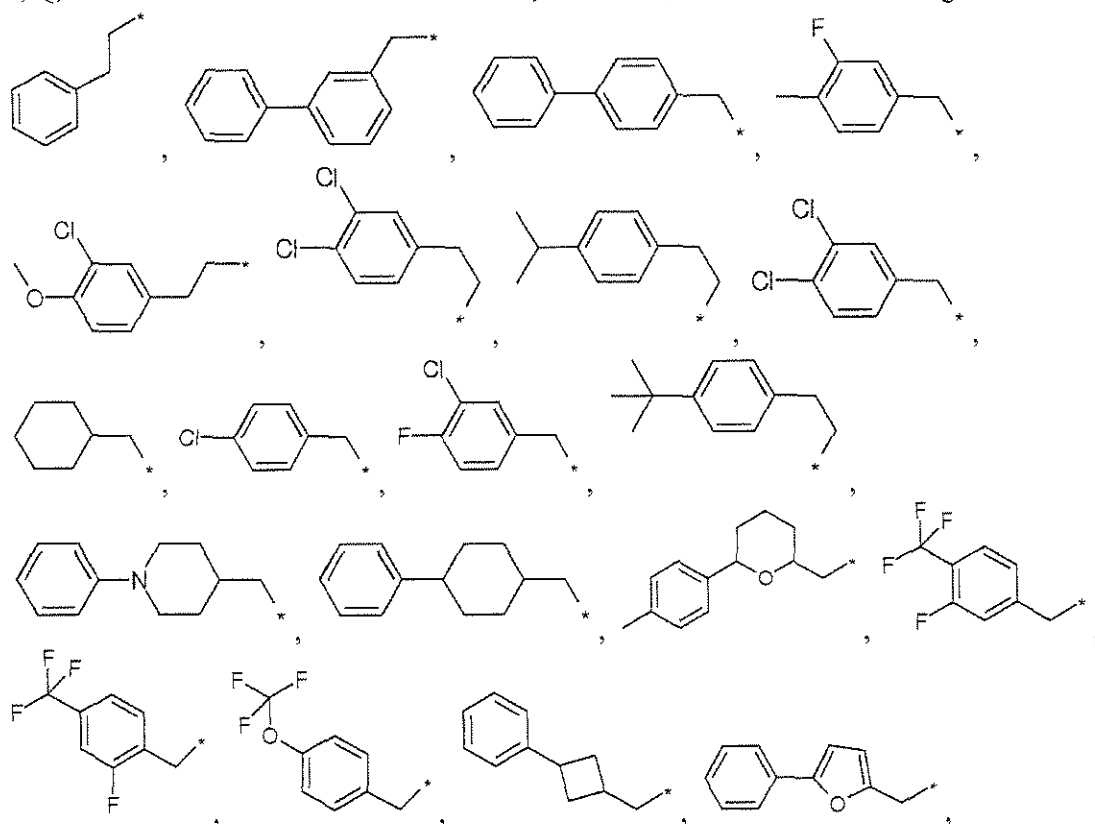
on two neighbouring ring atoms, such that an annellated ring is formed.

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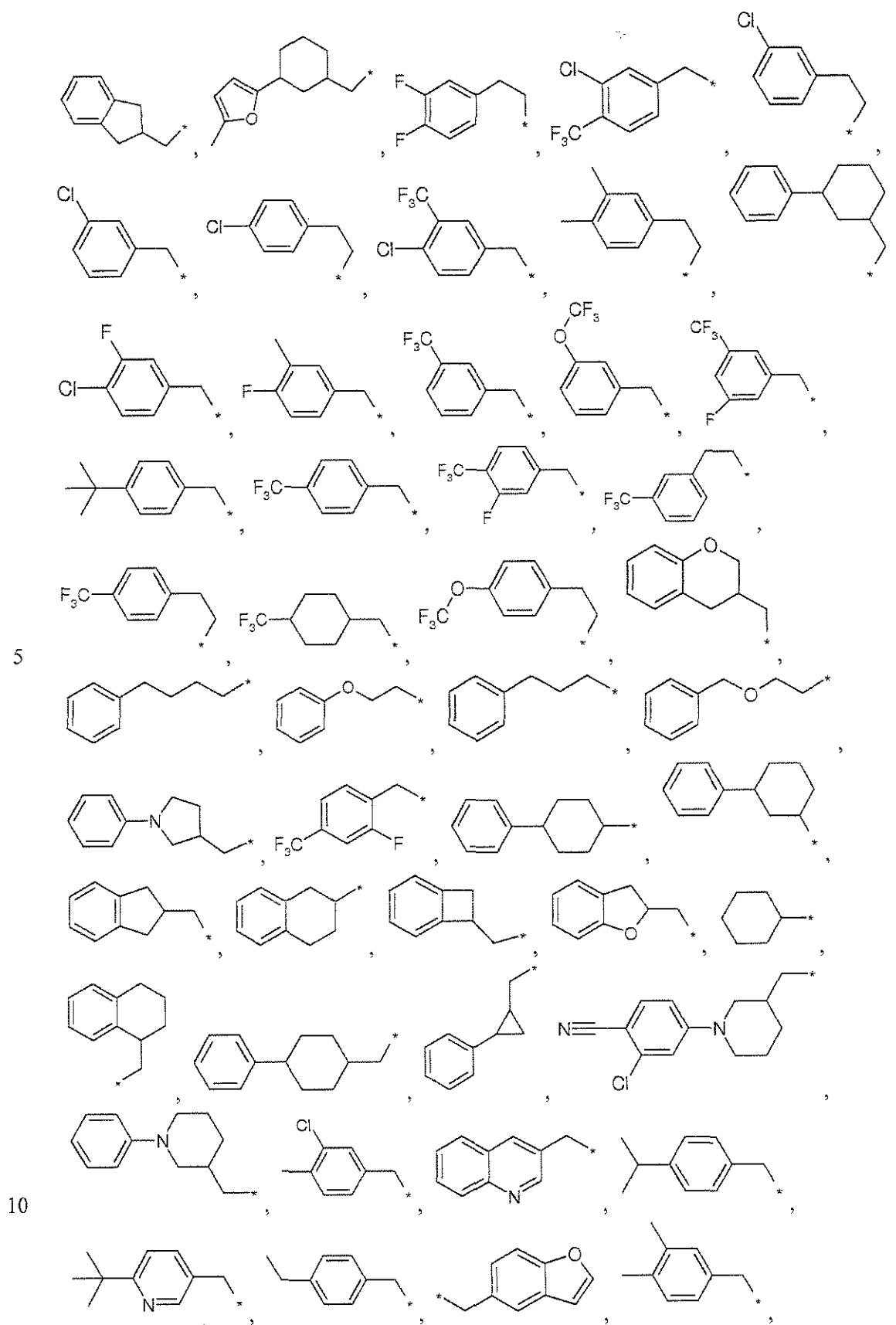
Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, A, L₂, Z, Q, and n as herein before or below defined, wherein R₁ is -L₁-R₇,

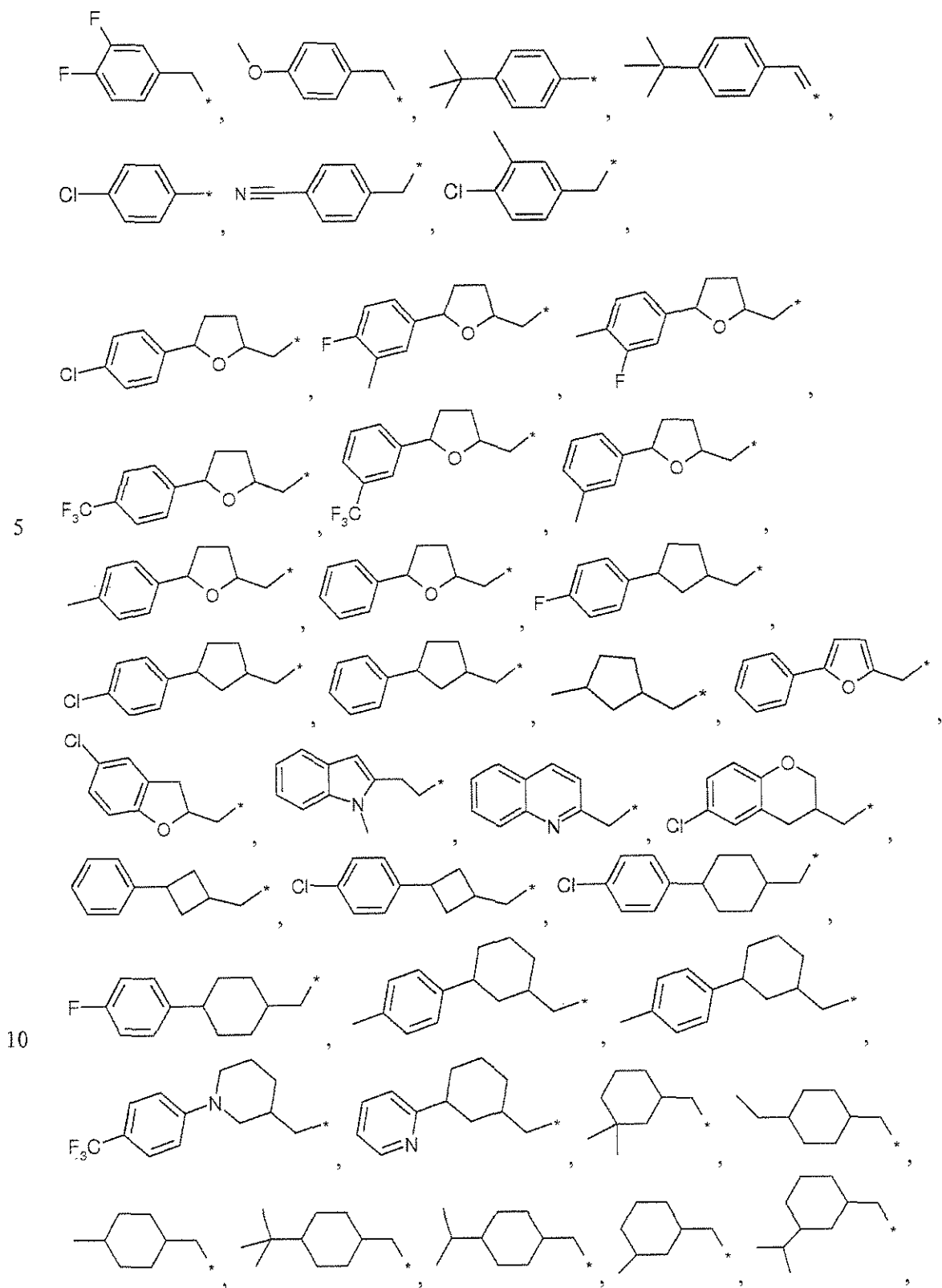
and wherein L₁ is a linker selected from among a bond, methylene, ethylene, methenylene,
10 and ethenylene and wherein L₁ is optionally substituted with one or more of methyl or ethyl
and wherein L₁ optionally comprises one or more -O- atoms.

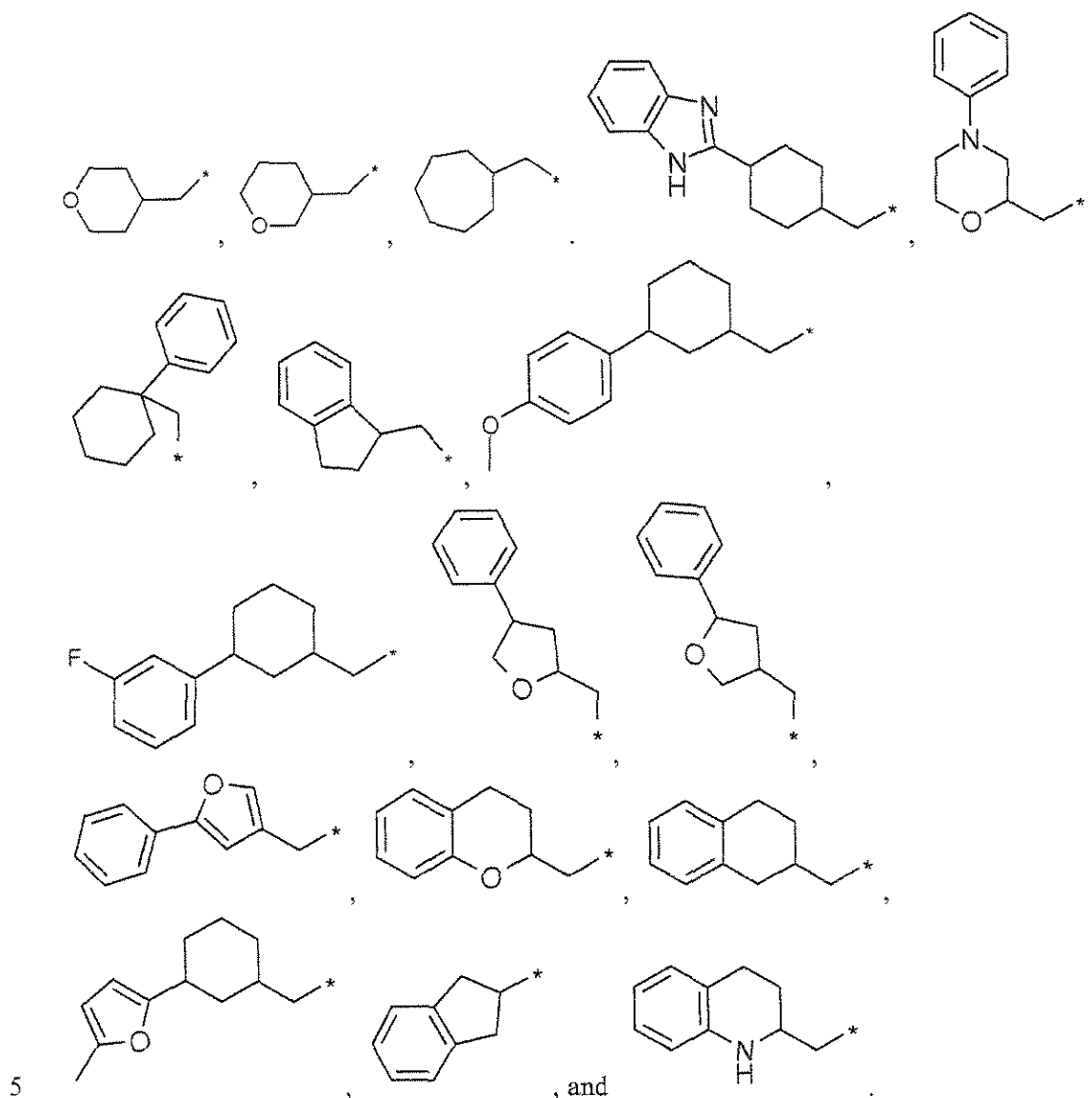
Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, A, L₂, Z, Q, and n as herein before or below defined, wherein R₁ is selected from among



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- Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH₂, -C≡CH, and -OCH₃, more preferred from among H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, and -OCH₃.
- 15 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_2 is selected from among -H, -Methyl, -Ethyl, -Br, and -OCH₃.

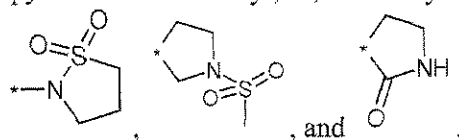
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_3 is selected from among -H, and

5 -methyl.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_4 and R_5 are independently selected from

10 among an electron pair, -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8 , R_8'), with R_8 and R_8' independently being selected from among -H and -C₁-C₆-alkyl,

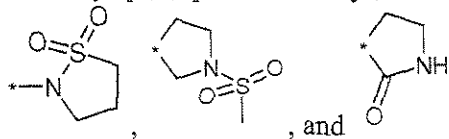
wherein R_4 and R_5 are optionally independently substituted with one or more groups selected

15 from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃,20 -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅,25 -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -phenyl,30 -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, -3-methyl-[1,2,4]oxadiazol-5-yl,

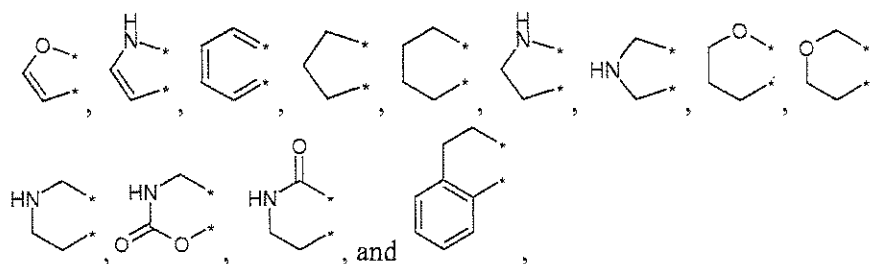
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,

35 R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_4 and R_5 are independently selected from among an electron pair, -H, -amino, -piperidinyl, -tetrahydropyranyl, and -pyrrolidinyl,

- wherein R_4 and R_5 are optionally independently substituted with one or more groups selected from among -fluoro, -CF₃, -hydroxy, -O-CH₃, -OCF₃, -CN, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₃H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl,
- 15 -3-methyl-[1,2,4]oxadiazol-5-yl,



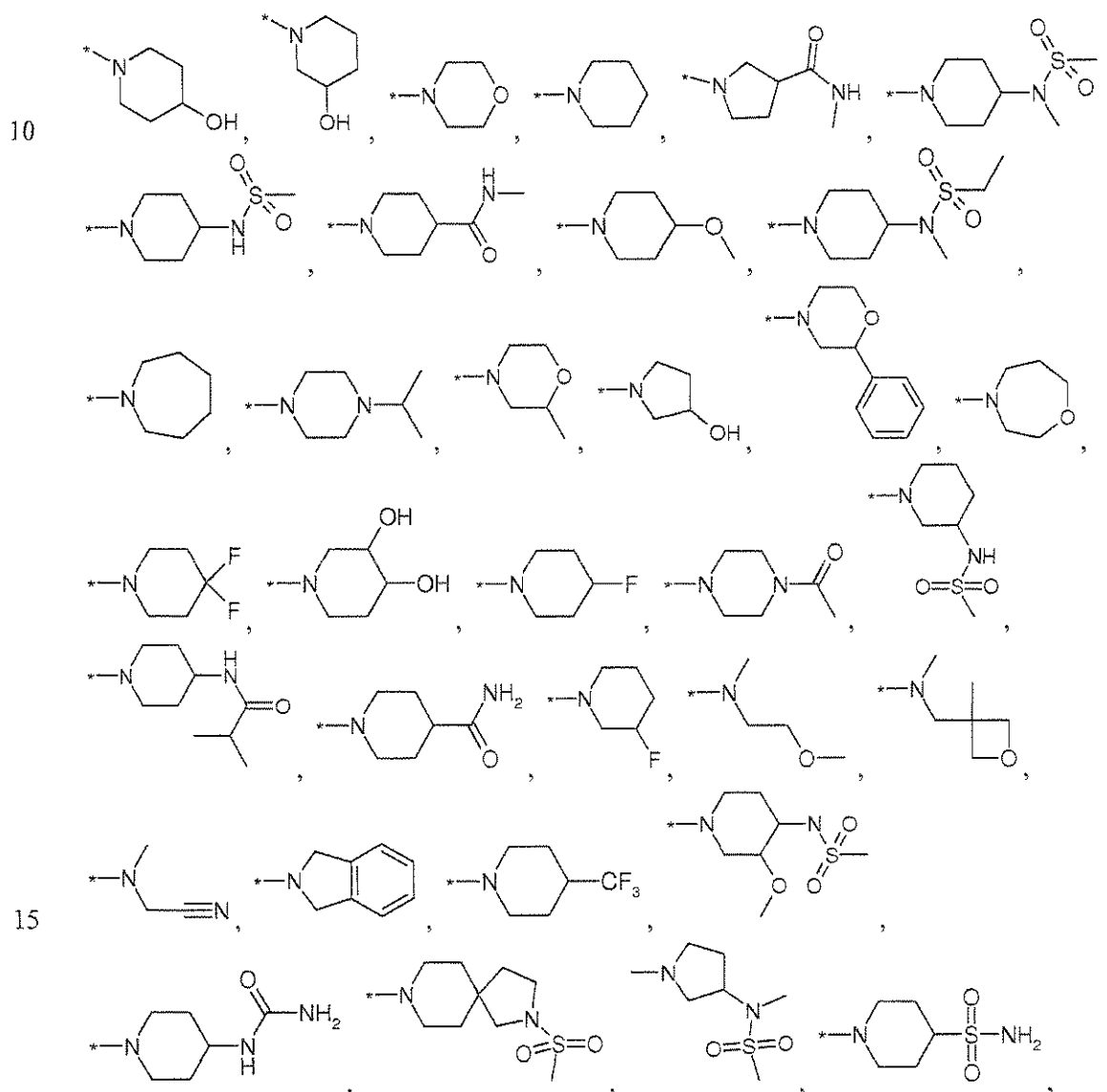
- Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , A , L_1 , Z , Q , and n as herein before or below defined, wherein R_4 and R_5 are independently a group of the structure -L₂-R₁₈, wherein L₂ is selected from among -NH-, -N(CH₃)- and -N(C₂H₅)-, wherein R₁₈ is selected from among -tetrahydropyranyl-, -cyclopropyl-, -cyclobutyl-, -cyclopentyl-, -cyclohexyl-, -cycloheptyl-, -cyclooctyl-, -pyrrolidinyl-, -piperidinyl-, -piperazinyl-, -morpholinyl-, -chromanyl-, -octahydro-pyrano-pyrrolyl-, -octahydro-pyrano-pyridinyl-, -octahydro-pyrano-oxazinyl-, -oxaspirodecanyl-, and -tetrahydro-naphthyridinyl, wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, and -C(O)-O-C₂H₅.
- 30 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_4 , R_5 and R_{18} are optionally further bi-valently substituted by one or more groups selected from among



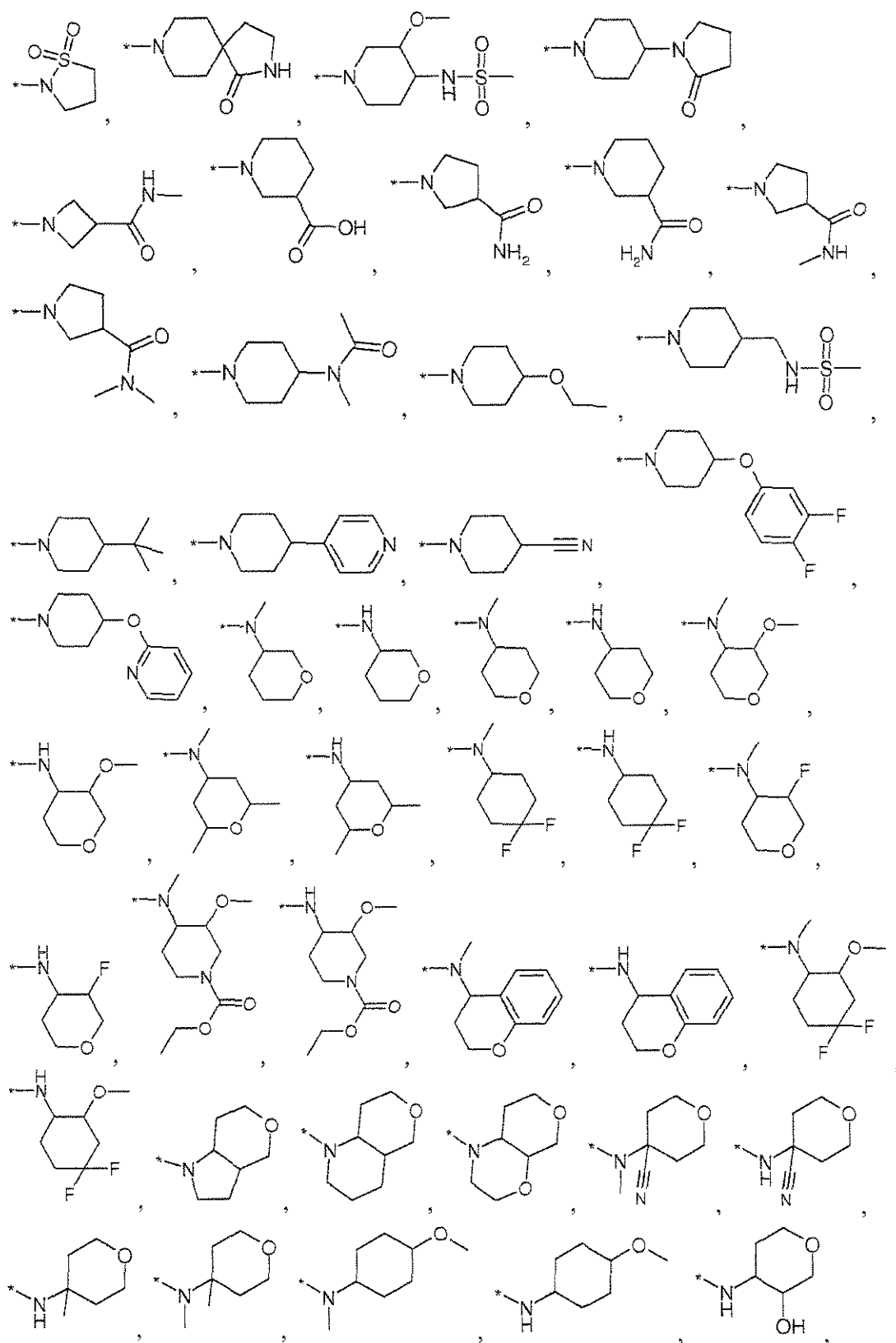
on one ring atom or on two neighboring ring atoms, such that spirocyclic or annellated rings are formed.

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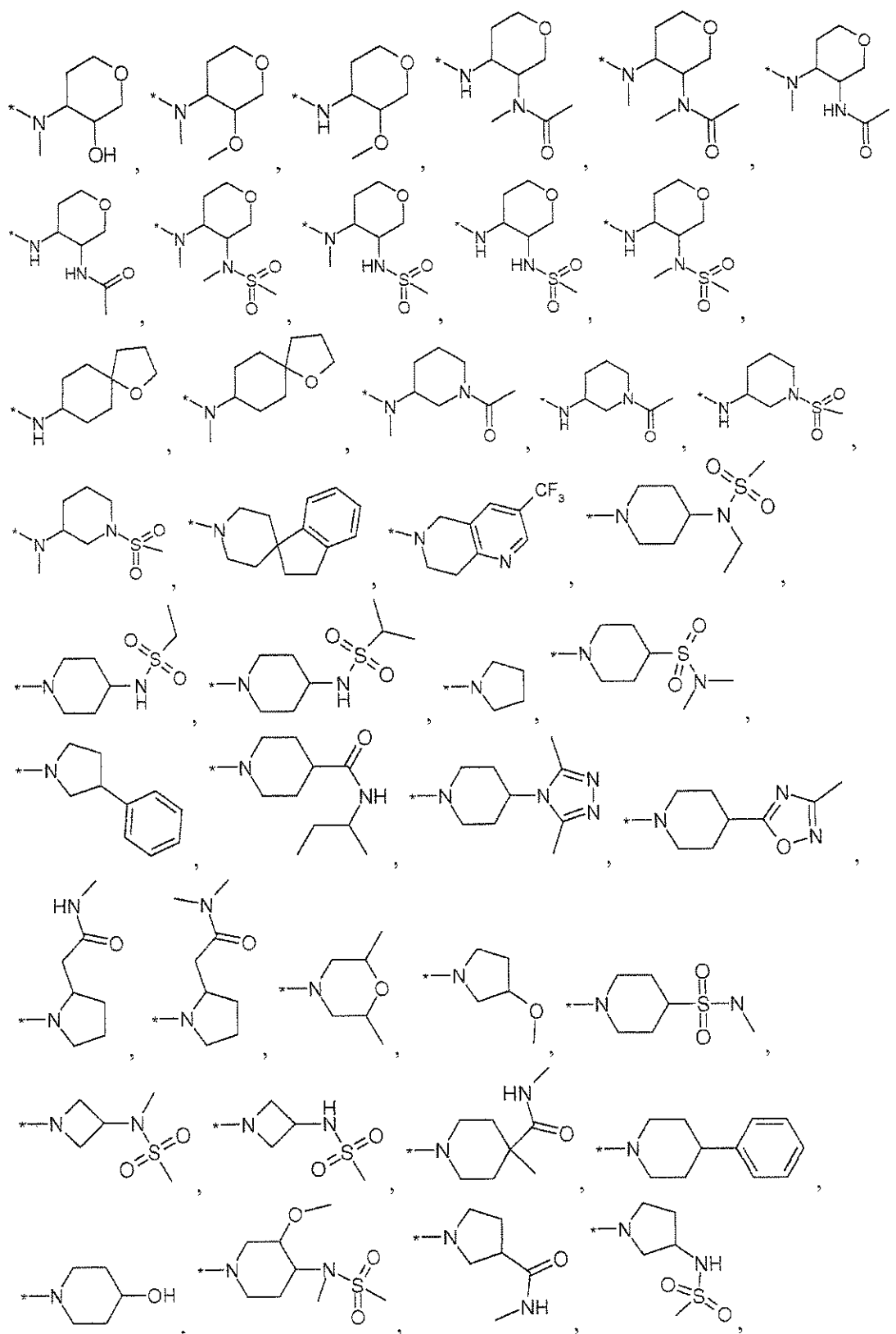
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Z , Q , and n as herein before or below defined, wherein R_4 is selected from among

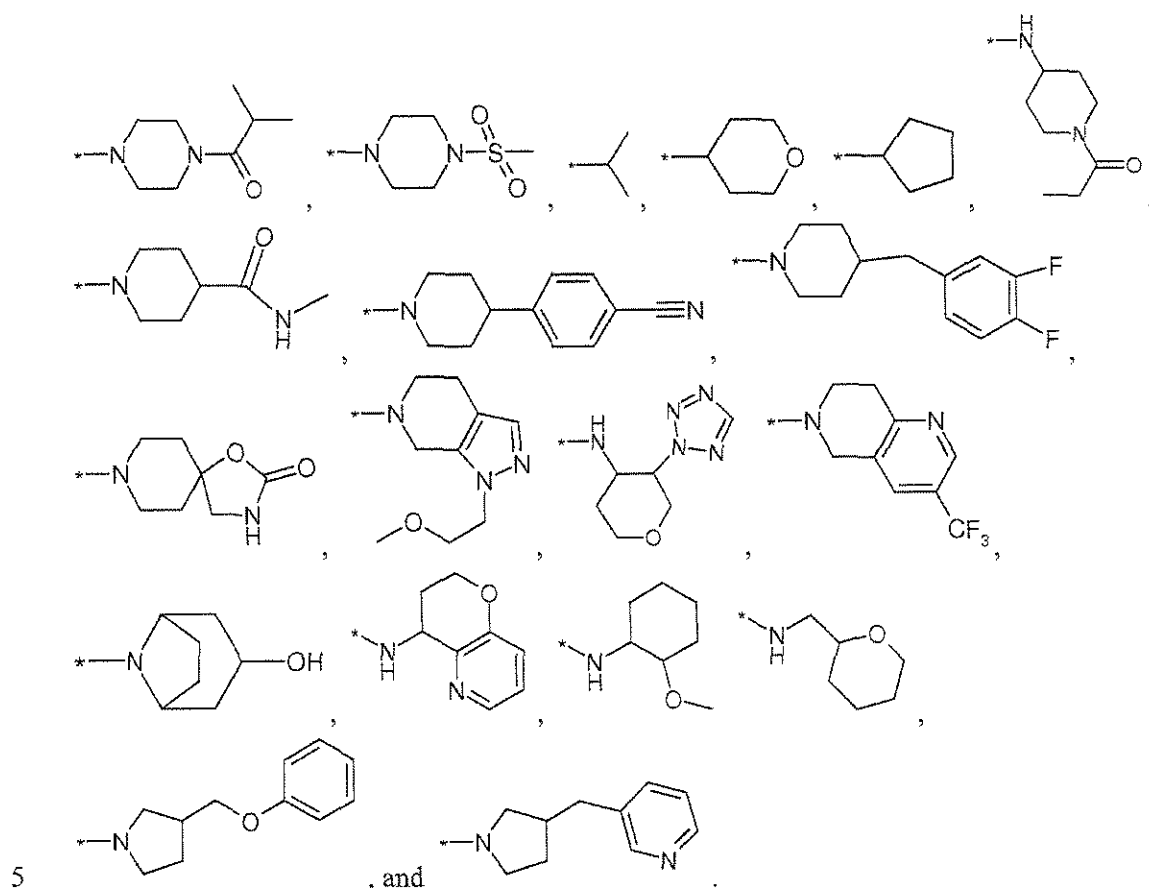


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Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, A, L₁, L₂, Z, Q, and n as herein before or below defined, wherein R₅ is selected from among an electron pair, -H, and -C(O)-NH₂.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, A, L₁, L₂, Z, Q, and n as herein before or below defined, wherein R₆ is selected from among -H, -CH₃, -C₂H₅, -O-CH₃, -O-C₂H₅, -F, -CF₃, and -OCF₃, and more preferred wherein R₆ is selected from among H. and -O-CH₃, and most preferred wherein R₆ is -H.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, L₁, L₂, Z, Q, and n as herein before or below defined, wherein A is selected from among a single bond, =CH-, -CH₂-, -O-, and -NH-, and more preferred wherein A is selected from among -O- and -NH-, and most preferred wherein A is -NH-.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , A , L_1 , L_2 , Q , and n as herein before or below defined, wherein Z is selected from among C , and N , and more preferred wherein Z is C .

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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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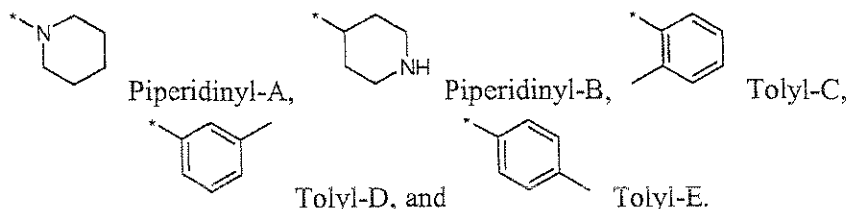
Definitions

Unless otherwise stated, all the substituents are independent of one another. If for example there might be a plurality of C_1 - C_6 -alkyl groups as substituents in one group, in the case of three substituents C_1 - C_6 -alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

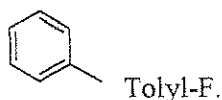
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Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking 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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By the term "branched or unbranched, saturated or unsaturated C_1 - C_6 -carbon chain" it is meant a chain of carbon atoms, which is constituted by six 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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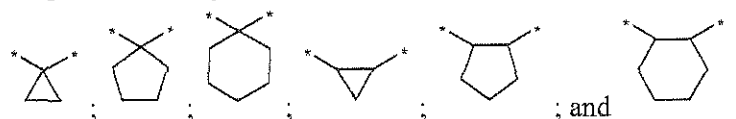
By the term "C₁-C₆-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C₁-C₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms.

- 5 Alkyl groups with 1 to 4 carbon atoms are preferred. Examples for alkyl groups with 1-6 carbon atoms include: methyl, ethyl, *n*-propyl, *iso*-propyl, *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
10 forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

- By the term "C₁-C₈-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 8 carbon atoms. By the term
15 "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 "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 "C₀-C₄-alkylene" are
20 meant branched and unbranched alkylene groups with 0 to 4 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,
25 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.

30

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:



35

By the term "C₂-C₆-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term

"C₂-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 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 a single bond as well as on the other side 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 alkylene groups with 2 to 6 carbon atoms. 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" 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.

By the term "C₂-C₆-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term "C₂-C₄-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 C₂-C₆-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.

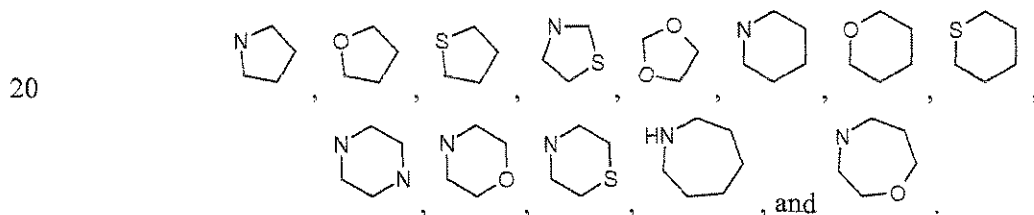
By the term "C₂-C₈-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 8 carbon atoms and by the term "C₂-C₆-alkynylene" are meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. Examples of C₂-C₈-alkynylenes include: 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, pentynylene and

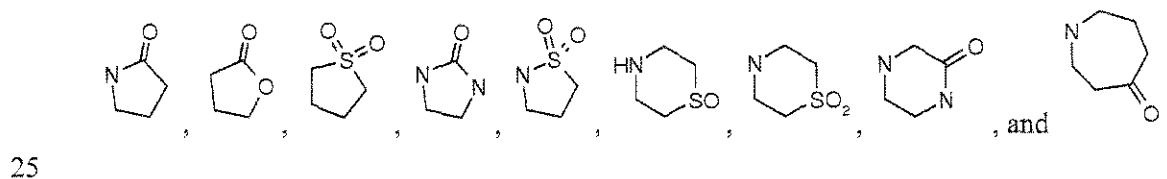
- 5 hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1, 1-dimethylethynylene, 1, 2-dimethylethynylene.

- 10 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.

- By the term "-C₃-C₈-heterocyclyl" are meant three-, four-, five-, six-, or seven-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
- 15 molecule through a carbon atom or through a nitrogen atom, if there is one. By the term "-C₅-C₈-heterocyclyl" are meant five-, six-, or seven-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. Examples include:



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

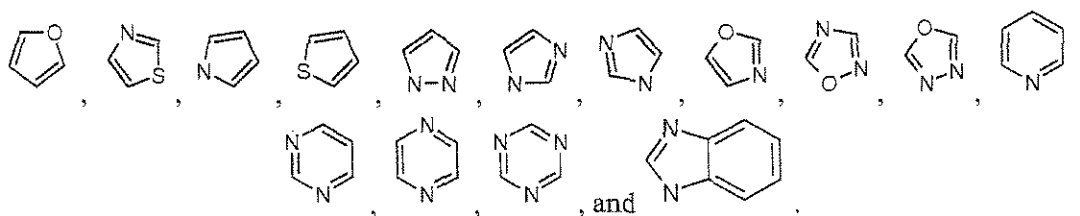


- By the term "C₃-C₈-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 8 carbon atoms. Likewise, by the term "C₃-C₆-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples of C₃-C₈-cycloalkyls include:
- 30 cyclopropyl, cyclobutyl, 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.

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.

- 5 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.

- 10 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:

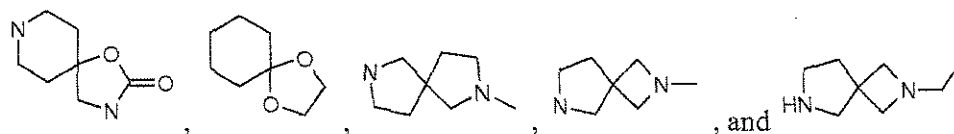


Preferred are "C₅-C₆-heteroaryl" groups whereas aromatic rings are meant five- or six-membered heterocyclic aromatic groups. Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, 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. By the term "spiro-C₃-C₈-heterocyclyl" (spiro) are meant 3-8 membered, 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 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, if R is hydrogen, the compound of formula (I) 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.

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 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , $R_{9'}$, R_{10} , R_{11} , $R_{11'}$, R_{12} , R_{13} , $R_{13'}$, R_{14} , R_{15} , $R_{15'}$, R_{16} , R_{17} , R_{18} , A, L₁, L₂, Z, Q, and n in each case are independently selected of one another.

Therapeutic applications

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

Cell culture:

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).

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 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.

15 **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.

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 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 hK_i) 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).

All of the above-referenced examples have been found to have an activity in this assay of 10 µM or less.

Example	hKi	CCR2 % ctrl @ 10 μ M
1	32	1
2	222	13
3	204	14
4	1593	43
5	616	26
6	1928	41
7	306	16
8	1023	36
9	974	32
10	650	27
11	1710	38
12	664	29
13	1332	42
14	387	22
29	2097	40
30	446	18
31	790	28
32	37	2
33	22	0
34	62	4
35	24	5
36	10	1
37	11	4
38	69	13
39	36	2
40	174	9
41	11	6
42	433	16
43	566	17
44	1639	27
45	501	17
46	225	12
47	222	14
48	1778	26
49	97	7

Example	hKi	CCR2 % ctrl @ 10 μ M
15	200	14
16	1904	40
17	302	18
18	3505	52
19	269	40
20	303	24
21	2660	51
22	466	24
23	169	7
24	4029	58
25	2406	47
26	914	30
27	620	25
28	4176	58
59	55	5
60	44	5
61	46	2
62	38	3
63	54	7
64	65	8
65	176	8
66	138	8
67	1423	27
68	98	7
69	63	7
70	80	6
71	117	12
72	81	7
73	38	2
74	71	2
75	67	7
76	132	12
77	650	27
78	740	28
79	89	10

Example	hKi	CCR2 % ctrl @ 10 μ M
50	928	22
51	290	13
52	175	12
53	18	4
54	356	13
55	200	17
56	127	8
57	93	10
58	336	12
89	770	29
90	127	10
91	236	23
92	175	14
93	123	6
94	211	8
95	170	2
96	939	21
97	665	17
98	214	2
99	1826	32
100	395	18
101	986	35
102	224	15
103	1605	30
104	617	31
105	687	31
106	405	13
107	232	12
108	627	20
109	213	11
110	527	28
111	464	27
112	378	21
113	3306	46
114	62	8
115	847	33

Example	hKi	CCR2 % ctrl @ 10 μ M
80	53	7
81	52	8
82	43	4
83	43	3
84	69	4
85	55	13
86	39	3
87	78	9
88	58	6
119	1033	37
120	499	30
121	147	15
122	415	23
123	542	26
124	361	20
125	446	25
126	399	23
127	665	35
128	445	26
129	336	21
130	4266	50
131	55	6
132	672	31
133	205	15
134	399	23
135	888	19
136	773	14
137	634	14
138	145	6
139	443	9
140	692	16
141	422	7
142	529	8
143	422	8
144	91	7
145	181	17

Example	hKi	CCR2 % ctrl @ 10 μ M
116	198	16
117	285	19
118	2162	41
149	41	10
150	12	3
151	14	7
152	44	7
153	27	1
154	123	15
155	76	8
156	18	8
157	1147	23
158	6	0
159	25	4
160	43	3
161	1996	30
162	3798	43
163	1560	32
164	353	15
165	222	15
166	227	16
167	246	16
168	51	9
169	2287	54
170	705	31
171	356	16
172	736	28
173	89	6
174	2718	53
175	434	14
176	648	31
177	1252	43
178	27	0

Example	hKi	CCR2 % ctrl @ 10 μ M
146	3	7
147	40	8
148	119	4
179	1637	42
189	4812	60
181	3607	58
182	2991	53
183	426	45
184	908	30
185	4209	53
186	78	8
187	256	15
188	3934	53
189	170	13
190	783	27
191	519	20
192	1446	37
193	1536	35
194	491	25
195	141	14
196	666	19
197	33	4
198	58	1
199	534	9
200	108	5
201	101	6
202	292	7
203	641	11
204	123	6
205	135	11
206	44	3
207	1180	35
208	99	7

Example	hKi	CCR2 % ctrl @ 10 μ M
209	177	7
210	83	0
211	140	5
212	731	24
213	430	14
214	711	20
215	2146	42
216	4283	59
217	4326	54
218	281	8
219	476	22
220	979	27
221	172	12
222	1306	31
223	244	14
224	1230	35
225	21	0
226	1170	36
227	333	22
228	331	16
229	1133	39
230	1845	45
231	215	15
232	924	34
233	194	8
234	401	19
235	460	26
236	175	14
237	133	9
238	239	14
228a	1564	9
228b	2	4
228c	29	0
228d	91	1

Example	hKi	CCR2 % ctrl @ 10 μ M
239	2319	33
240	104	7
241	522	21
242	516	21
243	1615	40
244	366	24
245	555	15
246	306	2
247	149	6
248	576	17
249	3249	36
250	1263	32
251	439	75
252	38	6
253	350	17
254	101	11
255	33	5
256	438	25
257	186	14
258	64	4
259	277	16
260	493	20
261	120	8
262	224	13
263	1968	27
264	41	3
265	462	23
266	149	
267	487	20
268	119	5
228e	3720	40
228f	15	1
228g	169	6
228h	5	0

Example	hKi	CCR2 % ctrl @ 10 μ M
269	2340	36
270	179	9
271	1608	15
272	155	8
273	1435	27
274	4421	48
275	593	19
276	1842	23
277	1376	34
278	1078	32
279	192	9
280	1435	32
281	1012	24
282	1527	39
283	4421	48
284	1514	42
275a	29	0
275b	26	3

Example	hKi	CCR2 % ctrl @ 10 μ M
285	1306	35
286	965	19
287	2547	33
288	738	13
289	1667	34
290	1601	28
291	3123	32
292	136	15
293	717	27
294	230	16
295	140	0
296	69	3
297	164	10
298	599	17
299	70	6
300	136	8
275c	2932	38
275d	318	10

Example	hKi
228go	54
228gp	1354
228ga	23
228gb	3828
228gc	561
228gd	1094
228ge	37
228gf	145
228gg	1026
228gh	4066
228gi	1101
228gj	55
228gk	44
228gl	537
228gm	28
228gn	333
275da	4
275db	33
275dc	11
275dd	40
275de	16
275df	15
275dg	12
275dh	3
275di	1
275dj	4
159a	10
159b	7
159c	13
159d	15

Example	hKi
159e	28
159f	14
159g	15
159h	39
159i	24
159k	22
159l	22
159m	9
159n	233
159o	12
159p	7
159q	10
159r	2578
159s	1314
159t	1202
159u	29
159w	9
159y	169
159x	147
159z	11
159aa	18
159ba	11
159ca	3
159da	5
159ea	7
159fa	35
159ga	28
159ha	27
159ia	17
159ja	18

Example	hKi
159ka	19
159la	19
159ma	20
159na	21
159oa	29
159pa	32
159qa	19
159ra	22
159sa	22
159ta	27
159ua	23
159wa	33
159ya	18
159xa	21
159za	6
159ab	27
159bb	48
159cb	39
159db	16
159eb	72
159fb	199
159gb	39
159hb	20
159ib	15
159jb	39
159kb	24
159lb	12
159mb	14
159nb	88
159ob	118

Example	hKi
159pb	10
159qb	69
159rb	54
159sb	21
159tb	13
159ub	18
159wb	16
159yb	15
159xb	6
159zb	15
159ac	5936
159bc	3492
159cc	10
159dc	38
159ec	961
159fc	13
159gc	26
228ha	32
301	22
302	32
275dk	17
275dl	372

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

5 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,

10 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.

15 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:

20 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,

25 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

30 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.

35

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 IU 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, 5 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 10 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 asthma, anemia, cachexia, and the like), chronic salicylate intoxication, and the like.

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Cardiovascular Diseases

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac 25 stroke syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic arteriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, 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 25 inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, 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 30 disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, 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 CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation, 35 treatment or therapy.

Neurologic Diseases

The present invention also provides a method for modulating or treating at least one neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: Neuropathic pain such as low back pain, hip pain, leg pain, non-herpetic

5 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 sclerosis, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy, thalamic pain syndrome, post-

10 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

15 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 supra- nucleio Palsy; structural

20 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

25 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

30 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

35 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.

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, viral-associated hemaphagocytic syndrome, viral 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.

- 5 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.

Combinations

- 10 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
- 15 betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, MRP4-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof, such as for example combinations of compounds of formula I with one or two compounds selected from among
- betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists,
 - anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and

20 LTD4-antagonists,

 - PDE4-inhibitors, corticosteroids, EGFR-inhibitors and LTD4-antagonists
 - EGFR-inhibitors, PDE4-inhibitors and LTD4-antagonists
 - EGFR-inhibitors and LTD4-antagonists
 - CCR3-inhibitors, iNOS-inhibitors (inducible nitric oxide synthase-inhibitors), (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (hereinafter referred to as "BH4") and the derivatives

25 thereof as mentioned in WO 2006/120176 and SYK-inhibitors (spleen tyrosine kinase-inhibitors)
 - anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors and MRP4-inhibitors.
- The invention also encompasses combinations of three active substances, each selected from
- 30 one of the above-mentioned categories of compounds.

- The betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbutoleol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine,
- 35 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-dicethyl-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-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 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.

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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.

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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.

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

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

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

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

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Particularly preferred is the steroid selected from among flunisolide, beclomethasone, 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-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.

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

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

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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, Cl-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-

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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)-
 5 (+)-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
 10 pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Particularly preferably the PDE4-inhibitor is selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, CI-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-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
 20 pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the above-mentioned
 25 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,
 30 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.

The EGFR-inhibitors used are preferably compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-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-cyclopentylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino]-7-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)amino} methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{{4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{{4-(morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl} amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{{4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl} amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-

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

- phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-
 [(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-
 yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-
 yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-
 5 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-
 10 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-
 15 [(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-
 20 {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-
 25 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-
 30 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]-
 35 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-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, 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.

It is particularly preferable within the scope of the present invention to use those EGFR-inhibitors which are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-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-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-

- amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-
- 5 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,
- 10 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)-
- 15 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]-
- 20 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-
- 25 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-
- 30 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-
- 35 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.

Particularly preferred EGFR-inhibitors according to the invention are the 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-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-fluorophenyl)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.

5

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, dimenhhydrinate, 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
- 5 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,
- 10 taurochenodeoxycholate, taurocholate, taurodeoxycholate, tauroolithocholate, tauroolithocholic acid sulphate, topotecan, trequinsin and zaprinast, dipyrindamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.
- 15 Preferably the invention relates to the use of MRP4-inhibitors for preparing a pharmaceutical composition for the treatment of respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors, the MRP4-inhibitors preferably being selected from among N-acetyl-dinitrophenyl-cysteine, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-S-glutathione, estradiol 3,17-disulphate, flurbiprofen, glycocholate, glycolithocholic acid
- 20 sulphate, ibuprofen, indomethacin, indoprofen, lithocholic acid sulphate, MK571, PSC833, sildenafil, taurochenodeoxycholate, taurocholate, tauroolithocholate, tauroolithocholic acid sulphate, trequinsin and zaprinast, dipyrindamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.
- 25 The invention relates more preferably to the use of MRP4-inhibitors for preparing a pharmaceutical composition for treating respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors according to the invention, the MRP4-inhibitors preferably being selected from among dehydroepiandrosterone 3-sulphate, estradiol 3,17-disulphate,
- 30 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.) .
- 35 By acid addition salts with pharmacologically acceptable acids are meant, for example, salts selected from among the hydrochlorides, hydrobromides, hydroiodides, hydrosulphates, hydrophosphates, hydromethanesulphonates, hydronitrates, hydromalates, hydroacetates, hydrobenzoates, hydrocitrate, hydrofumarates, hydrotartrates, hydrooxalates, hydrosuccinates, hydrobenzoates and hydro-*p*-toluenesulphonates, preferably the

hydrochlorides, hydrobromides, hydrosulphates, hydrophosphates, hydrofumarates and hydromethanesulphonates.

- The invention further relates to pharmaceutical preparations which contain a triple
- 5 combination of the PDE4B-inhibitors, MRP4-inhibitors and another active substance according to the invention, such as, for example, an anticholinergic, a steroid, an LTD4-antagonist or a betamimetic, and the preparation thereof and the use thereof for treating respiratory complaints.
- 10 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-
- 15 ornithine), L-NIL (N^o-iminoethyl-lysine), (S)-6-acetimidoethylamino-2-amino-hexanoic acid (1*H*-tetrazol-5-yl)-amide (SC-51) (*J. Med. Chem.* 2002, 45, 1686-1689), 1400W, (S)-4-(2-acetimidoethylamino-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-
- 20 chloro-5-fluorobenzonitrile (WO 01/62704), 2-((1*R*.3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-6-trifluoromethyl-nicotinonitrile (WO 2004/041794), 2-((1*R*.3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-4-chloro-benzonitrile (WO 2004/041794), 2-((1*R*.3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-benzonitrile (WO 2004/041794), (2*S*,4*R*)-2-amino-4-(2-chloro-5-trifluoromethyl-phenylsulphanyl)-4-thiazol-5-
- 25 yl-butan-1-ol (WO 2004/041794), 2-((1*R*.3*S*)-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), (1*S*.5*S*.6*R*)-7-chloro-5-methyl-2-aza-bicyclo[4.1.0]hept-2-en-3-ylamine (ONO-1714)
- 30 (*Biochem. Biophys. Res. Commun.* 2000, 270, 663-667), (4*R*.5*R*)-5-ethyl-4-methyl-thiazolidin-2-ylideneamine (*Bioorg. Med. Chem.* 2004, 12, 4101), (4*R*.5*R*)-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]-ethylcarbamoyl}-2-
- 35 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]-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.

Other iNOS-inhibitors which may be used within the scope of the present invention are
5 antisense oligonucleotides, particularly antisense oligonucleotides that bind iNOS-coding
nucleic acids. For example, WO 01/52902 describes antisense oligonucleotides, particularly
antisense-oligonucleotides, which bind iNOS-coding nucleic acids, for modulating the
expression of iNOS. Those iNOS-antisense-oligonucleotides as described particularly in WO
01/52902 may therefore also be combined with the PDE4-inhibitors of the present invention
10 on the basis of their similar activity to the iNOS inhibitors.

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

15 **Pharmaceutical formulations**

Suitable forms for administration are for example tablets, capsules, solutions, syrups,
emulsions or inhalable powders or aerosols. The content of the pharmaceutically effective
compound(s) in each case should be in the range from 0.1 to 90 wt.%, preferably 0.5 to 50
wt.% of the total composition, i.e. in amounts which are sufficient to achieve the dosage
20 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
25 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.

30 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
35 magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl
cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise
several layers.

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

Syrups containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a
10 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 such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.

15 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 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.

20 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.
25 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).

30 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
35 substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

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.

- 5 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.

10 Inhalable powders

- 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),
15 polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred. Methods of preparing the
20 inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

Propellant-containing inhalable aerosols

- The propellant-containing inhalable aerosols which may be used according to the invention
25 may contain 1 dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant
30 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 use according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants,
35 antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

Propellant-free inhalable solutions

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 from inorganic or organic acids. Examples of particularly suitable inorganic acids include

5 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 use the acids which have already formed an acid addition salt with one of the active

10 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 invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

15 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

20 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

25 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

30 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

35 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.

5 Experimental procedures and synthetic examples

LIST of ABBREVIATIONS

	ACN	acetonitrile
	APCI	atmospheric pressure chemical ionization (in MS)
10	Ctrl	control
	DAD	diode array detector
	DMA	<i>N,N</i> -dimethylacetamide'
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
15	EI	electron impact (in MS)
	ESI	electrospray ionization (in MS)
	ex	example
	GC/MS	gas chromatography with mass spectrometric detection
	h	hour(s)
20	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluoro-phosphate
	HPLC	high performance liquid chromatography
	HPLC/MS	coupled high performance liquid chromatography-mass spectrometry
	min	minutes
25	MS	mass spectrometry
	NMR	nuclear magnetic resonance
	<i>R_t</i>	retention time (in HPLC)
	sec	secondary
	TBTU	<i>O</i> -(1 <i>H</i> -benzo-1,2,3-triazol-1-yl)- <i>N,N,N',N'</i> - tetramethyluronium
30		tetrafluoroborate
	tert	tertiary
	TFA	trifluoroacetic acid
	TLC	thin-layer chromatography
	UV	ultraviolet absorption

35

ANALYTICAL METHODS

HPLC methodsMethods:

- 1A

5 Column: Sunfire MS-C8, 5 μ m, 4.6 x 100 mm

 Mobile phase: A = (10 nM aqueous solution of NH₄COOH) + 10% ACN;
 B = ACN + 10% (10 nM aqueous solution of NH₄COOH).

 Flow rate: 1500 μ L/min

 Gradient: A/B (95/5%) for 1 min then to A/B (5/95%) in 10 min for 2 min.
 - 1E

10 Column: Symmetry C8, 5 μ m, 3 x 150 mm

 Mobile phase: A = (10 nM aqueous solution of NH₄COOH) + 10% ACN;
 B = ACN + 10% (10 nM aqueous solution of NH₄COOH).

 Flow rate: 1200 μ L/min

15 Gradient: A (100%) for 1.5 min then to B (100%) in 10 min for 3 min
 - 1E (Fusion)

 Column: Synergy Fusion RP80A, 4 μ m, 4.6 x 100 mm

 Mobile phase: A = (10 nM aqueous solution of NH₄COOH) + 10% ACN;
 B = ACN + 10% (10 nM aqueous solution of NH₄COOH).

20 Flow rate: 1200 μ L/min

 Gradient: A (100 %) for 1.5 min then to B (100 %) in 10 min for 3 min
 - 1E (Hvdro)

 Column: Synergy Hydro RP80A, 4 μ m, 4.6 x 100 mm

 Mobile phase: A = (10 nM aqueous solution of NH₄COOH) + 10% ACN;
 B = ACN + 10% (10 nM aqueous solution of NH₄COOH).

25 Flow rate: 1200 μ L/min

 Gradient: A (100 %) for 1.5 min then to B (100 %) in 10 min for 3 min
- Equipment:
- 30 Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD,
- Detection: UV @ 254nm
- Detection: Finnigan MSQ, quadrupole
- Ion source: APCI

Method:

- 1F

35 Column: Xterra MS-C8, 3.5 μ m, 4.6x50 mm

 Mobile phase: A= (H₂O+ 0.1% TFA) + 10% ACN; B=ACN

 Flow rate: 1300 μ L/min

Gradient: A (100%) then to A/B (10/90%) in 3.25 min for 0.75 min

• **1Fa**

Column: Xterra MS-C18, 5 μ m, 4.6x50 mm

5 Mobile phase: A= (H₂O+ 0.1% NH₄COOH) + 10% ACN; B=ACN

Flow rate: 1300 μ L/min

Gradient: A (100%) then to A/B (10/90%) in 3.25 min for 0.75 min

10 **Equipment:**

Instrument: HPLC/MS Waters. Hplc Alliance 2695 DAD, ZQ Quadrupole

Detection: UV @ 254nm

Detection: Waters ZQ, Quadrupole;

Ion source: ESI

15

Methods:

• **2A**

Column: X-Terra MS C18 4.6x50mm, 3.5 μ m;

Column Temperature: 40.0°C

20 Mobile phase: A = H₂O + 0.1% TFA; B= ACN + 0.1% TFA

Flow rate: 1500 μ L/min

Gradient:	Time	A%	B%
	0.00	95.00	5.00
	2.00	0.00	100.00
25	2.49	0.00	100.00
	2.50	95.00	5.00

• **2B**

Column: X-Terra MS C18 4.6x50mm, 3.5 μ m;

30 Column Temperature: 40.0°C

Mobile phase: A = H₂O + 0.1% TFA; B= ACN + 0.1% TFA

Flow rate: 1000 μ L/min

Gradient:	Time	A%	B%
	0.00	95.00	5.00
35	0.40	95.00	5.00
	4.00	2.00	98.00
	4.35	2.00	98.00
	4.50	95.00	5.00

- **2C**

Column: Sunfire C18 4.6x50mm, 3.5µm;
 Column Temperature: 40.0°C
 Mobile phase: A = H₂O + 0.1% TFA; B= ACN + 0.1% TFA
 Flow rate: 1500 µL/min
 Gradient:

Time:	A%	B%
0.00	95.00	5.00
2.00	0.00	100.00
2.49	0.00	100.00
2.50	95.00	5.00

Equipment

Instrument: Waters ZQ2000 mass spectrometer
Detection: HP1100 HPLC + DAD (Wavelength range: 210 to 500 nM)
 + Gilson 215 Autosampler
Ion source: ESI +

Method:

- **2Ca**

Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm
 Mobile phase: A = water + 0,1% HCOOH; B = ACN + 0,1% HCOOH
 Flow rate: 1.6 ml/min
 Gradient:

A %	B %	Time [min]
90	10	0.00
10	90	2.70
10	90	3.00
90	10	3.30

- **2Cb**

Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm
 Mobile: A = water + 0,1% HCOOH; B = MeOH
 Flow rate: 1.6 ml/min
 Gradient:

A %	B %	Time [min]
90	10	0.00
0	100	2.50
0	100	3.50

Equipment

Instrument: Agilent Technology; HP 1200 Series , DAD SL
Detection: UV 240 - 254 nm

Detection: Waters ZQ Single Quad

Ion source: ESI +

Method:

5

• **2F**

Column: Symmetry Shield RP8, 5 μ m, 4.6 x 150 mm

Mobile phase: A = (H₂O + HCOOH 0.1%) + 10% ACN

B = ACN + 10% (H₂O + 0.1% HCOOH)

Flow rate: 1000 μ L/min

10

Gradient: A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min

• **2M**

Column: Symmetry Shield RP8, 5 μ m, 4.6 x 150 mm

Mobile phase: A = (H₂O + HCOOH 0.1%) + 10% ACN

15

B = ACN + 10% (H₂O + 0.1% HCOOH)

Flow rate: 1200 μ L/min

Gradient: A/B (90/10 %) for 1.5 min then to A/B (5/95 %) in 10 min for 2 min

Equipment:

20

Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD, LCQDuo Ion Trap

Detection: UV λ 254 nm

Detection: Finnigan LCQDuo Ion Trap

Ion source: ESI

25

Method:

• **2G**

Eluent: A= H₂O+ 0.05% TFA; B= ACN

Column: Waters SunFire C18 30x100mm 5 μ m

30

Gradient: slope 5 %/min

Initial: Flow= 40 mL/min %A= 80 %B= 20

8 min Flow= 40 mL/min %A= 40 %B= 60

9 min Flow= 40 mL/min %A= 40 %B= 60

10 min Flow= 40 mL/min %A= 5 %B= 95

35

11 min Flow= 40 mL/min %A= 5 %B= 95

11.5 min Flow= 40 mL/min %A= 80 %B= 20

Stop run after 12 min Pre-run method: Initial condition for 3 min

Equipment:

5	<u>Detector MS Waters ZQ:</u> File: APrep_ESI.ipr Polarity: ESI+ Mass range: 130 to 900 amu	<u>Detector DAD Waters 996:</u> Start Wavelength: 210 nm End Wavelength: 600 nm Resolution: 1.2 nm Sampling rate: 1 spectra/sec
10	<u>Sample Manager mod Waters 2767:</u> Injection type: partial loop Injection Volume: set to Open Access Login mask Syringe size: 5000 uL Trigger: mixed Total scan UV plus MS A Loop Volume: 5000 uL	<u>Make up pump mod Waters 515:</u> Flow = 1000 µL/min Solvent = ACN /Water/Formic acid (90/10/0.1) Splitter: 1:1000
15		

20 **Method:**• **2G a**

Column: BEH C18, 1.8 µm, 2.1 x 100 mm
Mobile phase: A = (H₂O + NH₄COOH 0.1%)
B = ACN + 10% H₂O
Flow rate: 450 µL/min
Gradient: 100% A for 1.5 min then to 100% B in 2.2 min

• **2Gb**

Column: BEH C18, 1.7 µm, 2.1 x 50 mm
Mobile phase: A = H₂O 90%+0.1% TFA + 10% ACN
B = ACN + 10% H₂O
Flow rate: 480 µL/min
Gradient: A/B(90:10) , then to A/B (10:90) in 1.2 minutes for 0.46 minute

35 **Equipment:**

Instrument: UPLC/MS Acquity Waters
Detection: UV λ 254 nm
Detection: Waters SQD, Quadrupole
Ion source: ESI

Method:

- **2H (isocratic)**

5 Column: DAICEL (IC) 5 μ m, 4.6x250 mm
 Mobile phase: A = (hexane + 0,2% diethylamine); B = (MeOH/EtOH 50/50%).
 A/B = 50/50%
 Flow rate: 1 ml/min

10

- **2I (isocratic)**

 Column: DAICEL AS-H 5 μ m, 4.6x250 mm
 Mobile phase: A = Hexane ; B = EtOH (con AS-H), IPA (con AD-H)
 A/B = 98/2%
 Flow rate: 1 ml/min

15

Equipment

Instrument: LC Agilent Technologies. HPLC 1100 Serie, DAD Version A.
Detection: UV 220 - 300nm

20

GC-MS methods:**Method:**

- **3A**

25 Column: Agilent DB-5MS, 25m x 0.25mm x 0.25 μ m
 Carrier gas: Helium, 1 ml/min constant flow
 Oven Program: 50°C (hold 1 min.), to 100°C in 10°C / min, to 200°C in 20°C /
 min, to 300°C in 30°C / min

Equipment

30 **Instrument:** GC/MS Finnigan TRACE GC, TRACE MS quadrupole
 Detection: TRACE MS quadrupole
 Ion source: EI

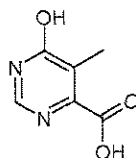
MICROWAVE HEATING:

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

35

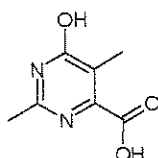
SYNTHESIS OF INTERMEDIATES

Intermediate 1a



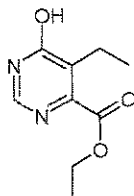
Potassium hydroxide (37.9 g, 0.67 mol) was suspended in 200 ml of dry ethanol, formamidine acetate (28.1 g, 0.27 mol) and diethyl oxalpropionate (50 ml, 0.27 mol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to room temperature and the precipitate 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 desired compound were obtained.

Intermediate 1b

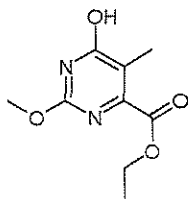


was synthesized in analogy to Intermediate 1a, starting from acetamidine hydrochloride.

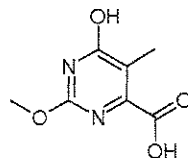
Intermediate 1c



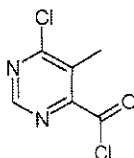
Potassium-tert-butyrate (185.4 g, 1.65 mol) was dissolved in 650 ml of dry ethanol and added slowly at -10°C to a suspension of 2-ethyl-3-oxo-succinic-acid diethyl ester (274.3 g, 1.27 mol) and formamidine acetate (171.4 g, 1.65 mol). The reaction mixture was stirred at room temperature overnight, concentrated in vacuum and ice water was added. The mixture was acidified by a 37% aqueous solution of hydrochloric acid until pH=5 and extracted with chloroform. After drying the organic layer, evaporation of the solvent in vacuum and crystallization from ethyl acetate/ hexane (2:3) gave 38 g (0.19 mol) of the desired compound.

Intermediate 1d

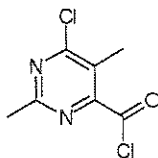
A suspension of sodium tert-butoxide (3.9 g, 40.5 mmol) in 25 ml dry ethanol was added to a solution of diethyl oxalpropionate (3.0 ml, 16.2 mmol) and O-methylisourea hydrochloride (2.15 g, 19.5 mmol) in 25 ml dry ethanol and the reaction mixture was refluxed for 18h. The reaction mixture was allowed to cool to room temperature and the precipitate removed by filtration. The filtrate was concentrated in vacuum, and the residue was purified by reversed phase HPLC to give the desired product (752 mg, 3.5 mmol).

Intermediate 1e

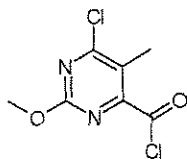
Intermediate 1d (550 mg, 2.6 mmol) was dissolved in a 4 M aqueous solution of sodium hydroxide (3.0 ml, 12.0 mmol) and stirred for 3 h at room temperature. The reaction mixture was acidified with concentrated hydrochloric acid to yield the desired product as precipitate (443 mg, 2.4 mmol).

Intermediate 2a

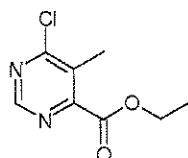
Intermediate 1a (7.0 g, 45.4 mmol) was suspended in 35 ml of thionyl chloride (0.45 mol), 0.10 ml of DMF was added and the reaction mixture was refluxed for 1h. The reaction mixture was concentrated in vacuum. 8.6 g (45 mmol) of the desired product were obtained and used in the next steps without further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

Intermediate 2b

was synthesized in analogy to Intermediate 2a, starting from Intermediate 1b.

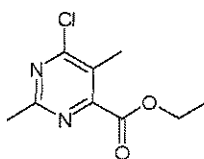
Intermediate 2c

was synthesized in analogy to Intermediate 2a, starting from Intermediate 1e.

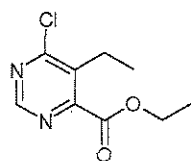
5 Intermediate 3a

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.

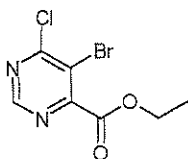
The reaction mixture was allowed to reach room temperature and stirred for 1h. Potassium carbonate was filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/ethyl acetate=95/5%). 5.3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

15 Intermediate 3b

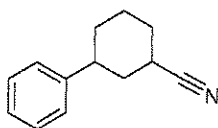
was synthesized in analogy to Intermediate 3a, starting from Intermediate 2b.

Intermediate 3c

Intermediate 1c (38 g, 0.19 mol) was added to a mixture of phosphorpentachloride (40.3 g, 0.19 mol) in 240 ml of phosphoroxychloride. The reaction mixture was refluxed until a clear solution was observed. The reaction mixture was concentrated in vacuum. The crude product obtained was purified by distillation in vacuum. 12 g (94.5 mmol) of the desired compound were obtained and used in the next steps without further purification.

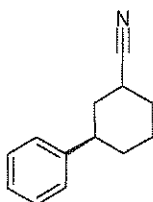
Intermediate 3d

5-Bromo-6-hydroxy-pyrimidine-4-carboxylic acid ethyl ester (63 g, 0.26 mol) was suspended in 140 ml of phosphoroxychloride. Phosphorpentachloride (54 g, 0.26 mmol) was added and the reaction mixture was refluxed 72h. The reaction mixture was concentrated in vacuum and the crude product was suspended and stirred in warmed-up hexane (50°C); a precipitate was formed and filtered off. The filtrate was concentrated under vacuum to obtain 64 g (243 mmol) of the desired product which was used in the next steps without further purification.

10 **Intermediate 4a**

3-Phenylcyclohexanone (500 mg, 2.87 mmol) and 1-isocyanomethanesulfonyl-4-methylbenzene (750 mg, 3.84 mmol) in 10 ml of 1,2-dimethoxyethane were stirred at 0°C. A solution of potassium tert-butoxide (650 mg, 5.79 mmol) in 10 ml of 1,2-dimethoxyethane and 20 ml of tert-butanol was added dropwise and the reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether and washed with ice water. The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. 439 mg (2.3 mmol) of the desired product were obtained.

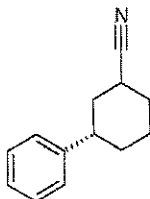
20

Intermediate 4b

was synthesized in analogy to Intermediate 4a, starting from (R)-3-Phenylcyclohexanone.

25 GC/MS (method 3A) R_t = 11.52 min and 11.68 min (diastereoisomeric mixture)
 $[M]^+ = 185$

30

Intermediate 4c

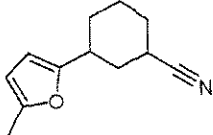
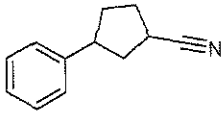
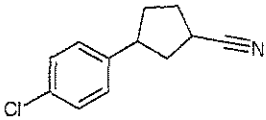
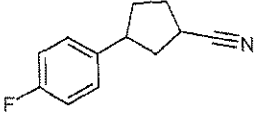
was synthesized in analogy to Intermediate 4a, starting from (S)-3-Phenylcyclohexanone.

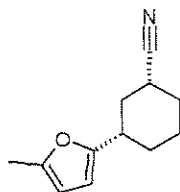
GC/MS (method 3A) $R_t \approx 11.50$ min and 11.65 min (diastereoisomeric mixture)

5 $[M]^+ = 185$

The following intermediates were synthesized in analogy to Intermediates 4a.

Starting ketone	Intermediate	STRUCTURE
3-(4-Chloro-phenyl)-cyclohexanone	4d	
3-(4-Fluoro-phenyl)-cyclohexanone	4e	
3-(4-Methoxy-phenyl)-cyclohexanone	4f	
3-(4-Methyl-phenyl)-cyclohexanone	4g	
3-(3-Fluoro-phenyl)-cyclohexanone	4h	
3-isopropyl-cyclohexanone	4i	

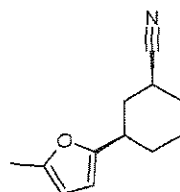
3-(5-Methyl-furan-2-yl)- cyclohexanone	4j	
3-Phenylcyclopentanone	4k	
3-(4-Chloro-phenyl)- cyclopentanone	4l	
3-(4-Fluoro-phenyl)- cyclopentanone	4m	

Intermediate 4n

Intermediate 4j (400 mg, 2.11 mmol) was purified by flash chromatography (Biotage SP1 cartridge 25g; eluent: cyclohexane/ethyl acetate = 99/1%). 60 mg (0.22 mmol) of diastereoisomerically pure cis-intermediate was eluted as second fraction (relative stereochemistry assigned by NMR).

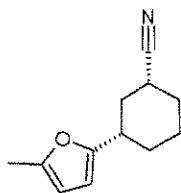
GC/MS (method 3A) $R_t = 9.62$ min

$[M]^+ = 189$

Intermediate 4o

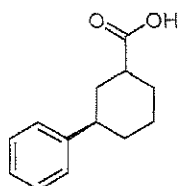
Intermediate 4n (120 mg, 4.22 mmol) was separated by chiral semipreparative HPLC. 20 mg of enantiomerically pure intermediate 4o were obtained (absolute stereochemistry unknown).

Chiral HPLC (method 2I (isocratic)) $R_t = 6.94$ min

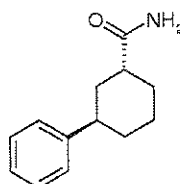
Intermediate 4p

Further elution of the column gave 20 mg of enantiomerically pure intermediate 4p (absolute stereochemistry unknown).

- 5 Chiral HPLC (method 2I (isocratic)) $R_t = 7.27$

Intermediate 5

- Intermediate 4b (2.1 g, 11.28 mmol) was stirred under reflux in 20 ml of 96% sulfuric acid and 20 ml of water overnight. The reaction mixture was cooled, treated with a 30% aqueous solution of sodium hydroxide and ice and washed with dichloromethane. The basic water phase was treated with 37% aqueous solution of hydrochloric acid. The acidic aqueous solution was extracted with dichloromethane. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. 1.85 g (9.1 mmol) of the desired compound were obtained as a diastereoisomeric mixture and used in the next steps without further purification.

Intermediate 6a

- Intermediate 5 (1.85 g, 9.06 mmol, mixture of 2 diastereomers) and triethylamine (2.02 ml, 14 mmol) were stirred at 0°C in 10 ml of tetrahydrofuran. A solution of ethylchloroformate (1.29 ml, 13.58 mmol) in 5 ml of tetrahydrofuran was added dropwise and the reaction mixture was stirred at 0°C for 1h. Then, 10 ml of a 30% aqueous solution of ammonium hydroxide were added dropwise and the reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was concentrated under vacuum, dissolved with dichloromethane, washed with a 1M aqueous solution of sodium hydroxide, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge 70g; eluent: dichloromethane/methanol=99/1%). 145 mg (0.71 mmol) of diastereoisomerically pure

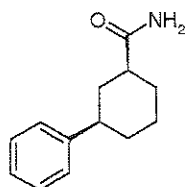
(1R,3R)-3-phenyl-cyclohexanecarboxylic acid amide (relative stereochemistry assigned by NMR) were obtained.

GC/MS (method 3A) $R_t = 12.88$ min

$[M]^+ = 203$

5

Intermediate 6b



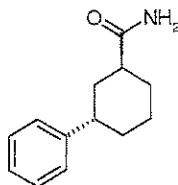
Further elution of the column gave 230 mg (1.13 mmol) of the diastereoisomerically pure (1S,3R)-3-phenyl-cyclohexanecarboxylic acid amide (relative stereochemistry assigned by NMR).

10

GC/MS (method 3A) $R_t = 13.03$ min

$[M]^+ = 203$

Intermediate 6c



15

Intermediate 4c (300 mg, 1.61 mmol) was stirred under reflux in 2 ml of 96% sulfuric acid and 2 ml of water for 3h. The reaction mixture was cooled, treated with a 30% aqueous solution of sodium hydroxide and ice and washed with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge 20g; eluent: dichloromethane/methanol=99/1%). 37 mg (0.18 mmol) of the diastereomerically pure (1S,3S)-3-phenyl-cyclohexanecarboxylic acid amide were obtained (relative stereochemistry assigned by NMR).

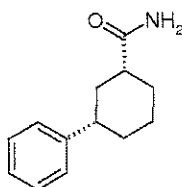
20

GC/MS (method 3A) $R_t = 12.88$ min

25

$[M]^+ = 203$

Intermediate 6d



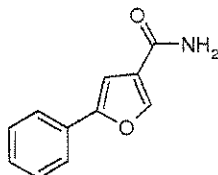
Further elution of the column gave 40 mg of the diastereomerically pure (1R,3S)-3-phenyl-cyclohexanecarboxylic acid amide (0.2 mmol) (relative stereochemistry assigned by NMR).

GC/MS (method 3A) $R_t = 13.03$ min

$[M]^+ = 203$

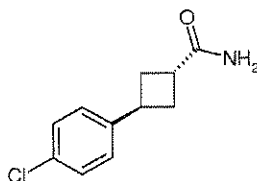
5

Intermediate 6e



5-Bromo-3-furan carboxylic acid (1.0 g, 5.23 mmol), phenylboronic acid (0.77 g, 6.28 mmol),
10 tetrakis(triphenylphosphine)palladium(0) (1.21 g, 1.04 mmol) and a 2M solution of sodium carbonate (6.28 ml, 12.57 mmol) were dissolved in 12 ml of 1,2-dimethoxy-ethane and the reaction mixture was stirred under nitrogen atmosphere at 80°C for 18h. The reaction mixture was cooled to room temperature, diluted with dichloromethane and treated with a 1M aqueous solution of hydrochloric acid until pH 1. The organic phase was separated, dried over sodium
15 sulphate and concentrated under vacuum. The carboxylic acid was obtained and used without further purification for the synthesis of intermediate 6e in analogy to intermediate 6a.

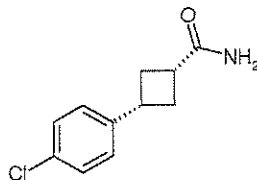
Intermediate 6f



20 Intermediate 6f was synthesized in analogy to intermediate 6a, starting from trans 3-(4-chlorophenyl)-cyclobutan carboxylic acid (prepared as described in literature for the preparation of trans 3-phenyl-cyclobutan-carboxylic acid: Wiberg, K.B.; Dailey, W.P.; Walker, F.H.; Waddell, S.T.; Crocker, L.S.; Newton, M. Journal of the American Chemical Society; 1985, 107, 7247 - 7257).

25

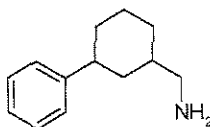
Intermediate 6g



Intermediate 6g was synthesized in analogy to Intermediate 6a, starting from cis 3-(4-chlorophenyl)-cyclobutan carboxylic acid (prepared as described in literature for the
30 preparation of cis 3-phenyl-cyclobutan-carboxylic acid: Wiberg, K.B.; Dailey, W.P.; Walker,

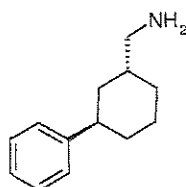
F.H.; Waddell, S.T.; Crocker, L.S.; Newton, M. Journal of the American Chemical Society; 1985, 107, 7247 - 7257).

Intermediate 7a



5 Intermediate 4a (390 mg, 2.10 mmol) and Raney-Nickel (10 mg) in 10 ml of 1M solution of ammonia in ethanol was stirred under a hydrogen atmosphere (4 bar) overnight. The reaction mixture was filtered on a celite pad and concentrated under vacuum. The crude product was purified by flash chromatography (dichloromethane/methanol/NH₃(30% aqueous solution)=
10 95/5/0.1%) to obtain 217 mg (1.15 mmol) of the desired product.

Intermediate 7b

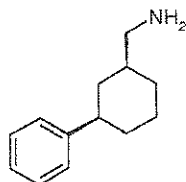


2.85 ml of a 1M solution of lithium aluminium hydride (2.85 mmol) in tetrahydrofuran was dissolved in 10 ml of tetrahydrofuran and stirred at 0°C under nitrogen atmosphere.
15 Intermediate 6a (145 mg, 0.71 mmol) in 10 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred at 0°C for 2h and then quenched with water and ice. The reaction mixture was extracted with dichloromethane. The organic phase was washed with a 1M aqueous solution of sodium hydroxide, brine, dried over sodium sulfate and concentrated
20 under vacuum. 100 mg (0.55 mmol) of the desired product were obtained.

GC/MS (method 3A) $R_t = 11.53$ min

$[M]^+ = 189$

Intermediate 7c

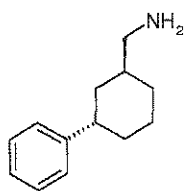


25 was synthesized in analogy to Intermediate 7b, starting from Intermediate 6b.

GC/MS (method 3A) $R_t = 11.47$ min

$[M]^+ = 189$

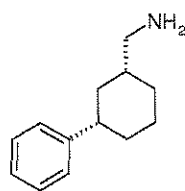
30

Intermediate 7d

was synthesized in analogy to Intermediate 7b, starting from Intermediate 6c.

GC/MS (method 3A) $R_t = 11.53$ min

5 $[M]^+ = 189$

Intermediate 7e

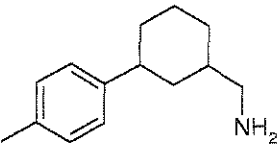
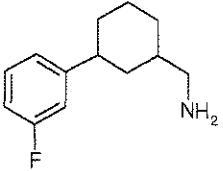
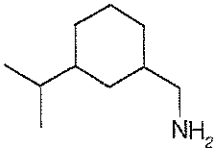
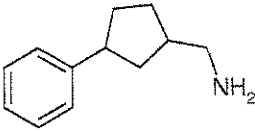
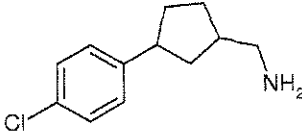
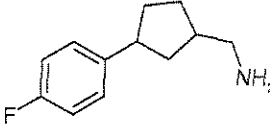
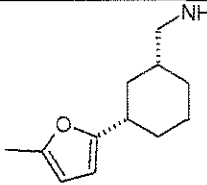
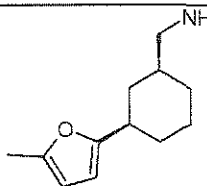
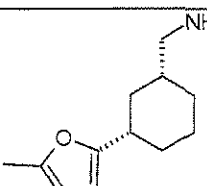
10 was synthesized in analogy to Intermediate 7b, starting from Intermediate 6d.

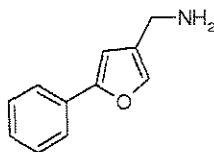
GC/MS (method 3A) $R_t = 13.03$ min

$[M]^+ = 189$

15 The following intermediates were synthesised in atalogy to Intermediate 7a.

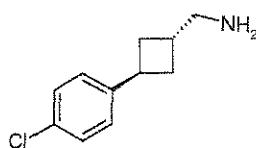
Starting Intermediate	Intermediate	STRUCTURE
4d	7f	
4e	7g	
4f	7h	

4g	7i	
4h	7j	
4i	7k	
4k	7l	
4l	7m	
4m	7n	
4n	7o	
4o	7p	
4p	7q	

Intermediate 7r

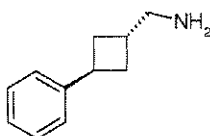
was synthesized in analogy to intermediate 7b, starting from intermediate 6e.

5

Intermediate 7s

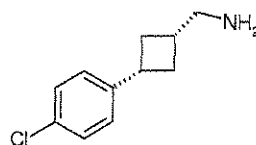
was synthesized in analogy to intermediate 7b, starting from intermediate 6f.

10

Intermediate 7t

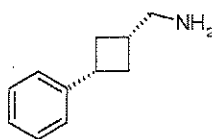
was obtained and isolated as side product in the preparation of Intermediate 7s

15

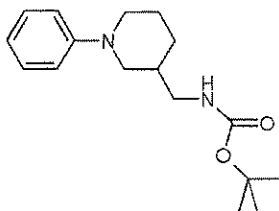
Intermediate 7u

was synthesized in analogy to Intermediate 7b, starting from Intermediate 6g.

20

Intermediate 7v

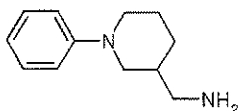
was obtained and isolated as side product in the preparation of Intermediate 7u.

5 **Intermediate 8a**

Tris(dibenzylideneacetone)dipalladium (1.71g, 1.87 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (2.32g, 3.72 mmol) were stirred in 30 ml of toluene for 10 min under argon atmosphere.

- 10 Piperidine-3-yl-methyl-carbamic acid tert-butyl ester (2 g, 9.33 mmol), bromobenzene (1.27 ml, 0.01 mol) and sodium tert-butoxide (1.43 g, 14.93 mmol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was concentrated under vacuum, the crude product was dissolved in dichlorometane and the organic phase was filtered on a celite pad. The organic phase was washed with an aqueous saturated sodium carbonate solution, with brine, dried over sodium sulfate, concentrated under vacuum.
- 15 The crude product obtained was dissolved in methanol and loaded onto a SCX cartridge (25 g). After washing with methanol the product was eluted with a 2M solution of ammonia in methanol. 1.17 g (4.03 mmol) of the desired product were obtained and used in next steps without any other purification.

20

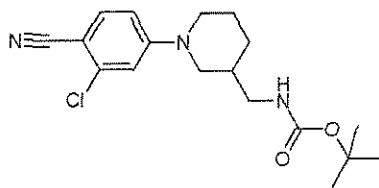
Intermediate 9a

- To a solution of Intermediate 8a (1.1 g, 3.79 mmol) in 10 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (15 ml, 60 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight before being concentrated under vacuum.
- 25 The crude product was purified by flash chromatography (Isolute silica gel cartridge: 50g; eluent: dichloromethane/ methanol=95/5%). 250 mg (1.31 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 8a and 9a.

Starting amine	Starting bromide	Inter-mediate	STRUCTURE	Inter-mediate	STRUCTURE
(S)-1-Pyrrolidin-3-ylmethyl-carbamic acid tert-butyl ester	bromo-benzene	8b		9b	
(R)-1-Pyrrolidin-3-ylmethyl-carbamic acid tert-butyl ester	bromo-benzene	8c		9c	
Piperidine-3-yl-methyl-carbamic acid tert-butyl ester	1-bromo-4-trifluoromethyl-benzene	8d		9d	

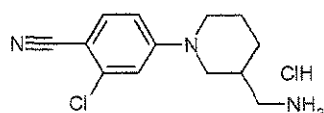
Intermediate 10



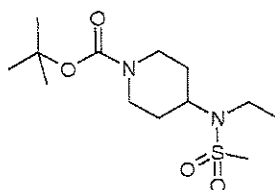
5

Piperidine-3-yl-methyl-carbamic acid tert-butyl ester (100 mg, 0.47 mmol), 2-chloro-4-fluoro-benzonitrile (72.5 mg, 0.47 mmol) and N,N-diisopropylethylamine (0.160 ml, 1.23 mmol) were dissolved in 10 ml of DMF and the reaction mixture was stirred at 125 °C overnight. The reaction mixture was concentrated under vacuum and the crude product was purified by flash chromatography (Isolute silica gel cartridge: 5g; eluent: ethyl acetate). 125 mg (0.36 mmol) of the desired compound were obtained.

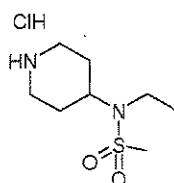
10

Intermediate 11

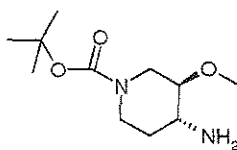
- To a solution of Intermediate 10 (125 mg, 0.36 mmol) in 5 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (0.12 ml, 480 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight before being concentrated under vacuum. 102 mg (0.36 mmol) of the desired compound were obtained.

Intermediate 12

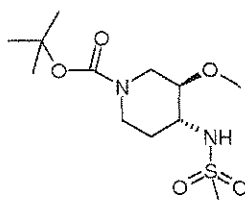
- A solution of 4-methanesulfonylamino-piperidine-1-carboxylic acid tert-butyl ester (500 mg; 1.79 mmol) in 5 ml of acetonitrile was cooled to -5°C, iodoethane (308 mg, 1.79 mmol) and sodium hydride (96 mg, 3.59 mmol) were added; the reaction mixture was allowed to warm to room temperature and stirred for 72h. The reaction mixture was concentrated under vacuum; the residue was dissolved in ethyl acetate and washed with an aqueous saturated sodium bicarbonate solution and then with water. The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge: 10 g, eluent: dichloromethane) to obtain 332 mg (1.1 mmol) of the desired compound.

Intermediate 13

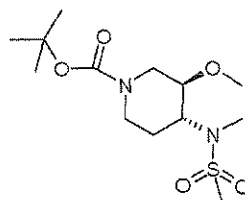
- To a solution of intermediate 12 (330 mg, 1.1 mmol) in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid in 1,4-dioxane (4.06 ml, 16 mmol) was added dropwise; the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum to obtain 262 mg (1.1 mmol) of the desired compound.

Intermediate 14

trans-4-Azido-3-methoxy-piperidine-1-carboxylic acid tert-butyl ester (1.6 g, 6.24 mmol), Pd/C 10% (200 mg) and acetic acid (1.6 ml) were dissolved in 25 ml of methanol and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 3h. The reaction mixture was filtered on a celite pad and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1 cartridge 65i, eluent: dichloromethane/methanol=95/5%). 900 mg (3.91 mmol) of the desired compound were obtained.

Intermediate 15a

Intermediate 14 (900 mg, 3.91 mmol) and N,N-diisopropylethylamine (0.86 ml, 5 mmol) were dissolved in 25 ml of dichloromethane. The reaction mixture was cooled to 0°C and methanesulfonylchloride (0.33 ml, 4.30 mmol) was added. The reaction mixture was stirred at 0°C for 20 min, then, water was added. The organic phase was separated, washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica cartridge: 10g, eluent: hexane/ethyl acetate=50/50%). 170 mg (0.55 mmol) of the desired compound were obtained.

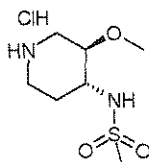
Intermediate 15b

Intermediate 15a (350 mg, 1.13 mmol) and potassium carbonate (157 mg, 1.13 mmol) were dissolved and stirred in 15 ml of acetonitrile. A solution of iodomethane (0.071 ml, 1.13 mmol) in 5 ml of acetonitrile was added dropwise and the reaction mixture was warmed to 60°C overnight. The reaction mixture was concentrated under vacuum and the crude product

was dissolved in ethyl acetate. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, separated, dried over sodium sulfate and concentrated under vacuum. 300 mg (0.93 mmol) of the desired compound were obtained and used in the next steps without further purification.

5

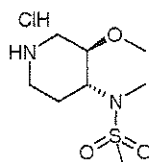
Intermediate 16a



Intermediate 15a (170 mg, 0.55 mmol) in 2 ml of 1,4-dioxane was stirred at 10°C. A 4M solution of hydrochloric acid in 1,4-dioxane (8 ml, 32 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 5h. The reaction mixture was concentrated under vacuum to obtain 115 mg (0.55 mmol) of the desired compound.

10

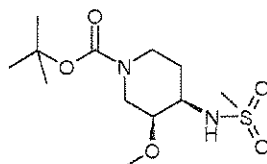
Intermediate 16b



15

was synthesized in analogy to Intermediate 16a, starting from Intermediate 15b.

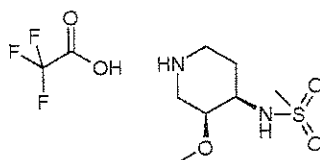
Intermediate 17



was synthesized in analogy to Intermediate 15a, starting from (3S,4R)-4-amino-3-methoxy-piperidine-1-carboxylic acid tert-butyl ester.

20

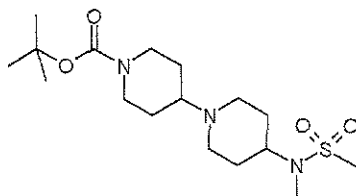
Intermediate 18



Intermediate 17 (660 mg, 2.14 mmol) in 10 ml of 1,4-dioxane was stirred at 10°C. Trifluoroacetic acid (2 ml, 26 mmol) was added dropwise and the reaction mixture was stirred at room temperature 18h. The reaction mixture was concentrated under vacuum to obtain 600 mg (1.86 mmol) of the desired compound, used in the next step without further purification.

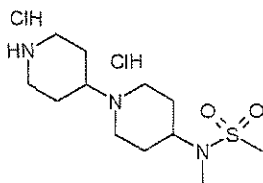
5

Intermediate 19a



- 10 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.
- 15 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.

Intermediate 20a

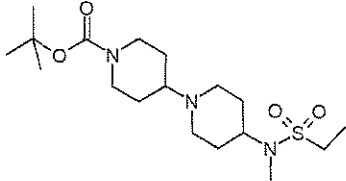
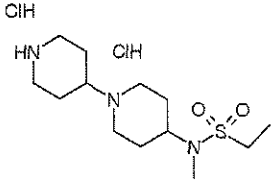
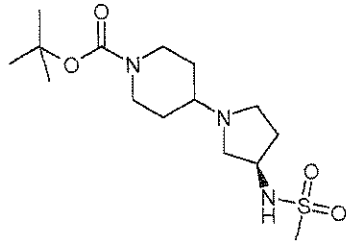
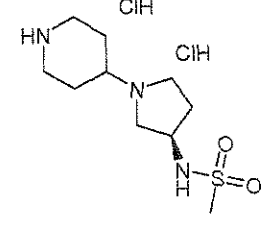
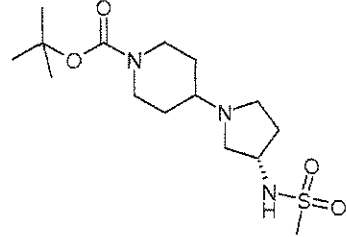
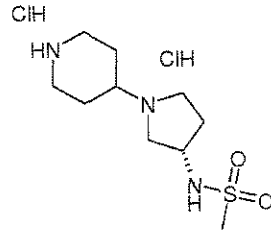
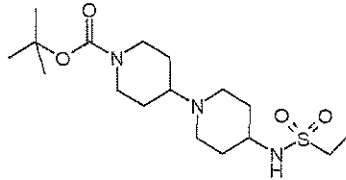
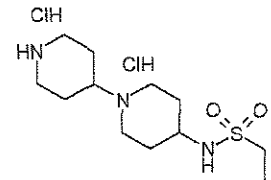


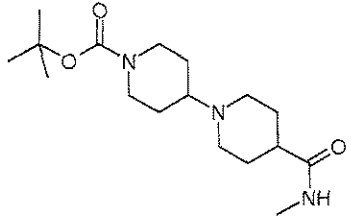
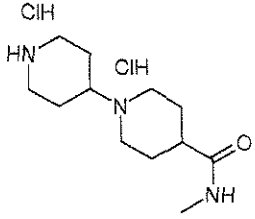
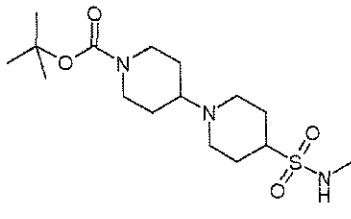
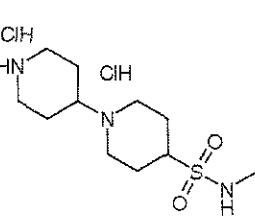
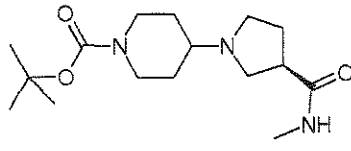
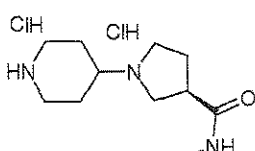
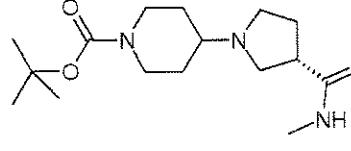
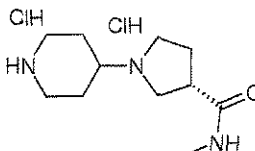
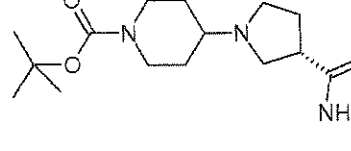
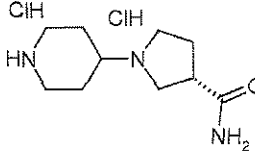
20

Intermediate 19a (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.

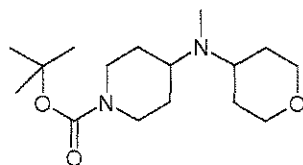
25

The following intermediates were synthesized in analogy to Intermediates 19a and 20a.

Starting ketone	Starting amine	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
1-(tert-butoxycarbonyl)-4-oxopiperidine	Ethanesulfonic acid methylpiperidin-4-ylamide	19b		20b	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(R)-N-Pyrrolidin-3-ylmethanesulfonamide	19c		20c	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-N-Pyrrolidin-3-ylmethanesulfonamide	19d		20d	
1-(tert-butoxycarbonyl)-4-oxopiperidine	Ethanesulfonic acid piperidin-4-ylamide	19e		20e	

1-(tert-butoxycarbonyl)-4-oxopiperidine	Piperidine-4-carboxylic acid methyl amide	19f		20f	
1-(tert-butoxycarbonyl)-4-oxopiperidine	Piperidine-4-sulfonic acid methyl amide	19g		20g	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(R)-Pyrrolidine-3-carboxylic acid methyl amide	19h		20h	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-Pyrrolidine-3-carboxylic acid methyl amide	19i		20i	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(S)-Pyrrolidine-3-carboxylic acid amide	19j		20j	

1-(tert-butoxycarbonyl)-4-oxopiperidine	16a	19k		20k	
1-(tert-butoxycarbonyl)-4-oxopiperidine	(R)-Pyrrolidine-3-carboxylic acid amide	19l		20l	
1-(tert-butoxycarbonyl)-4-oxopiperidine	47b	19lf		20lf	
1-(tert-butoxycarbonyl)-4-oxopiperidine	47c	19lg		20lg	

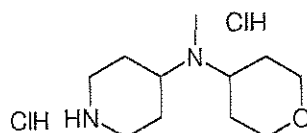
Intermediate 19la

- 5 4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 1.87 mmol) was suspended in 10 ml of 1,2-dichloroethane. Tetrahydro-pyran-4-one (0.17 ml, 1.87 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (593 mg, 2.80 mol) was added and the reaction mixture was stirred for

18 h. 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 (Isolute silica gel cartridge 10g; eluent: 5 dichloromethane/methanol=94/6%). 240 mg (0.80 mmol) of the desired compound were obtained.

Intermediate 20la



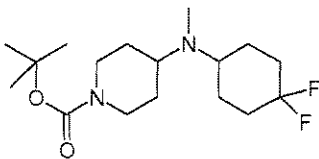
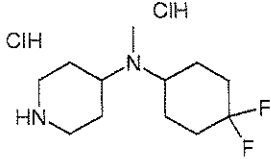
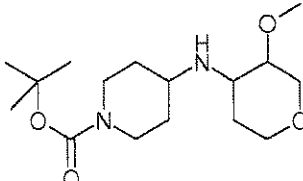
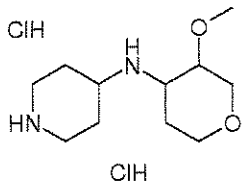
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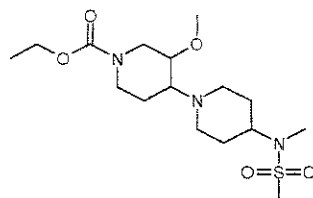
Intermediate 19la (240 mg, 0.80 mmol) was suspended in 10 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (2.0 ml, 8.0 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum. 200 mg (0.74 mmol) of the desired compound were obtained.

15

The following intermediates were synthesized in analogy to Intermediates 19la and 20la

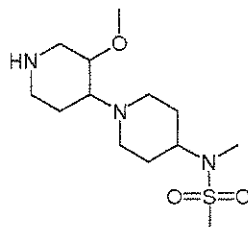
Starting amine	Starting ketone	Carbamate Intermediate	STRUCTURE	Amino Intermediate	STRUCTURE
4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	3-Methoxy-tetrahydropyran-4-one	19lb		20lb	
4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	2,6-dimethyl-tetrahydropyran-4-one	19lc		20lc	

4-Methylamino-piperidine-1-carboxylic acid tert-butyl ester	4,4-difluoro-cyclohexanone	19ld		20ld	
4-amino-piperidine-1-carboxylic acid tert-butyl ester	3-Methoxy-4-tetrahydropyran-4-one	19le		20le	

Intermediate 19m

5 N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (1.13 g, 4.95 mmol) was suspended in 10 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (2.6 ml, 14.9 mmol) and N-carbethoxy-3-methoxy-piperidin-4-one (1 g, 4.95 mmol) were added and the reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (3.16 g, 14.85 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.

10 The organic phase was dried over sodium sulfate and concentrated under vacuum. 1.5 g (3.97 mmol) of the desired compound were obtained and used without further purification.

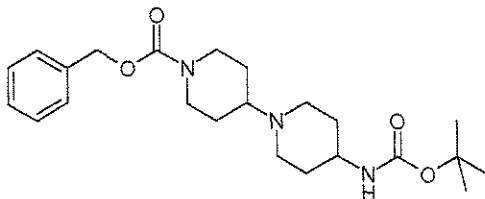
Intermediate 20m

15

Intermediate 19m (1.5g, 3.97 mmol) and potassium hydroxide (4.46 g, 7.94 mmol) were suspended in 25 ml of ethanol and the reaction mixture was stirred under reflux overnight.

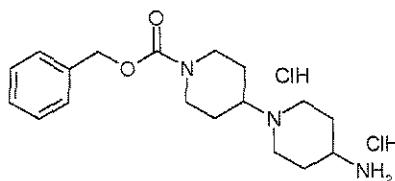
The reaction mixture was concentrated under vacuum and the crude product was loaded on a SCX cartridge (25g) and eluted with a 2M solution of ammonia in methanol. 1.2 g (3.97 mmol) of the desired compound were obtained.

5 **Intermediate 21**



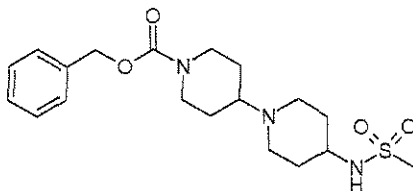
Piperidin-4-yl-carbamic acid tert-butyl ester (6 g, 30 mmol) and 1-(benzyloxycarbonyl)-4-oxopiperidine (9.6 g, 48 mmol) were dissolved in 50 ml of dichloromethane and the reaction mixture was stirred at room temperature for 30 min; sodium triacetoxyborohydride (12.23 g, 57.5 mmol) was added and the reaction mixture was stirred at room temperature overnight. 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 treated with acetone/isopropyl ether and the precipitate obtained was filtered off. 8.4g (20 mmol) of the desired product were obtained.

15 **Intermediate 22**



To a solution of intermediate 21 (8.4 g, 20 mmol) in 150 ml of 1,4-dioxane previously cooled to 0°C, 12.6 ml (50 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise; the reaction mixture was allowed to warm to room temperature and was stirred at that temperature overnight. The solid precipitated from the reaction mixture was filtered off and dried at 50°C under vacuum to obtain 6g (15 mmol) of the desired compound.

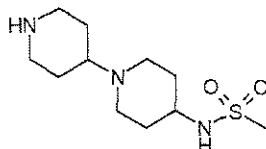
20 **Intermediate 23**



Intermediate 22 (6.0 g, 15 mmol) was suspended in 55 ml of dichloromethane; triethylamine (6.43 ml, 46 mmol) was added and the reaction mixture was cooled to 0°C and stirred at that

temperature for 30 min. Methanesulfonyl chloride (1.43 ml, 18 mmol) in 5 ml of dichloromethane was added dropwise. The reaction mixture was stirred at 0°C for 1h; then water was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was treated with diisopropyl ether, the precipitate was filtered off and dried. 5 g (13 mmol) of the desired product were obtained.

Intermediate 24

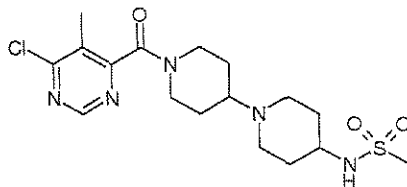


10

Intermediate 23 (5 g, 13 mmol) was dissolved in 50 ml of methanol; acetic acid (1.5 ml, 25.3 mmol) and Pd/C 10% (500 mg) were added in sequence and the reaction mixture was stirred under a hydrogen atmosphere (3 bar) at room temperature for 5 days. The reaction mixture was filtered on a celite pad and the organic phase was loaded on a SCX cartridge (10g). After washing with methanol, the desired compound was eluted with a 2M solution of ammonia in methanol. 3.7 g (4.6 mmol) of the title compound were obtained.

15

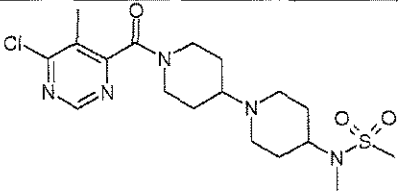
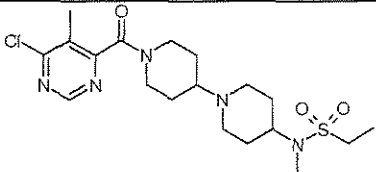
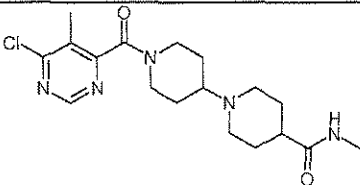
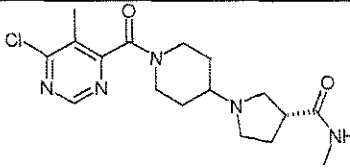
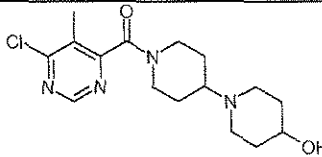
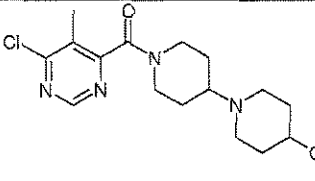
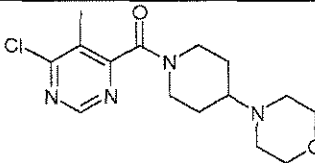
Intermediate 25a

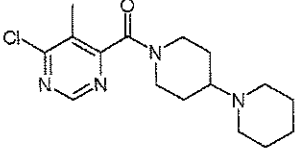
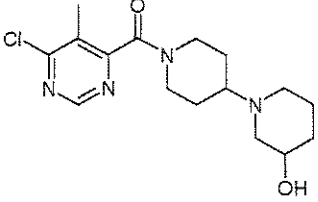
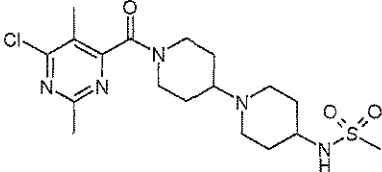
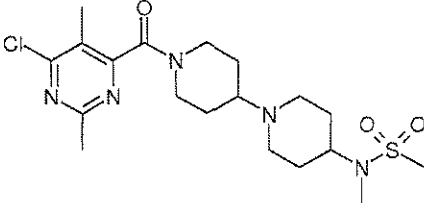
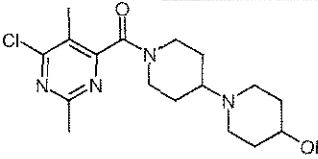
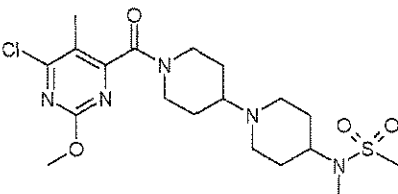
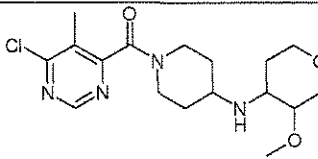


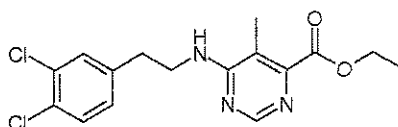
Intermediate 24 (1.1 g, 4.21 mmol) was suspended in 20 ml of dry dichloromethane, N,N-diisopropylethylamine (1.47 ml, 8.42 mmol) and DMF (137 μ l, 1.67 mmol) were added and the reaction mixture was stirred under nitrogen atmosphere and cooled to 0°C. Intermediate 2a (812 mg, 4.21 mmol) in 5 ml of dichloromethane was added dropwise and the reaction mixture was allowed to warm up to room temperature and stirred for 1.5h; 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: 10g; eluent: dichloromethane/methanol=95/5%). 1.0 g (2.41 mmol) of the title compound were obtained.

25
30

The following intermediates were synthesized in analogy to Intermediate 25a.

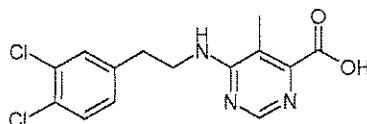
Core Intermediate	Piperidine Intermediate	Chloro-pyrimidine Intermediate	STRUCTURE
2a	20a	25b	
2a	20b	25c	
2a	20f	25d	
2a	20h	25e	
2a	[1,4']-Bi-piperidinyl-4-ol	25f	
2a	4-Methoxy-[1,4']bi-piperidinyl	25g	
2a	4-Piperidin-4-yl-morpholine	25h	

2a	[1,4']Bi-piperidinyl	25i	
2a	[1,4']-Bi-piperidinyl-3-ol	25j	
2b	24	25k	
2b	20a	25l	
2b	[1,4']-Bi-piperidinyl-4-ol	25m	
2c	20a	25n	
2a	20le	25o	

Intermediate 26a

Intermediate 3a (10 g, 49.35 mmol) and N,N-diisopropylethylamine (17 ml, 99 mmol) were dissolved in 20 ml of dry DMF; 2-(3,4-dichloro-phenyl)-ethylamine (9.57 g, 49.35 mmol) in 10 ml of dry DMF was added and the reaction mixture was stirred at 90°C for 2h. The reaction mixture was cooled to room temperature, water was added and the reaction mixture was extracted with dichloromethane; the organic phase was concentrated under vacuum, the crude product was suspended and stirred in diethyl ether and the precipitate was filtered off and dried. 10.2 g (28.8 mmol) of the desired compound were obtained.

Intermediate 27a



Intermediate 26a (10.0 g, 28.25 mmol) was dissolved in 70 ml of ethanol and a solution of LiOH (3.52 g, 83.88 mmol) in 70 ml of water was added. The reaction mixture was stirred at 70°C for 1 hour, concentrated under vacuum and the remaining aqueous solution was acidified by 20 ml of 4M solution of hydrochloric acid in 1,4-dioxane; the precipitate formed was filtered off and dried. 8.6 g (26.37 mmol) of the desired product were obtained.

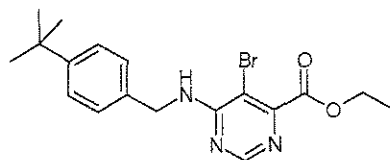
15

The following intermediates were synthesized in analogy to Intermediates 26a and 27a.

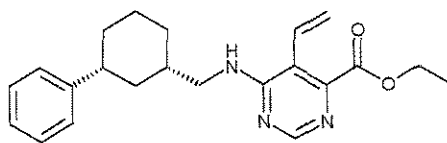
Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE
3a	3,4-Dichloro-benzyl-amine	26b		27b	
3a	4-tert-butyl-benzyl-amine	26c		27c	
3a	biphenyl-3-ylmethan-amine	26d		27d	

3b	4-tert-butyl-benzyl-amine	26e		27e	
3c	2-(3,4-dichlorophenyl)-ethylamine	26f		27f	
3c	biphenyl-3-yl-methan-amine	26g		27g	
3d	biphenyl-3-yl-methan-amine	26h		27h	
3a	Inter-mediate 7c	26ha		27ha	
3d	Inter-mediate 7c	26hb		27hb	
3a	Inter-mediate 7p	26hc		27hc	
3a	Inter-mediate 7q	26hd		27hd	
3a	Inter-mediate 7t	26he		27he	

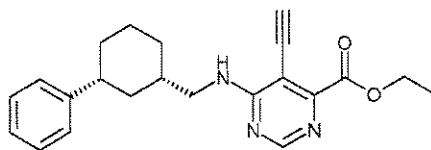
3a	Inter- mediate 7v	26hf		27hf	
3b	Inter- mediate 7t	26hr		27hr	
3b	Inter- mediate 7v	26hs		27hs	

Intermediate 26i

Intermediate 3d (2 g, 7.53 mmol) and N,N-diisopropylethylamine (1.97 ml, 11.3 mmol) were dissolved in 15 ml of dry DMF; 4-tertbutyl-benzylamine (1.6 ml, 9.04 mmol) was added and the reaction mixture was stirred at 60°C for 18h. The reaction mixture was cooled to room temperature, water was added and the reaction mixture was extracted with dichloromethane; the organic phase was concentrated under vacuum and the crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: hexane/ethyl acetate = 70/30%). 1.5 g (3.82 mmol) of the desired compound were obtained.

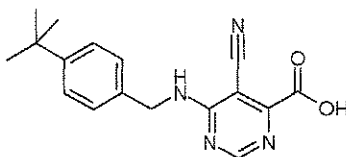
Intermediate 26ib

Intermediate 26hb (75 mg, 179 μmol), tributyl(vinyl)tin (200 μl, 685 μmol) and bis(triphenylphosphine)palladium chloride (13 mg, 18 μmol) were added to 3 ml 1,2-dichloroethane. The reaction mixture was heated in the microwave for 4 h at 120°C. Then, the solvent was removed in vacuum and the residue was purified by reversed phase HPLC to give the desired product (56 mg, 117 μmol).

Intermediate 26ic

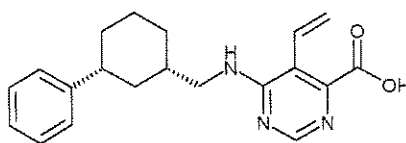
was synthesized in analogy to intermediate 26ib, starting from intermediate 26hb and tributyl(ethynyl)tin.

5

Intermediate 27i

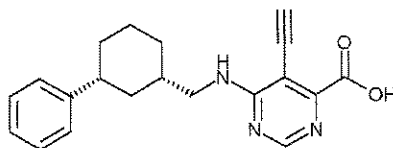
Intermediate 26i (500 mg, 1.27 mmol) and CuCN (114 mg, 1.27 mmol) were dissolved in 5 ml of DMA and the reaction mixture was stirred at 100°C overnight. The reaction mixture was cooled, diluted with dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. 30 mg (0.1 mmol) of the crude product were obtained and used in the next step without purification.

10

Intermediate 27ib

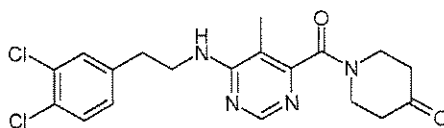
15

was synthesized in analogy to 27a starting from intermediate 26ib.

Intermediate 27ic

20

was synthesized in analogy to 27a starting from intermediate 26ic.

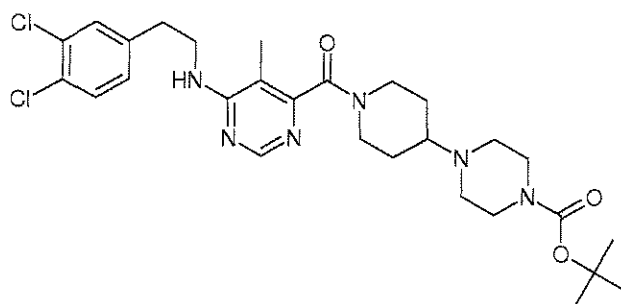
Intermediate 28a

Intermediate 27a (4 g, 12.14 mmol), TBTU (3.9 g, 12.14 mmol) and N,N-diisopropylethylamine (5.34 ml, 30.35 mmol) were dissolved in 25 ml of DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 30 min; then piperidin-4-one hydrochloride (1.66 g, 12.14 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, with a 1M aqueous solution of sodium hydroxide, with brine, then dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/methanol= 95/5%). 2.2 g (5.4 mmol) of the desired compound were obtained.

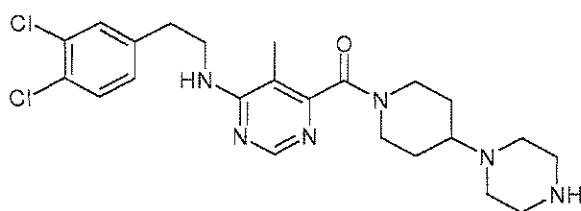
The following intermediates were synthesized in analogy to intermediate 28a.

Acid Intermediate	Amine	Intermediate	STRUCTURE
27b	Piperidin-4-one	28b	
27c	Piperidin-4-one	28c	
27d	Piperidin-4-one	28d	
27g	Piperidin-4-one	28e	
27c	Azepan-4-one	28f	

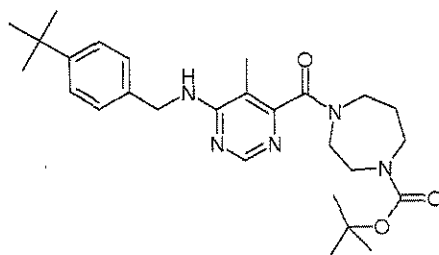
27e	Piperidin-4-one	28g	
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Intermediate 29

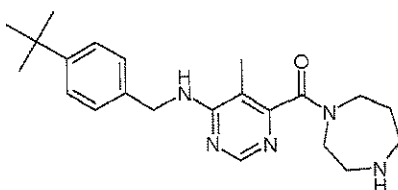
- 5 Intermediate 28a (500 mg, 1.22 mmol), piperazine-1-carboxylic acid tert-butyl ester (228 mg, 1.23 mmol) and 2-picoline borane complex (131.3 mg, 1.22 mmol) in 15 ml of methanol were stirred at room temperature for 72h; the reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with water, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product
- 10 was purified by flash chromatography (Isolute silica gel cartridge: 20g; eluent: dichloromethane/methanol=98/2%). 280 mg (0.48 mmol) of the desired compound were obtained.

15 **Intermediate 30**

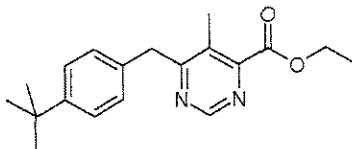
- Intermediate 29 (280 mg, 0.48 mmol) was dissolved in 6 ml of 1,4-dioxane; 4 ml (16 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under
- 20 vacuum. 240 mg (0.46 mmol) of the desired compound were obtained.

Intermediate 31

- Intermediate 27c (500 mg, 1.67 mmol), TBTU (643 mg, 2 mmol) and N,N-diisopropylethylamine (0.29 ml, 1.67 mmol) were dissolved in 5 ml of DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 min; then [1,4]diazepan-1-carboxylic acid tert-butyl ester (334 mg, 1.67 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated solution of sodium bicarbonate. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was suspended in diisopropyl ether and stirred, the solid obtained was filtered and dried. 700 mg (1.45 mmol) of the desired compound were obtained.

Intermediate 32

- Intermediate 31 (600 mg; 1.24 mmol) was suspended in 5 ml of diethyl ether, 5 ml of a 1M solution of hydrochloric acid in diethyl ether was added dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum and the crude product was loaded on a SCX cartridge (10g) and eluted with a 2M solution of ammonia in methanol. 470 mg (1.23 mmol) of the title compound were obtained.

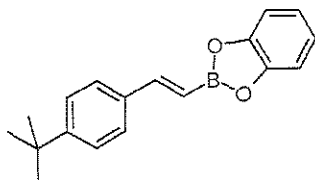
Intermediate 33

- Intermediate 3a (1.5 g, 7.47 mmol) and tetrakis(triphenylphosphine)palladium (143.9 mg, 0.12 mmol) were suspended in 40 ml of toluene under nitrogen atmosphere; 4-tert-butylbenzylzinc bromide (29.9 ml, 15 mmol) was added dropwise and then the reaction mixture was stirred at 20 °C for 8h. 5 ml of methanol, 40 ml of water and 100 ml of dichloromethane

were added. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column 40M+; eluent: dichloromethane/ethyl acetate=95/5%). 230 mg (0.74 mmol) of the desired compound were obtained.

5

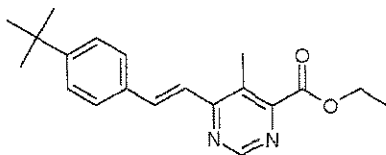
Intermediate 34



To a solution of 4-tert-butylphenylacetylene (5 ml, 28 mmol) in 20 ml of dry tetrahydrofuran under nitrogen atmosphere, a solution of catecholborane (3.41 ml, 31 mmol) in 20 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was refluxed for 2h and then concentrated under vacuum; the crude product obtained was dissolved in ethyl acetate and the organic phase was washed with a 2 M aqueous solution of hydrochloric acid. The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column 40M+; eluent: dichloromethane/ethyl acetate=95/5%). 230 mg (0.82 mmol) of the desired compound were obtained.

15

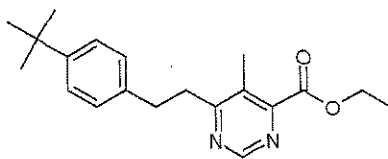
Intermediate 35



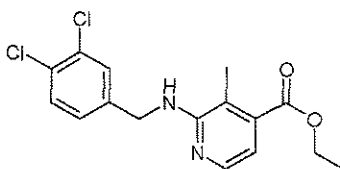
20

Intermediate 3a (600 mg, 3 mmol), intermediate 34 and tetrakis(triphenylphosphine)palladium (347 mg, 0.3 mmol) were dissolved in 3.6 ml of a 2 M aqueous solution of sodium carbonate and 40 ml of 1,2 dimethoxyethane. The reaction mixture was stirred at 80°C overnight. Water was added and the reaction mixture was extracted with dichloromethane. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product obtained was purified by flash chromatography (Biotage column 40M+; eluent: dichloromethane/ethyl acetate=95/5%). 550 mg (1.60 mmol) of the desired compound were obtained.

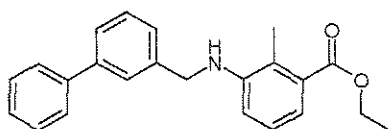
30

Intermediate 36

Intermediate 35 (250 mg, 0.77 mmol) was dissolved in 5 ml of ethanol and 5 ml of
5 tetrahydrofuran. Pd/C (35 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (1 atm) at room temperature overnight. The reaction mixture was filtered on a celite pad and concentrated under vacuum. 170 mg (0.52 mmol) of the desired compound were obtained.

Intermediate 37

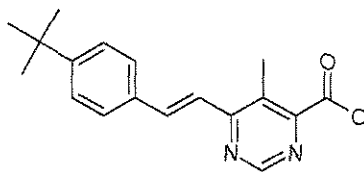
Palladium acetate (170 mg, 0.75 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (936
mg, 1.5 mmol) were dissolved in 25 ml of 1,4-dioxane and stirred at 40°C for 30 minutes. 2-
15 chloro-3-methylpyridine-4-carboxylic acid ethyl ester (500 mg, 2.5 mmol), 3,4-
dichlorobenzylamine (680 mg, 5 mmol) and cesium carbonate (715.5 mg, 3.76 mmol) were
added and the reaction mixture was refluxed for 48h. The solvent was concentrated under
vacuum and the crude product was loaded on a SCX cartridge (10g) and eluted with a 2M
solution of ammonia in methanol. The solvent was concentrated under vacuum and the crude
20 product obtained was purified by flash chromatography (Biotage column 25M+; eluent: ethyl
acetate). 250 mg (0.73 mmol) of the desired compound were obtained.

Intermediate 38

25 3-(Bromomethyl)biphenyl (150 mg, 0.58 mmol), sodium carbonate (188 mg, 1.75 mmol) and
3-amino-2-methyl-benzoic acid ethyl ester (0.1 ml, 0.58 mmol) were mixed in 2 ml of DMF
and stirred at 100°C for 2 hours. The solvent was then concentrated under vacuum and the

crude product was purified by reverse phase preparative HPLC. 131 mg (0.37 mmol) of the desired compound were obtained.

Intermediate 39a



5

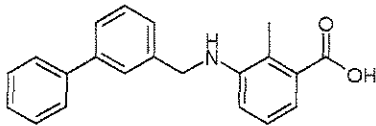
Intermediate 35 (300 mg, 0.92 mmol) was dissolved in 4 ml of ethanol and 4 ml of water. Lithium hydroxide (194 mg, 4.7 mmol) was added and the reaction mixture was stirred at 70°C for 2h, concentrated under vacuum and the remaining aqueous solution was acidified by 10 ml of a 4M solution of hydrochloric acid in 1,4-dioxane and extracted with dichloromethane; the organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. 250 mg (0.84 mmol) of the desired product were obtained.

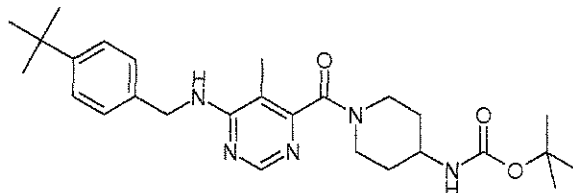
10

The following intermediates were synthesized in analogy to intermediate 39a

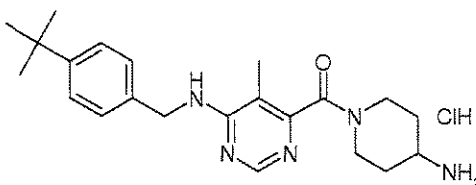
15

Ester Intermediate	Acid Intermediate	STRUCTURE
33	39b	
36	39c	
37	39d	

38	39e	
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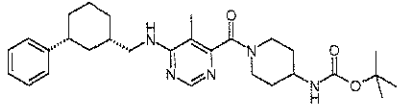
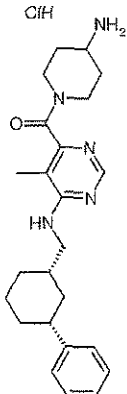
Intermediate 40a

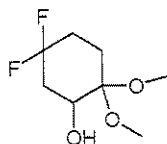
5 Intermediate 27c (660 mg, 2.20 mmol), TBTU (849 mg, 2.65 mmol) and N,N-diisopropylethylamine (0.57 ml, 3.31 mmol) were dissolved in 25 ml DMF. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 10 min; then piperidin
4-yl carbamic acid tert-butyl ester (441 mg, 2.20 mmol) was added and the reaction mixture
10 was stirred at room temperature for 18 h. The reaction mixture was diluted with
dichloromethane and washed with an aqueous saturated solution of sodium bicarbonate. The
organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The
crude product was purified by flash chromatography (Biotage SNAP column 50g; eluent:
dichloromethane/methanol=90/10%). 990 mg (2.05 mmol) of the desired compound were
15 obtained.

Intermediate 41a

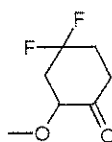
Intermediate 40a (990 mg, 2.05 mmol) was suspended in 50 ml of 1,4-dioxane, a 4M solution
20 of hydrochloric acid (8.5 ml, 34 mmol) in 1,4-dioxane was added dropwise. The reaction
mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated
under vacuum. 780 mg (18 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 40a and 41a.
25

Starting acid	Starting amine	Carbamate Intermediate	STRUCTURE	Amine intermediate	STRUCTURE
Intermediate 27ha	piperidin-4-yl carbamic acid tert-butyl ester	40b		41b	

Intermediate 42

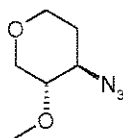
4,4-Difluorocyclohexanone (500 mg, 3.73 mmol) and potassium hydroxide (502 mg, 8.95 mmol) were dissolved in 10 ml of methanol. The reaction mixture was cooled to 0°C and a solution of iodine (1.04 g, 4.10 mmol) in 20 ml of methanol was added dropwise within 1 h. The reaction mixture was stirred at room temperature for 18 h, and then concentrated under vacuum. The crude product was stirred in 10 ml of dichloromethane and the precipitate was filtered off. The filtrate was concentrated under vacuum and 480 mg of the desired product (2.45 mmol) were obtained as an oil.

Intermediate 43

Sodium hydride (196 mg, 4.89 mmol) was suspended in 10 ml of tetrahydrofuran. The reaction mixture was cooled to 0°C and a solution of Intermediate 42 (480 mg, 4.45 mmol) in 5 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred at 0°C for 1 h, then iodomethane (0.305 ml, 4.89 mmol) was added. The reaction mixture was stirred at room

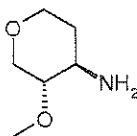
temperature for 4 h. 0.1 ml of a 37% aqueous solution of hydrochloric acid and 0.1 ml of water were added, then additional 0.3 ml of a 37% aqueous solution of hydrochloric acid were added. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under vacuum and 400 mg (2.44 mmol) of the desired product were obtained as an oil.

Intermediate 44



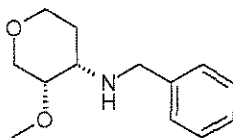
Iodomethane (3.48 ml, 55.88 mmol) was dissolved in 250 ml of tetrahydrofuran, the reaction mixture was stirred at 0°C under nitrogen atmosphere and sodium hydride (60% on mineral oil, 2.23 mg, 5.88 mmol) was added. After 15 minutes, trans 4-azido-tetrahydropyran-3-ol (4.0 g, 27.94 mmol) was added and the reaction mixture was allowed to reach room temperature and stirred for 18h. 50 ml of water were added, the organic phase was separated, dried over sodium sulphate and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (Biotage SNAP column 100g; eluent: dichloromethane/ethyl acetate=80/20%). 200 mg (1.27 mmol) of the desired regioisomer were obtained as trans racemate (relative configuration assigned by NMR).

Intermediate 45



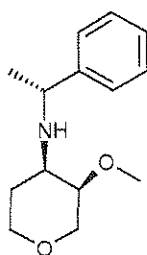
Intermediate 44 (200 mg, 1.27 mmol) was dissolved in 250 ml of methanol, Pd/C (50 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (4 bar) for 18h. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. 110 mg (0.84 mmol) of the desired product were obtained as trans racemate.

Intermediate 46a



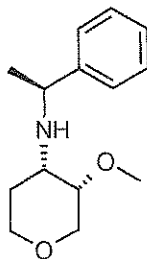
3-Methoxy-tetrahydro-pyran-4-one (500 mg, 3.84 mmol), benzylamine (0.42 ml, 3.84 mmol) and Raney-Nickel (100 mg) were suspended in 20 ml of dry ethanol and the reaction mixture was stirred under hydrogen atmosphere (4.5 bar) for 3 days. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. The crude product obtained was dissolved in 10 ml of methanol, loaded on a SCX cartridge (10g) and eluted with a 2M solution of ammonia in methanol. The solvent was concentrated under vacuum and the crude product obtained was purified by flash chromatography (Isolute cartridge 10g; eluent: dichloromethane/methanol=96/4%). 163 mg (0.73 mmol) of the desired product were obtained as cis racemate (relative configuration assigned by NMR).

Intermediate 46b



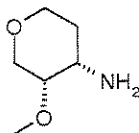
3-Methoxy-tetrahydro-pyran-4-one (1 g, 7.68 mmol), (R)-(+)-1-phenylethylamine (0.99 ml, 7.68 mmol) and Raney-Nickel (200 mg) in 10 ml dry ethanol were stirred under a hydrogen atmosphere (5 bar) for 15 days. The reaction mixture was diluted with 20 ml of methanol and 20 ml of tetrahydrofuran, stirred 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 obtained 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).

Intermediate 46c



was synthesised in analogy to Intermediate 46b, starting from 3-Methoxy-tetrahydro-pyran-4-one and (S)-(-)-1-phenylethylamine (diastereoisomeric purity confirmed and relative cis stereochemistry assigned by NMR).

Intermediate 47a

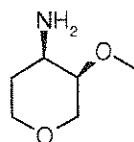


5

Intermediate 46a (163 mg, 0.73 mmol) was dissolved in 10 ml of methanol, Pd/C (50 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (4.5 bar) for 18h. The reaction mixture was filtered on a celite pad and the organic phase was concentrated under vacuum. 80 mg (0.61 mmol) of the desired product were obtained as cis racemate.

10

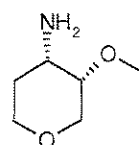
Intermediate 47b



Intermediate 46b (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.

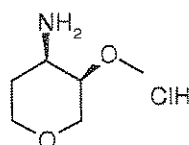
20

Intermediate 47c



was synthesised in analogy to Intermediate 47b, starting from Intermediate 46c

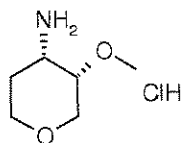
Intermediate 48b



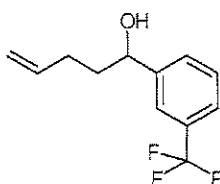
25

Intermediate 47b was stirred in diethyl ether and a 2M solution of hydrochloric acid in diethyl ether was added drop-wise until a white solid was formed. The reaction mixture was concentrated under vacuum, the crude product was suspended in methanol and the reaction mixture was concentrated under vacuum to give the desired hydrochloride.

5

Intermediate 48c

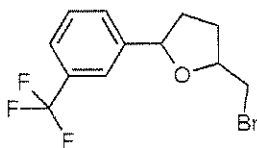
was synthesised in analogy to Intermediate 48b, starting from Intermediate 47c.

Intermediate 49a

10

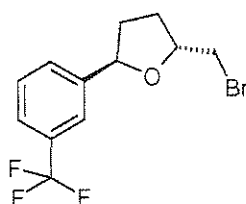
3-(trifluoromethyl)benzaldehyde (6.46 ml, 48.24 mmol) was dissolved in 80 ml of dry tetrahydrofuran, the reaction mixture was cooled to -78°C and a 0.5M solution of 3-butenylmagnesiumbromide in tetrahydrofuran (106.13 ml, 53.06 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 30 minutes. Then, the reaction mixture was allowed to reach room temperature and stirred 18h. Then, 100 ml of a saturated aqueous solution of ammonium chloride and 200 ml of ethyl acetate were added. the organic layer was separated, dried over sodium sulfate and concentrated under vacuum. 7.75 g (33.69 mmol) of the desired product were obtained.

20 **Intermediate 50a**

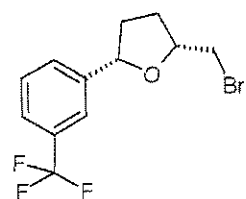


Intermediate 49a was dissolved in 70 ml of dry dichloromethane, the reaction mixture was stirred under nitrogen atmosphere at 0°C and N-bromosuccinimide was added. The reaction mixture was allowed to reach room temperature and stirred for 48h. The reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography (Isolera cartridge eluent: hexane/ethyl acetate= 90/10%) to obtain the desired product as diastereoisomeric mixture.

25

Intermediate 51a

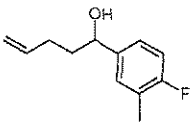
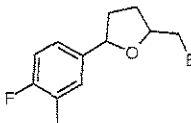
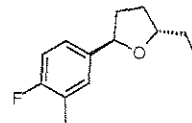
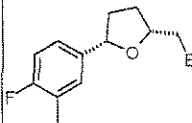
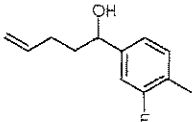
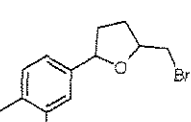
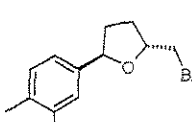
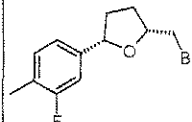
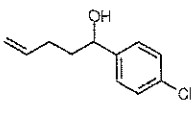
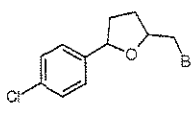
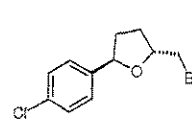
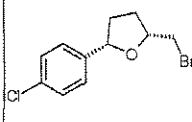
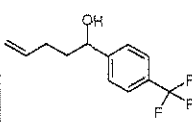
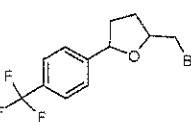
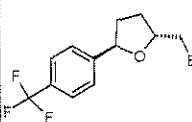
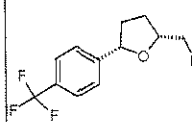
Intermediate 50a was purified by flash chromatography (Isolera cartridge; eluent: hexane/ethyl acetate= 98/2%). 2.3 g (7.44 mmol) of the trans diastereoisomer were obtained as racemic mixture (relative stereochemistry assigned by NMR).

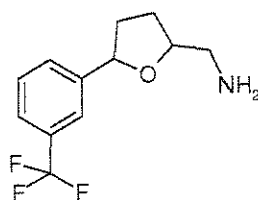
Intermediate 52a

Further elution of the column gave 1.05 g (3.39 mmol) of the cis diastereoisomer as racemic mixture (relative stereochemistry assigned by NMR).

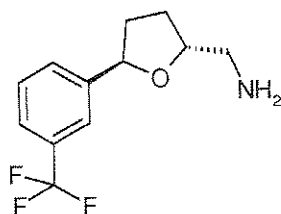
The following intermediates were synthesized in analogy to Intermediates 49a, 50a, 51a and 52a

Starting aldehyde	Intermediate	STRUCTURE	Intermediate	STRUCTURE	Intermediate	STRUCTURE	Intermediate	STRUCTURE
3-Methyl-benzaldehyde	49 b		50 b		51 b		52 b	
4-Methyl-benzaldehyde	49 c		50 c		51 c		52 c	

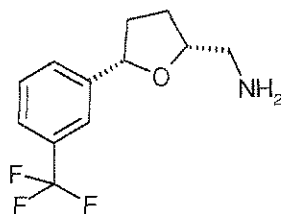
4-Fluoro-3-methyl- benzaldehyde	49 d		50 d		51 d		52 d	
3-Fluoro-4-methyl- benzaldehyde	49 e		50 e		51 e		52 e	
4-Chloro- benzaldehyde	49 f		50 f		51 f		52 f	
4-Trifluoromethyl- benzaldehyde	49 g		50 g		51 g		52 g	

Intermediate 53a

Intermediate 50a (1.7 g, 5.49 mmol) was dissolved in 5 ml of DMSO and the reaction mixture was stirred under nitrogen atmosphere at room temperature. Phtalimide potassium salt (2.54 g, 13.75 mmol) and sodium iodide (240 mg, 1.60 mmol) were added and the reaction mixture was stirred at 70°C for 18h. The reaction mixture was cooled to room temperature and diluted with 40 ml of a saturated aqueous sodium bicarbonate solution and with 100 ml of ethyl acetate. The organic layer was separated, dried on sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Isolera cartridge; eluent: hexane/ethyl acetate= 85/15%) to yield 1.2 g (3.2 mmol) of the phtalimido intermediate. The phtalimido intermediate (1.2g, 3.2 mmol) was dissolved in 15 ml of methanol. Hydrazine hydrate (1.24 ml, 25.60 mmol) was added and the reaction mixture was stirred at room temperature for 48h. The reaction mixture was concentrated under vacuum. The crude product was dissolved in 10 ml of dichlorometane, the organic layer was washed with water, separated, dried on sodium sulfate and concentrate under vacuum. 474 mg (1.93 mmol) of the desired product were obtained.

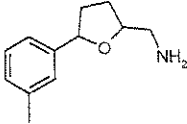
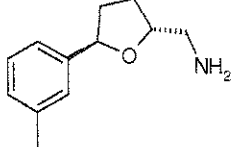
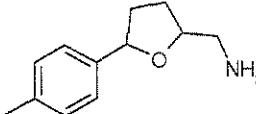
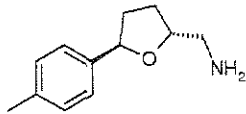
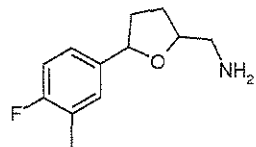
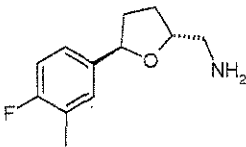
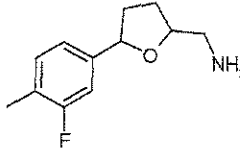
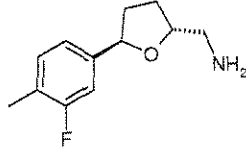
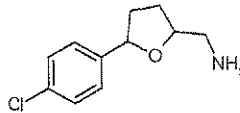
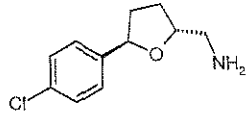
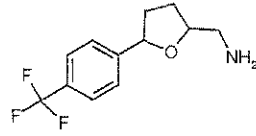
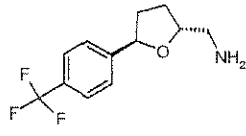
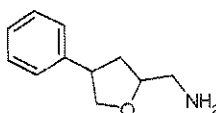
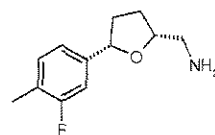
Intermediate 54a

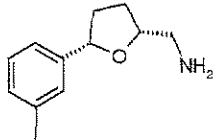
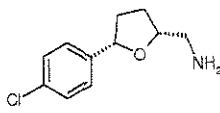
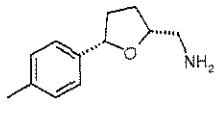
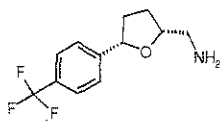
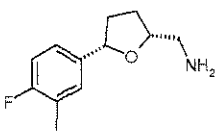
was synthesized in analogy to Intermediate 53a starting from intermediate 51a

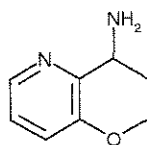
Intermediate 55a

was synthesized in analogy to Intermediates 53a starting from intermediate 52a.

The following intermediates were synthesized in analogy to Intermediates 53a, 54a and 55a.

Starting Intermediate	Intermediate	STRUCTURE	Starting intermediate	Intermediate	STRUCTURE
50b	53b		51b	54b	
50c	53c		51c	54c	
50d	53d		51d	54d	
50e	53e		51e	54e	
50f	53f		51f	54f	
50g	53g		51g	54g	
2-bromomethyl-4-phenyl-tetrahydro-furan	53h		52e	55e	

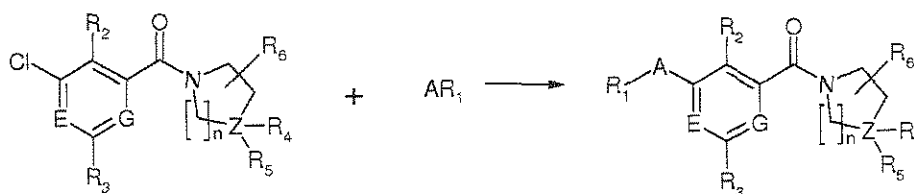
52b	55b		52f	55f	
52c	55c		52g	55g	
52d	55d				

Intermediate 56

- 5 2,3-Dihydro-pyrano[3,2-b]pyridine-4-one (250 mg, 1.7 mmol) and Raney-Nickel (25 mg) were added to a solution of ammonia in ethanol (10 ml) and the reaction mixture was stirred under hydrogen atmosphere (3 bar) for 18h at room temperature. Then, the catalyst was removed by filtration on a celite pad and the mixture was concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product (129 mg, 600
10 μmol).

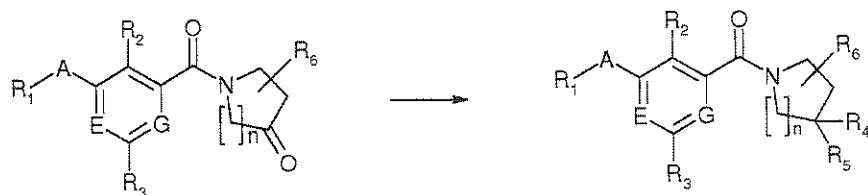
SYNTHESIS OF EXAMPLES

- 15 E and G within the scope of this invention denotes C or N, preferred nitrogen. The examples of this invention are synthesized according to the following general synthetic procedures:

Synthetic Procedure A:

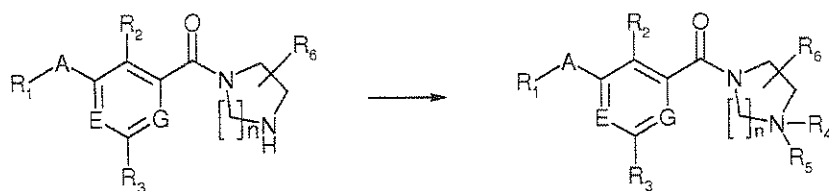
20

Examples: 1-159gc; 289-302

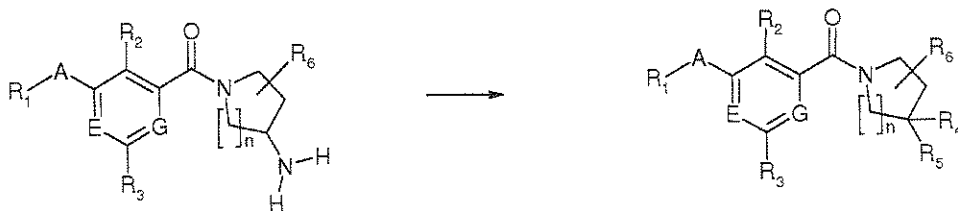
Synthetic Procedure B:

Examples: 160-247; 228a; 228ga-228gn; 229-247

5

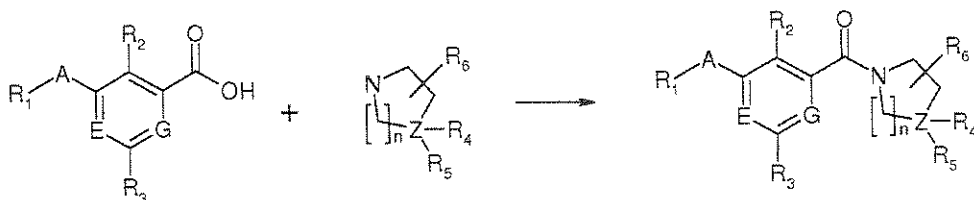


Examples: 286-288

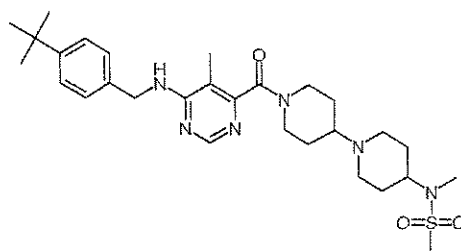


Examples: 228b-228g; 228go; 228gp

10 **Synthetic Procedure C:**



Examples: 248-283; 275a-275dj

Example 1

- Intermediate 25b (70 mg, 0.16 mmol), 4-tert-butyl-benzylamine (32 mg, 0.19 mmol) and N,N-diisopropyl-ethyl amine (0.042 ml, 0.24 mmol) in 2 ml of dry 1,4-dioxane were stirred at 70°C overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Silica Isolute cartridge 5g; eluent: ethyl acetate/methanol=90/10%). 16 mg (0.027 mmol) of the desired product were obtained.
- HPLC (Method 2F): R_t (min) = 7.59

$$[M+H]^+ = 557$$

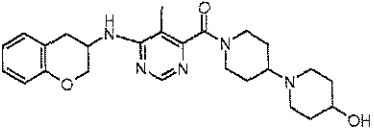
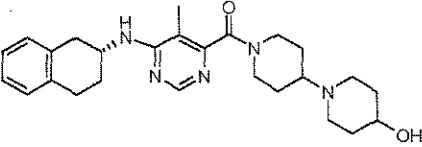
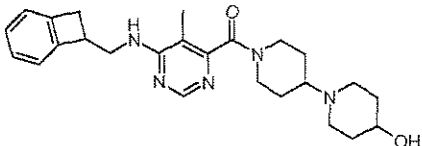
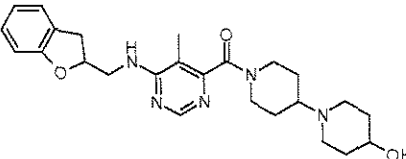
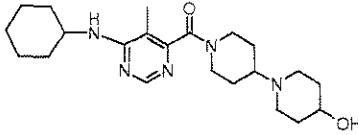
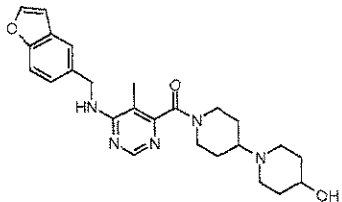
The following examples were synthesized in analogy to the preparation of Example 1.

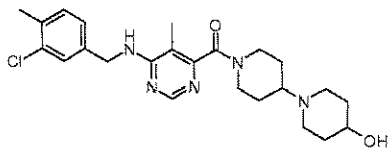
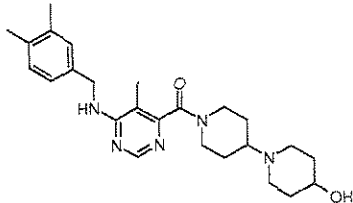
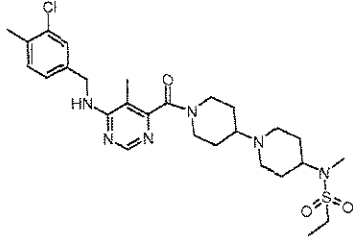
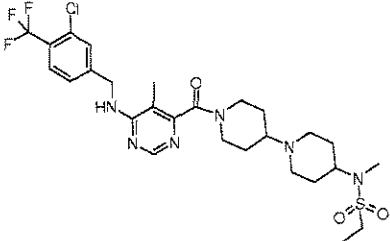
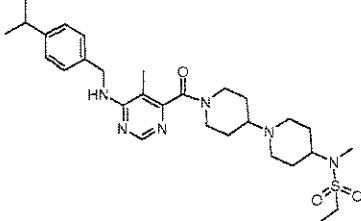
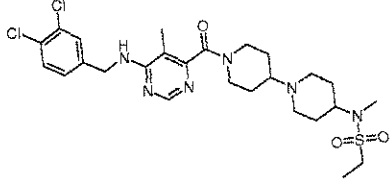
Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
2		25i	2-(3,4-dichloro-phenyl)-ethyl-amine	476	7.98	1E
3		25f	2-(3,4-dichloro-phenyl)-ethyl-amine	492	2.91	B

4		25f	3-trifluoromethylbenzylamine	478	6.77	1E
5		25f	4-trifluoromethoxybenzylamine	494	6.78	1E
6		25f	3-fluoro-5-trifluoromethylbenzylamine	496	6.73	1E
7		25f	4-tert-butylbenzylamine	466	7.45	1E
8		25f	3-trifluoromethoxybenzylamine	494	7.08	1E
9		25f	4-trifluoromethylbenzylamine	478	6.63	1E

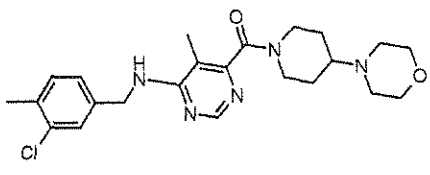
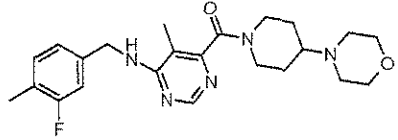
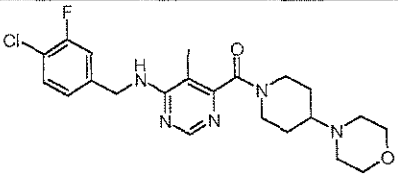
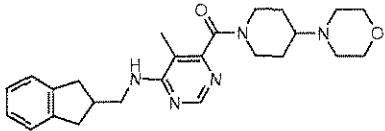
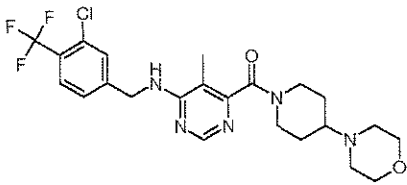
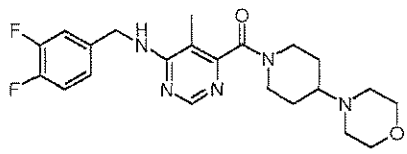
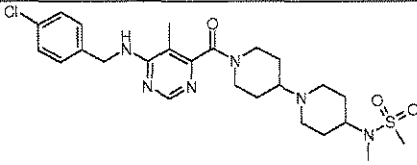
10		25f	3-fluoro-4-trifluoromethylbenzylamine	496	6.85	1E
11		25f	2-(3-(trifluoromethylphenyl)-ethylamine	492	7.23	1E
12		25f	2-(4-(trifluoromethylphenyl)-ethylamine	492	7.37	1E
13		25f	(4-(trifluoromethyl)cyclohexyl)-methanamine	484	6.82	1E
14		25f	2-(4-(trifluoromethoxyphenyl)-ethylamine	508	7.37	1E (Fusion)
15		25f	4-phenylbutylamine	452	7.15	1E

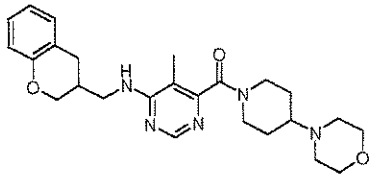
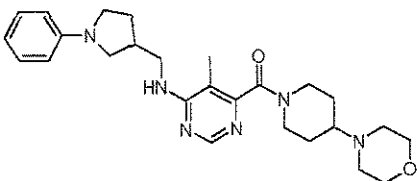
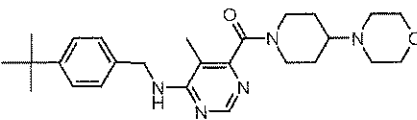
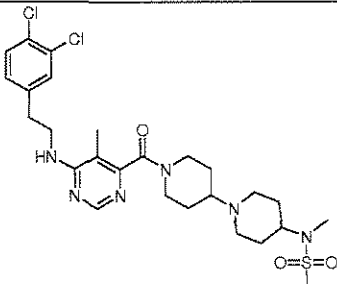
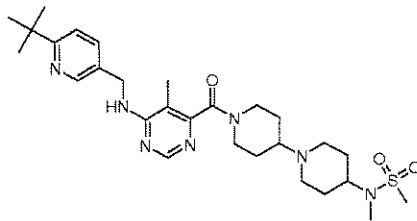
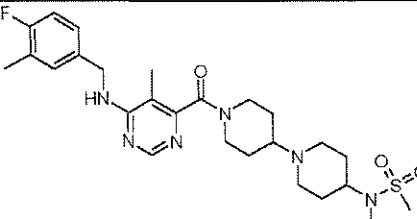
16		25f	2-phenoxylethyl-amine	440	7.10	1E (Fusion)
17		25f	3-phenylpropyl-amine	438	7.83	1E (Fusion)
18		25f	2-benzyloxyethyl-amine	454	5.83	1E (Hydro)
19		25f	chroman-3-yl-methan-amine	466	7.85	1E (Fusion)
20		25f	(1-phenylpyrrolidin-3-yl)-methan-amine	479	7.05	1E (Hydro)
21		25f	2-fluoro-4-trifluoromethylbenzyl-amine	496	8.38	1E (Fusion)
22		25f	4-phenylcyclohexyl-amine	478	9.38	1E (Fusion)
23		25f	indan-2-yl-methan-amine	450	6.55	1E (Hydro)

24		25f	chroman-3-ylamine	452	6.18	1E (Hydro)
25		25f	(R)-(1,2,3,4-tetrahydro-2-naphthalen-2-yl)amine	450	7.08	1E (Hydro)
26		25f	(1,2-dihydrocyclobuten-1-yl)methanamine	436	6.93	1E (Hydro)
27		25f	(2,3-dihydrobenzofuran-2-yl)methanamine	452	6.47	1E (Hydro)
28		25f	Cyclohexylamine	402	4.90	1E
29		25f	benzofuran-5-ylmethanamine	450	6.73	1E (Hydro)

30		25f	3-chloro-4-methylbenzylamine	458	7.75	1E (Hydro)
31		25f	3,4-dimethylbenzylamine	438	7.37	1E (Hydro)
32		25c	3-chloro-4-methylbenzylamine	563	6.98	2F
33		25c	3-chloro-4-trifluoromethylbenzylamine	617	9.47	1E (Hydro)
34		25c	4-isopropylbenzylamine	557	7.03	2F
35		25c	3,4-dichlorobenzylamine	583	8.65	1E (Hydro)

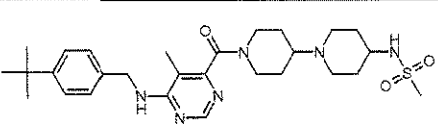
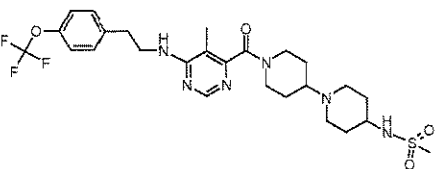
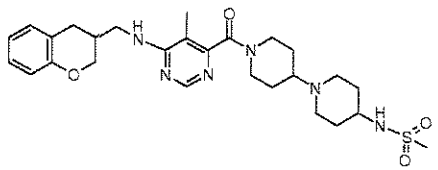
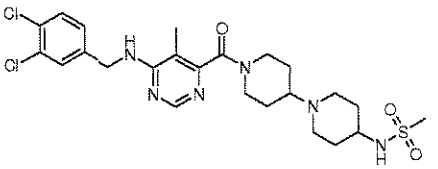
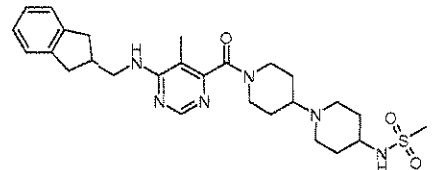
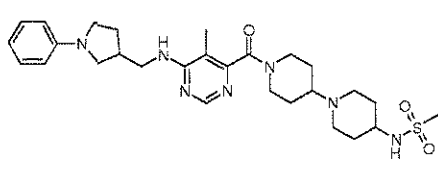
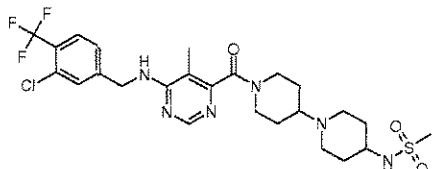
36		25c	2-(3,4-dichloro-phenyl)-ethyl-amine	597	9.72	1E (Hydro)
37		25c	4-tert-butyl-benzyl-amine	571	9.28	1E (Hydro)
38		25c	9a	598	1.45	2F
39		25c	4-chloro-3-fluoro-benzyl-amine	567	8.82	1E (Hydro)
40		25c	(1-phenyl-piperidin-4-yl)-methan-amine	598	8.98	1E (Hydro)
41		25c	9b	584	8.92	1E (Hydro)
42		25h	9a	479	8.67	1E (Hydro)

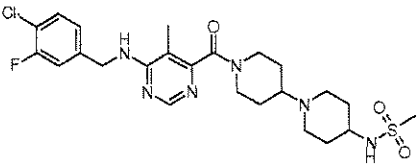
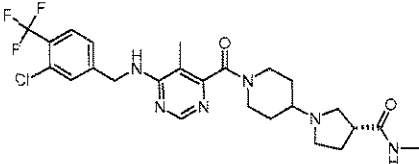
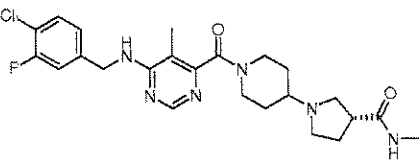
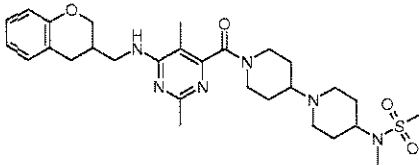
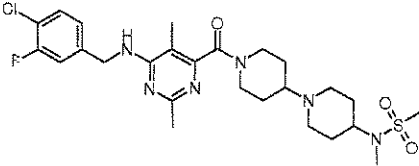
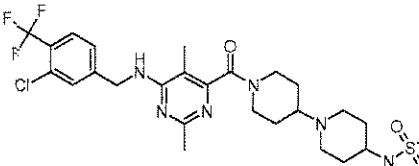
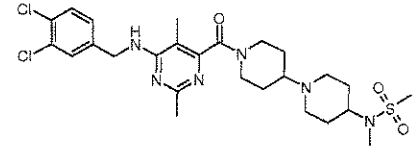
43		25h	3-chloro-4-methylbenzylamine	444	8.63	1E (Hydro)
44		25h	3-fluoro-4-methylbenzylamine	428	7.58	1E (Hydro)
45		25h	4-chloro-3-fluorobenzylamine	448	7.88	1E (Hydro)
46		25h	indan-2-ylmethanamine	436	8.27	1E (Hydro)
47		25h	3-chloro-4-(trifluoromethyl)benzylamine	498	7.30	2F
48		25h	3,4-difluorobenzylamine	432	4.20	2G
49		25b	4-chlorobenzylamine	535	7.38	2F

50		25h	chroman-3-ylmethanamine	452	7.85	1E (Hydro)
51		25h	(1-phenylpyrrolidin-3-yl)methanamine	465	8.93	1E (Hydro)
52		25h	4-tert-butylbenzylamine	452	7.18	2F
53		25b	2-(3,4-dichlorophenyl)ethylamine	583	7.97	1E (Hydro)
54		25b	(6-tert-butylpyridin-3-yl)methanamine	558	7.73	1E (Hydro)
55		25b	4-fluoro-3-methylbenzylamine	533	8.05	1E (Hydro)

56		25b	4-ethyl- benzyl- amine	529	8.35	1E (Hydro)
57		25b	chroman- 3- ylmethan amine	557	7.62	1E (Hydro)
58		25b	(1- phenyl- piperidin -4yl)- methan- amine	584	8.05	1E (Hydro)
59		25b	3-chloro- 4- methyl- benzyl- amine	549	8.22	1E (Hydro)
60		25b	(1- phenyl- pyrrolidi n-3-yl)- methan- amine	570	8.07-8.47	1E (Hydro)
61		25b	indan- 2yl- methan- amine	541	8.03	1E (Hydro)

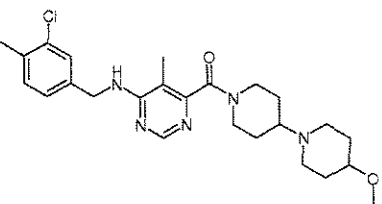
62		25b	3-chloro-4-trifluoromethylbenzylamine	603	8.68	1E (Hydro)
63		25b	4-chloro-3-fluorobenzylamine	553	7.55	1E (Hydro)
64		25b	4-isopropylbenzylamine	543	6.82	2F
65		25b	3-fluoro-4-methylbenzylamine	533	8.57	1E (Hydro)
66		25b	3-chlorobenzylamine	535	6.72	2F
67		25b	4-methoxybenzylamine	531	2.39	2F
68		25b	3-chloro-4-fluorobenzylamine	553	7.57	2F

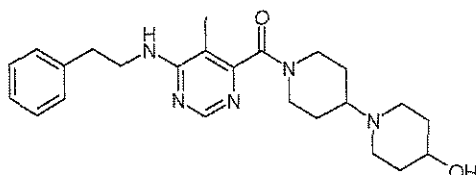
69		25a	4-tert-butylbenzylamine	543	7.97	1E (Hydro)
70		25a	4-trifluoromethoxybenzylamine	585	7.63	1E (Hydro)
71		25a	chroman-3-ylmethanamine	543	6.75	1E (Hydro)
72		25a	3,4-dichlorobenzylamine	555	7.30	1E (Hydro)
73		25a	indan-2-ylmethanamine	527	7.35	1E (Hydro)
74		25a	(1-phenylpyrrolidin-3-yl)methanamine	555	7.43-7.80	1E (Hydro)
75		25a	3-chloro-4-trifluoromethylbenzylamine	589	7.48	2F

76		25a	4-chloro-3-fluoro-benzyl-amine	539	2.07	1F
77		25e	3-chloro-4-trifluoro methyl-benzyl-amine	539	8.23	1E (Hydro)
78		25e	4-chloro-3-fluoro-benzyl-amine	489	7.33	1E (Hydro)
79		25l	chroman-3-ylmethanamine	571	8.13	1E (Hydro)
80		25l	4-chloro-3-fluoro-benzyl-amine	567	8.36	1E (Hydro)
81		25l	3-chloro-4-trifluoro methyl-benzyl-amine	617	9.12	1E (Hydro)
82		25l	3,4-dichloro-benzyl-amine	583	8.83	1E (Hydro)

83		25l	4-tert-butylbenzylamine	571	9.73	1E (Hydro)
84		25l	(1-phenylpyrrolidin-3-yl)methanamine	584	8.70-9.02	1E (Hydro)
85		25l	9c	584	9.1	1E (Hydro)
86		25l	indan-2-ylmethanamine	555	8.80	1E (Hydro)
87		25l	9a	598	8.97	1E (Hydro)
88		25k	3,4-dichlorobenzylamine	569	7.78	1E (Hydro)
89		25k	3-phenylcyclohexylamine	569	8.45	1E (Hydro)
90		25k	chroman-3-ylmethanamine	557	7.20	1E (Hydro)

91		25 m	2-(3,4-dichloro-phenyl)-ethyl-amine	506	7.87	1E
92		25 m	3,4-dichloro-benzyl-amine	492	7.62	1E
93		25d	(1-phenyl-pyrrolidin-3-yl)-methan-amine	520	7.70	1E (Hydro)
94		25g	4-isopropyl-benzyl-amine	466	6.71	2F
95		25g	4-chloro-3-fluoro-benzylam-ine	476	9.18	1E (Hydro)
96		25g	(1-phenyl-piperidin-4-yl)-methan-amine	507	9.55	1E (Hydro)
97		25g	9a	507	1.22	2F

98		25g	3-chloro-4-methylbenzyl-amine	472	9.62	1E (Hydro)
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Example 99

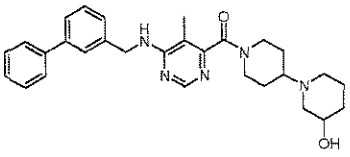
Intermediate 2a (200 mg, 1.047 mmol) was dissolved in 30ml of dichloromethane.

- 5 [1,4']Bipiperidiny-4-ol (192 mg, 1.047 mmol) was added and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated under vacuum and the crude product was dissolved in 1 ml of DMSO. Phenethylamine (0.6 ml, 4.73 mmol) and N,N-diisopropyl-ethyl amine (0.013 ml, 0.075 mmol) were added and the reaction mixture was stirred at 80°C overnight. The reaction mixture was concentrated under vacuum. The
- 10 the crude product was purified by reverse phase preparative HPLC. 331 mg (0.616 mmol) of the desired product were obtained.

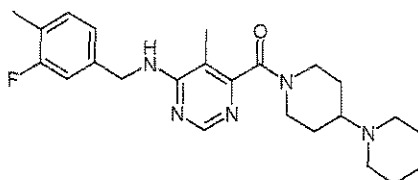
HPLC (Method C): R_t (min) = 1.34

$[M+H]^+ = 424$

- 15 The following examples were synthesized in analogy to the preparation of Example 99.

Ex #	STRUCTURE	Intermediate	Inter-mediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
100		2a	[1,4']-Bipiperidiny-3-ol	Biphenyl-3-yl-methan-amine	486	1.53	2C

101		2a	[1,4']Bip iperidiny -4-ol	Bipheny l-4-yl- methan- amine	486	1.51	2C	
102		2a	[1,4']Bip iperidiny -4-ol	Bipheny l-3-yl- methan- amine	486	1.52	2C	
103		6-chloro-pyrimidine-4-carbonyl chloride		[1,4']- Bipiperid in-yl-3-ol	Bipheny l-4-yl- methan- amine	472	1.59	2C

Example 104

Intermediate 25i (17 mg, 0.05 mmol), 3-fluoro-4-methyl-benzylamine (10 mg, 0.075 mmol) and diisopropyl-ethyl amine (0.013 ml, 0.075 mmol) in 1 ml of dry DMSO were stirred at 80°C overnight. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 20 mg (0.047 mmol) of the desired product were obtained.

HPLC (Method C): R_t (min) = 1.45

$[M+H]^+ = 426$

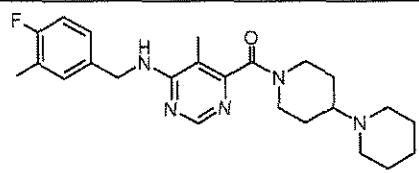
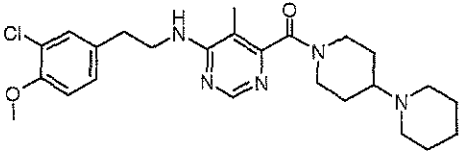
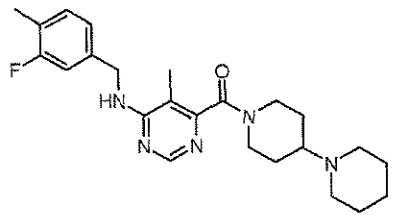
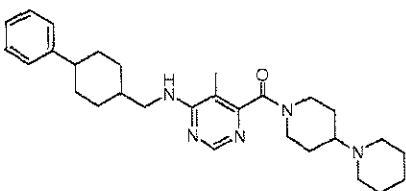
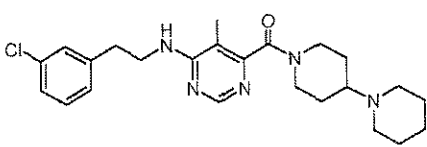
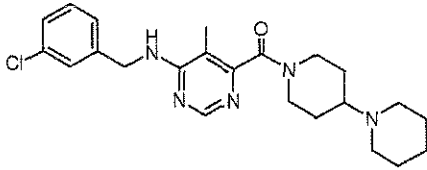
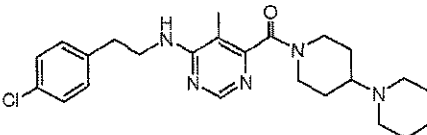
The following examples were synthesized in analogy to the preparation of Example 104.

Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
105		25f	2-(3-chloro-4-methoxy-phenyl)-ethyl-amine	488	1.43	2C
106		25f	2-(4-isopropyl-phenyl)-ethylamine	466	2.88	2B
107		25h	3,4-dichloro-benzyl-amine	464	5.6	1A
108		25f	Cyclohexyl-methan-amine	416	2.67	2B
109		25f	3,4-dichloro-benzyl-amine	478	2.81	2B
110		25f	4-chloro-benzyl-amine	444	1.6	2A

111		25f	3-chloro-4-fluoro-benzyl-amine	462	1.63	2A
112		25f	2-(4-tert-butyl-phenyl)-ethylamine	480	1.8	2A
113		25f	(1-phenyl-piperidin-4-yl)methan-amine	493	1.32	2A
114		25f	7a	492	7.42	2F
115		25f	2-(3,4-difluoro-phenyl)-ethylamine	460	1.61	2A
116		25f	3-chloro-4-trifluorome-thyl-benzyl-amine	512	1.74	2A
117		25f	4-chloro-3-fluoro-benzyl-amine	462	1.64	2A
118		25f	4-fluoro-3-methyl-benzyl-amine	442	1.61	2A

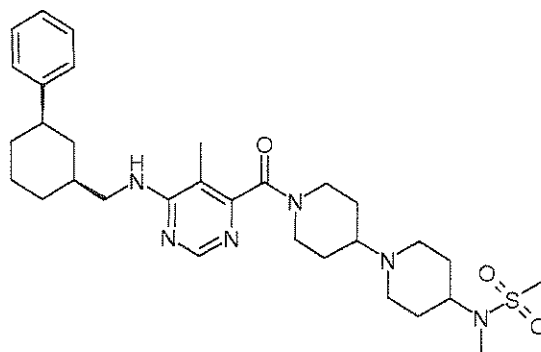
119		25f	2-(3-chloro-4-methoxyphenyl)-ethyl-amine	488	1.63	2A
120		25f	3-fluoro-4-methylbenzyl-amine	442	1.61	2A
121		25f	(4-phenylcyclohexyl)-methan-amine	492	1.78	2A
122		25f	2-(3-chloro-phenyl)-ethylamine	458	1.63	2A
123		25f	3-chloro-benzyl-amine	444	1.6	2A
124		25f	2-(4-chloro-phenyl)-ethylamine	458	1.65	2A
125		25f	4-chloro-3-trifluoromethyl-benzyl-amine	512	1.74	2A
126		25f	2-(3,4-dimethyl-phenyl)-ethylamine	452	1.68	2A

127		25i	4-chloro-benzyl-amine	428	1.65	2A
128		25i	3-chloro-4-fluoro-benzyl-amine	446	1.67	2A
129		25i	2-(4-tert-butyl-phenyl)-ethylamine	464	1.84	2A
130		25i	(1-phenyl-piperidin-4-yl)-methan-amine	477	1.37	2A
131		25i	7a	476	1.84	2A
132		25i	2-(3,4-difluoro-phenyl)-ethylamine	444	1.66	2A
133		25i	3-chloro-4-trifluoromethyl-benzyl-amine	496	1.79	2A
134		25i	4-chloro-3-fluoro-benzyl-amine	446	1.67	2A

135		25i	4-fluoro-3-methyl-benzyl-amine	426	1.65	2A
136		25i	2-(3-chloro-4-methoxy-phenyl)-ethylamine	472	1.66	2A
137		25i	3-fluoro-4-methyl-benzyl-amine	426	1.65	2A
138		25i	(4-phenylcyclohexyl)-methan-amine	476	1.84	2A
139		25i	2-(3-chloro-phenyl)-ethylamine	442	1.68	2A
140		25i	3-chloro-benzyl-amine	428	1.64	2A
141		25i	2-(4-chloro-phenyl)-ethylamine	442	1.69	2A

142		25i	4-chloro-3-trifluoromethylbenzylamine	496	1.79	2A
143		25i	2-(3,4-dimethylphenyl)ethylamine	436	1.72	2A
144		25f	7a	492	7.7	2H (iso-cratic)
145		25f	7a	492	10.2	2H (iso-cratic)

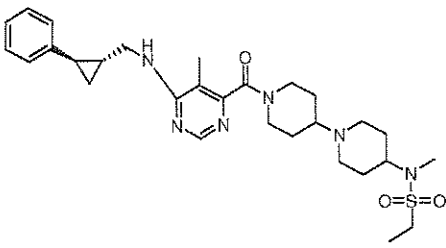
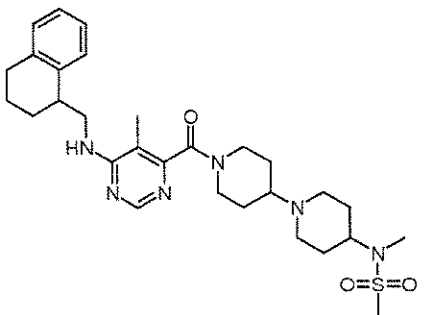
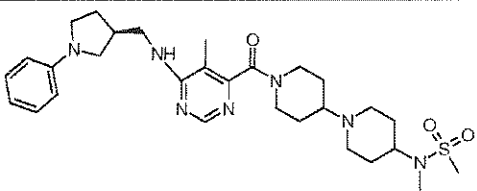
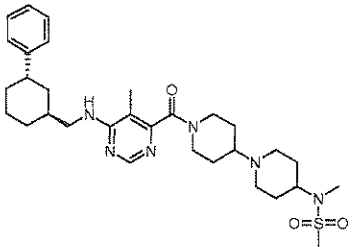
Example 146



- 5 Intermediate 25b (80 mg, 0.18 mmol) , Intermediate 7c (40 mg, 0.21 mmol) and N,N-diisopropyl-ethyl amine (0.046 ml, 0.26 mmol) in 0.2 ml of dry 1,4-dioxane were mixed in a microwave vial and reacted in the following conditions: Power 100, Ramp 5 min, Hold 2h, Temperature 150°C, Pression 150°C, Stirring. The reaction mixture was concentrated under vacuum and diluted with dichloromethane. The organic phase was washed with an aqueous
- 10 saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 36 mg (0.06 mmol) of the desired product were obtained.

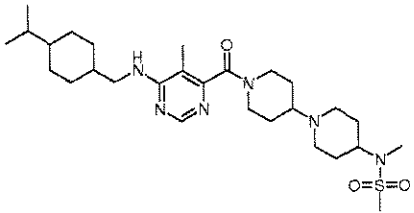
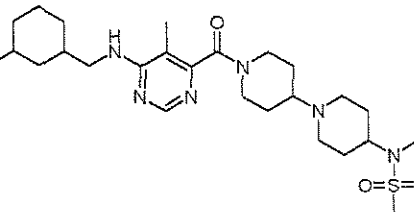
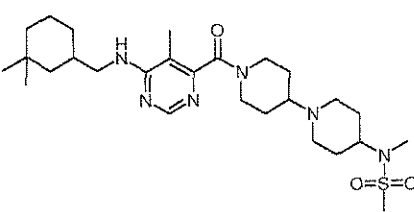
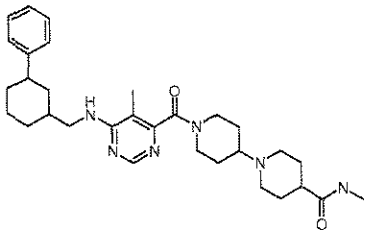
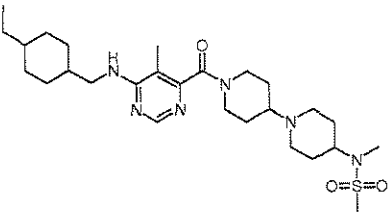
HPLC (Method 1E Hydro): R_t (min) = 9.52 $[M+H]^+ = 583$

The following examples were synthesized in analogy to the preparation of Example 146

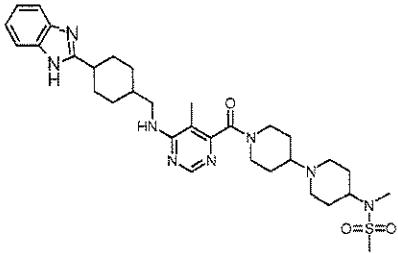
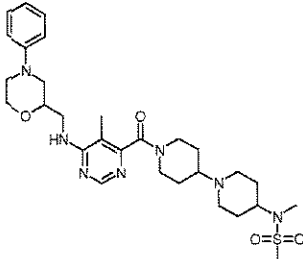
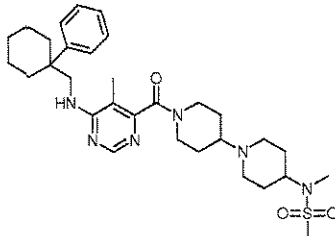
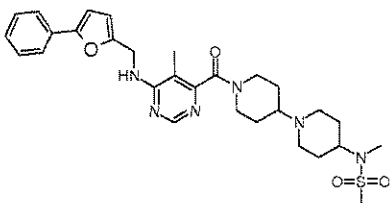
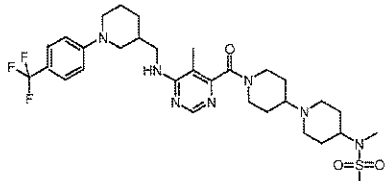
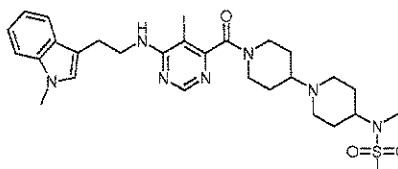
Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
147		25c	(trans-2-phenylcyclopropyl)methanamine	555	8.48	1E (Hydro)
148		25b	(1,2,3,4-tetrahydronaphthalen-1-yl)methanamine	555	8.62	1E (Hydro)
149		25b	9c	570	8.7	1E (Hydro)
150		25b	7d	583	9.12	1E (Hydro)

151		25b	7e	583	9.22	1E (Hydro)
152		25b	(trans-2-phenyl-cyclo-propyl)-methan-amine	541	8.03	1E (Hydro)
153		25b	2-(4-tert-butyl-phenyl)-ethyl-amine	571	9.42	1E (Hydro)
154		25b	11	643	8.65	1E (Hydro)
155		25b	9a	584	8.52	1E (Hydro)
156		25b	9b	570	8.48	1E (Hydro)
157		25b	Quinolin-3-ylmethan-amine	552	1.28	2F

158		25b	7b	583	9.48	1E (Hydro)
159		25l	9b	584	8.85	1E (Hydro)
159a		25n	7a	613	2.21	2Ca
159b		25n	4-tert-butylbenzylamine	587	1.89	2Ca
159c		25b	7m	603	9.88	1E (Hydro)
159d		25b	7l	569	9.62	1E (Hydro)
159e		25b	C-Cyclohexyl-methylamine	507	8.37	1E (Hydro)

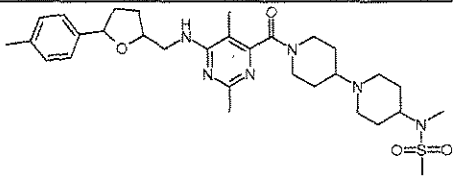
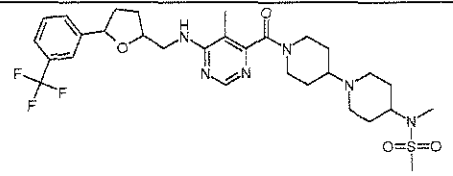
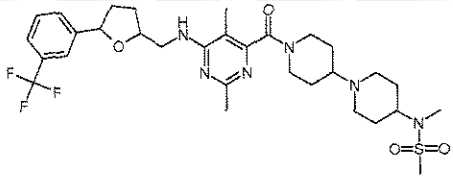
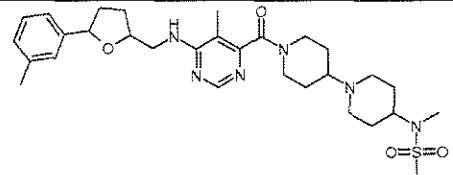
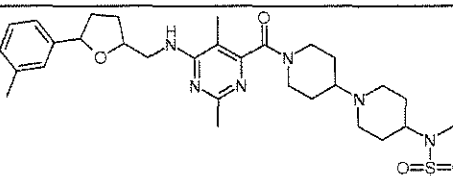
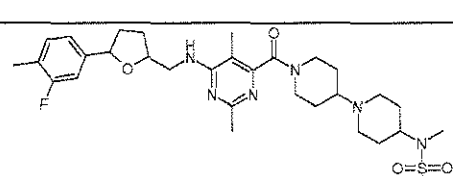
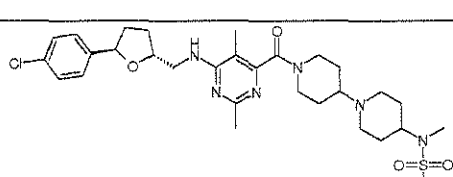
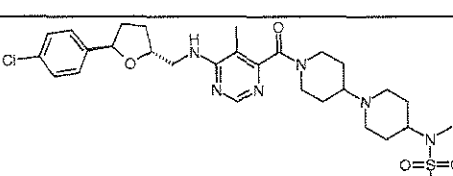
159f		25b	C-(4-isopropyl-cyclohexyl)-methyl-amine	549	10.12	1E (Hydro)
159g		25b	C-(3-methyl-cyclohexyl)-methyl-amine	521	9.25	1E (Hydro)
159h		25b	C-(3,3-dimethyl-cyclohexyl)-methyl-amine	535	9.68	1E (Hydro)
159i		25d	7a	533	9.53	1E (Hydro)
159k		25b	C-(4-ethyl-cyclohexyl)-methyl-amine	535	9.98	1E (Hydro)

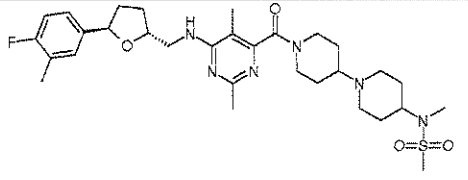
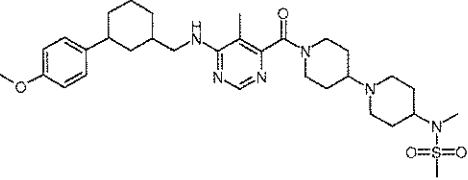
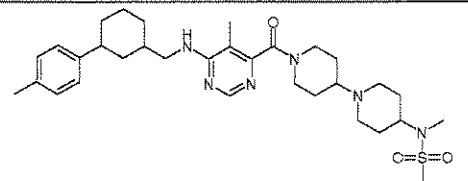
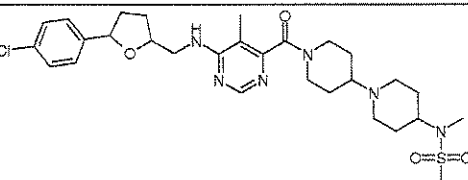
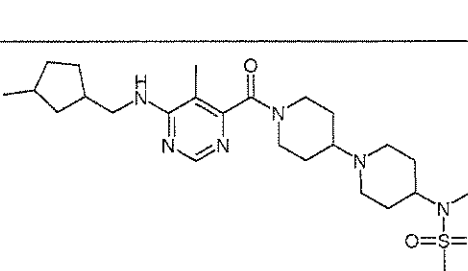
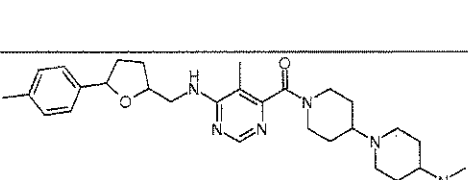
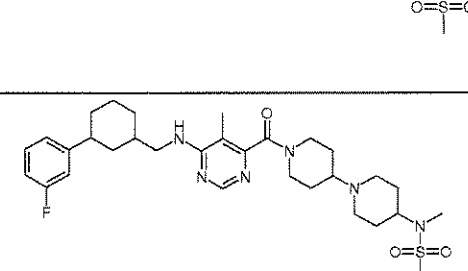
159l		25b	C-(4-methyl-cyclo-hexyl)-methyl-amine	521	9.28	1E (Hydro)
159m		25a	7a	569	9.33	1E (Hydro)
159n		25b	C-(3-pyridin-2-yl-cyclo-hexyl)-methyl-amine	584	7.90 8.05	1E (Hydro)
159o		25b	C-(4-tert-butyl-cyclo-hexyl)-methyl-amine	563	10.87	1E (Hydro)
159p		25d	7c	533	9.53	1E (Hydro)
159q		25b	7n	587	9.37	1E (Hydro)

159r		25b	C-[4-(1H-Benzimidazol-2-yl)-cyclohexyl]-methylaniline	623	7.17	1E (Hydro)
159s		25b	C-[(4-phenylmorpholin-2-yl)-methylaniline	586	7.73	1E (Hydro)
159t		25b	C-(1-phenylcyclohexyl)-methylaniline	583	9.5	1E (Hydro)
159u		25b	C-(5-phenylfuran-2-yl)-methylaniline	567	8.93	1E (Hydro)
159w		25b	9d	652	9.57	1E (Hydro)
159y		25b	2-(1-methyl-1H-indol-3-yl)-ethylaniline	568	8.2	1E (Hydro)

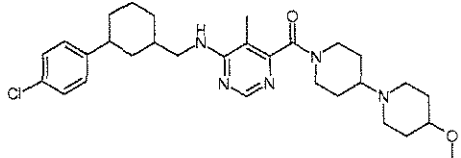
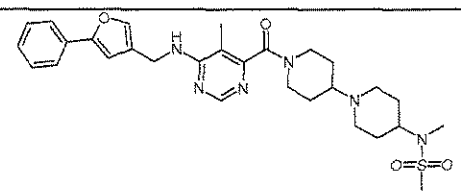
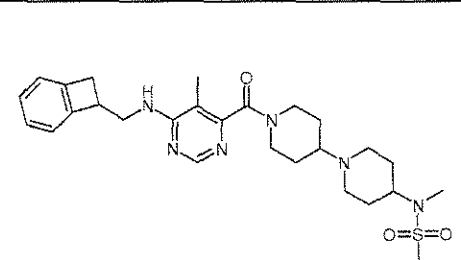
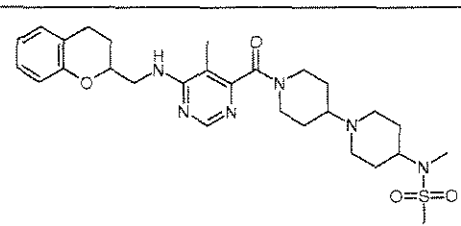
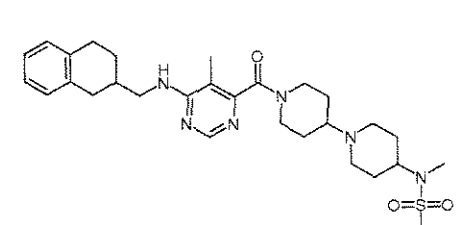
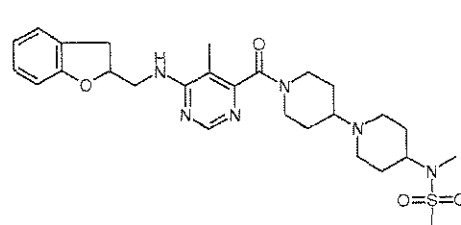
159x		25b	C-Indan-1-yl-methyl-amine	541	8.27	1E (Hydro)
159z		25b	7g	601	9.8	1E (Hydro)
159aa		25d	7g	551	9.47	1E (Hydro)
159ba		25a	7g	587	9.32	1E (Hydro)
159ca		25a	7f	603	9.95	1E (Hydro)
159da		25b	7f	617	10.5	1E (Hydro)
159ea		25d	7f	567	7.4	2F
159fa		25b	C-cycloheptyl-methyl-amine	521	8.88	1E (Hydro)

159ga		25l	54a	653	5.38	2M
159ha		25b	54a	639	5.94	2M
159ia		25b	54b	585	5.42	2M
159ja		25l	54b	599	4.76	2M
159ka		25l	55g	653	9.37	1E (Hydro)
159la		25b	55g	639	9.02	1E (Hydro)
159ma		25b	54g	639	9.07	1E (Hydro)
159na		25b	53e	603	8.6	1E (Hydro)

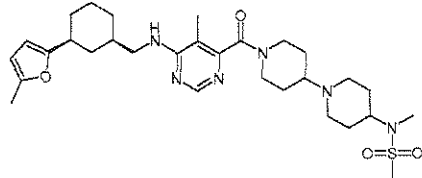
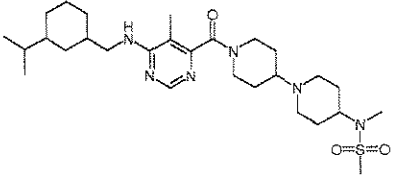
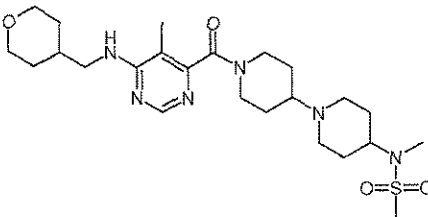
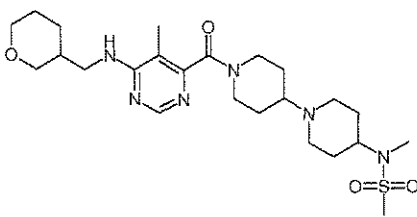
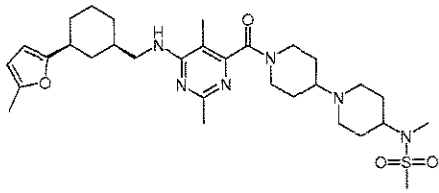
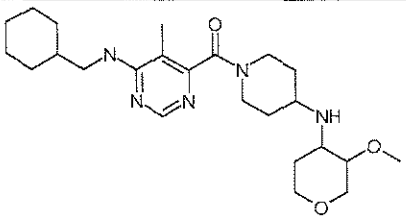
159oa		25l	53c	599	9.01	1E (Hydro)
159pa		25b	53a	639	8.38	1E (Hydro)
159qa		25l	53a	653	8.85	1E (Hydro)
159ra		25b	53b	585	7.86	1E (Hydro)
159sa		25l	53b	599	8.36	1E (Hydro)
159ta		25l	53e	617	9.03	1E (Hydro)
159ua		25l	54f	619	8.63	1E (Hydro)
159wa		25b	54f	605	8.10	1E (Hydro)

159ya		25l	54d	617	5.08	2M
159xa		25b	7h	613	9.95	1E (Hydro)
159za		25b	7i	597	10.52	1E (Hydro)
159ab		25b	53f	605	9.0	1E (Hydro)
159bb		25b	C-(3-methyl-cyclopentyl)-methyl-amine	507	8.53	1E (Hydro)
159cb		25b	53c	585	8.77	1E (Hydro)
159db		25b	7j	601	10	1E (Hydro)

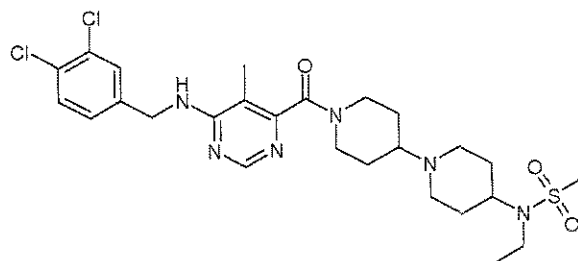
159eb		25b	53h	571	7.93	1E (Hydro)
159fb		25b	C-(5-phenyl-tetrahydrofuran-3-yl)-methyl-amine	571	7.83	1E (Hydro)
159gb		25b	54c	585	8.36	1E (Hydro)
159hb		25b	53g	639	8.94	1E (Hydro)
159lb		25l	53g	653	9.27	1E (Hydro)
159jb		25b	55c	585	8.38	1E (Hydro)
159kb		25g	7g	524	2.87	1Fa

159lb		25g	7f	540	3.02	1Fa
159mb		25b	7r	567	8.85	1E (Hydro)
159nb		25b	C- Bicyclo[4. 2.0]octa- 1(6),2,4- trien-7-yl- methyl- amine	527	7.53	1E (Hydro)
159ob		25b	C- Chroman- 2-yl- methyl- amine	557	7.9	1E (Hydro)
159pb		25b	C-(1,2,3,4- Tetra- hydro- naphthalen -2-yl)- methyl- amine	555	8.47	1E (Hydro)
159qb		25b	C-(2,3- Dihydro- benzo- furan-2-yl)- methyl- amine	543	7.4	1E (Hydro)

159rb		25b	C-(5-Chloro-2,3-Dihydro-benzo-furan-2yl)-methyl-amine	557	6.5	2F
159sb		25b	C-(6-Chloro-croman-3-yl)-methyl-amine	591	8.09	1E (Hydro)
159tb		25b	7s	589	9.8	1E (Hydro)
159ub		25b	7t	555	9.07	1E (Hydro)
159wb		25b	7u	589	9.7	1E (Hydro)
159yb		25b	7v	555	9.02	1E (Hydro)

159xb		25b	7o	587	9.55	1E (Hydro)
159zb		25b	7k	549	10.37	1E (Hydro)
159ac		25b	C-(tetrahydro-pyran-4-yl)-methylamine	509	5.92	1E (Hydro)
159bc		25b	C-(tetrahydro-pyran-3-yl)-methylamine	509	6.15	1E (Hydro)
159cc		25l	7o	601	5.40	2M
159dc		25o	C-cyclohexyl-methylamine	446	1.23	2Gb

159ec		25o	Indan-2-yl-amine	466	1.24	2Gb
159fc		25o	C-Indan-2-yl-methyl-amine	480	2.97	2Ga
159gc		25b	C-(1,2,3,4-Tetrahydroquinolin-2-yl)-methyl-amine	556	1.35	2Ca

Example 160

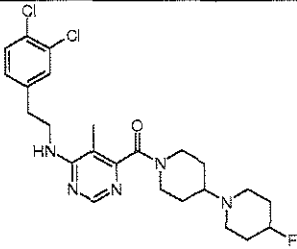
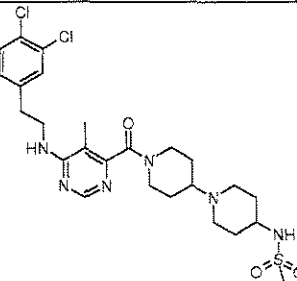
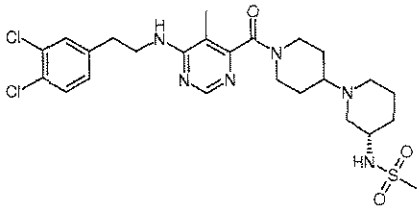
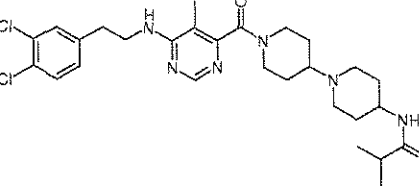
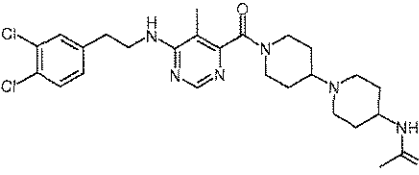
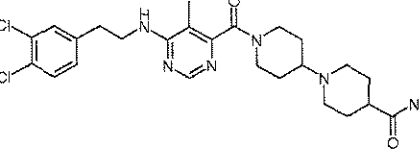
Intermediate 28b (80 mg, 0.20 mmol), Intermediate 13 (74 mg, 0.30 mmol) and N,N-diisopropyl-ethylamine (0.087 ml, 0.51 mmol) in 2 ml of dichloromethane were stirred at room temperature for 10 min. Sodium triacetoxyborohydride (129 mg, 0.61 mmol) was added and the reaction mixture was stirred at room temperature overnight. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 39 mg (0.06 mmol) of the desired product were obtained.

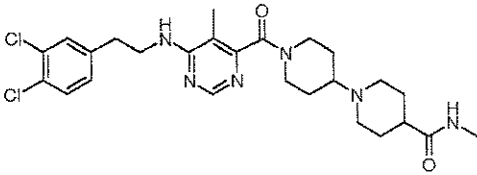
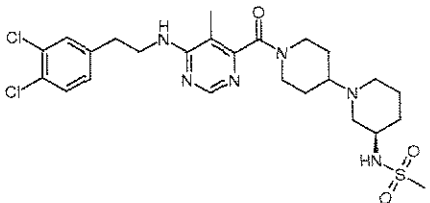
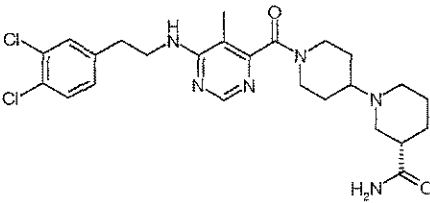
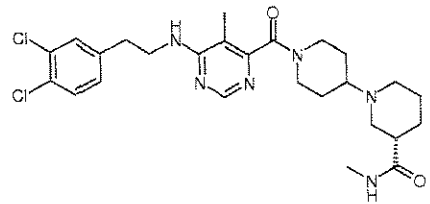
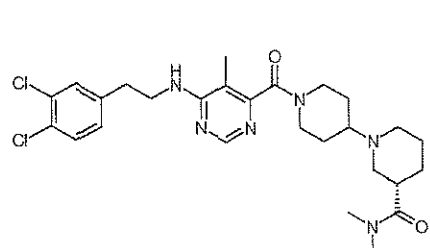
HPLC (Method 2F): R_t (min) = 7.25

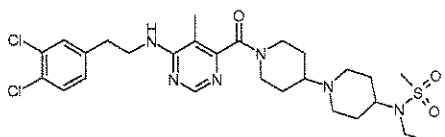
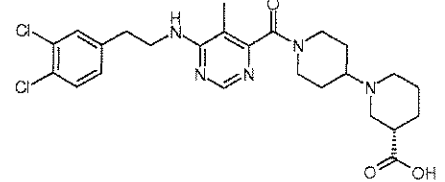
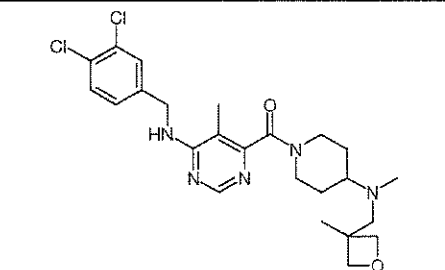
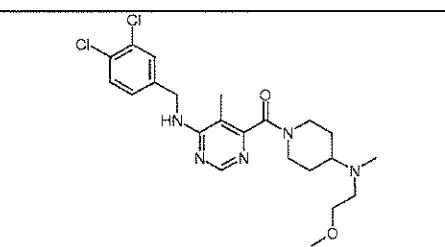
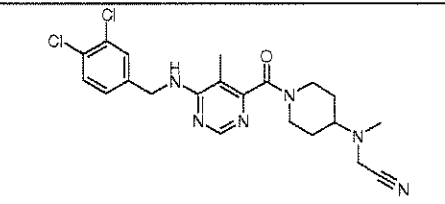
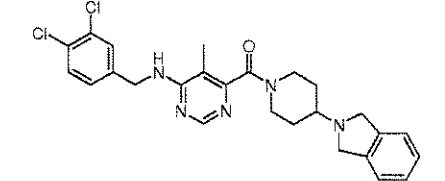
$[M+H]^+ = 583$

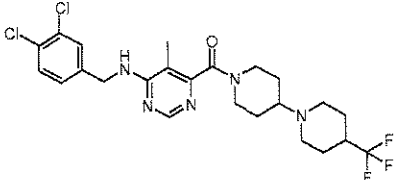
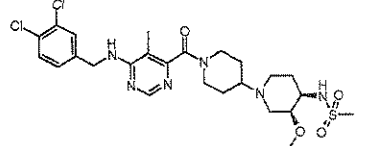
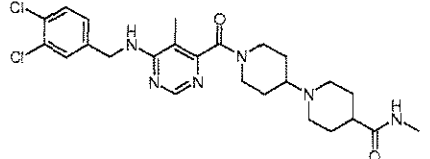
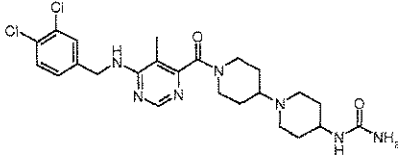
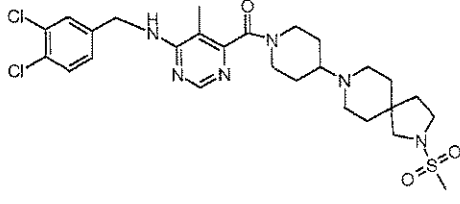
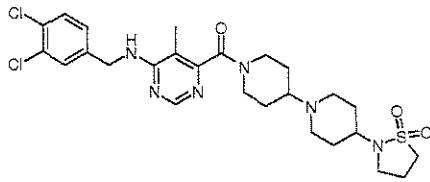
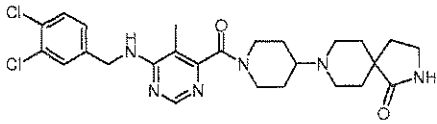
The following examples were synthesized in analogy to the preparation of Example 160.

Ex #	STRUCTURE	Intermediate	Amine or Ketone	$[M+H]^+$	HPL C R _e (min)	Method
161		28f	N-Methyl-N-piperidin-4-yl-methanesulfonamide	571	7.17	2F
162		28f	Morpholine	466	9.97-10.27	1E
163		28f	Pyrrolidine	450	7.06	2F
164		28a	4,4-difluoropiperidine	512	8.17	1E
165		28a	(R)-pyrrolidin-3-ol	478	7.62	1E
166		28a	(S)-pyrrolidin-3-ol	478	7.57	1E

167		28 a	4-fluoro- piperidine	494	7.37	2F
168		28 a	N- piperidin- 4-yl- methan- sulfon- amide	569	7.28	1E (Fusion)
169		28 a	(S)-N- piperidin- 3-yl- methan- sulfon- amide	569	8.50	1E
170		28 a	N- piperidin- 4-yl- isobuty- ramide	561	7.58	1E
171		28 a	N- piperidin- 4-yl- acetamide	533	7.07	2F
172		28 a	Piperidin- 4- carboxylic acid amide	519	7.07	1E (Fusion)

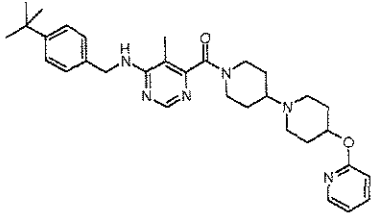
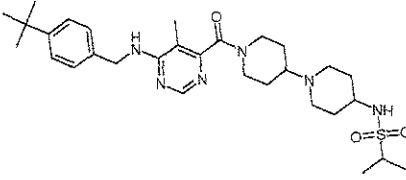
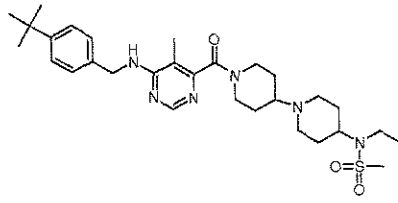
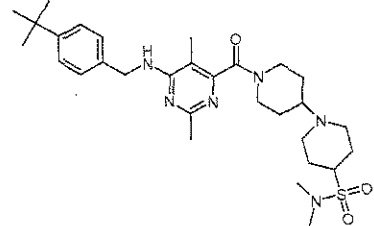
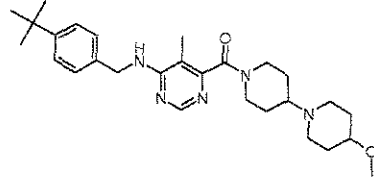
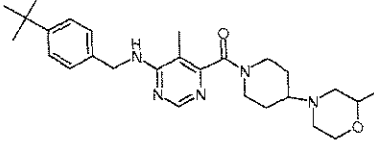
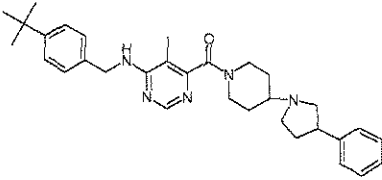
173		28 a	Piperidin-4-carboxylic acid methylamide	533	7.73	1E (Fusion)
174		28 a	(R)-N-piperidin-3-ylmethanesulfonamide	569	8.48	1E (Fusion)
175		28 a	(S)-piperidine-3-carboxylic acid amide	519	8.70	1E (Fusion)
176		28 a	(S)-piperidine-3-carboxylic acid methylamide	533	7.03	2F
177		28 a	(S)-piperidine-3-carboxylic acid dimethylamide	547	7.15	2F

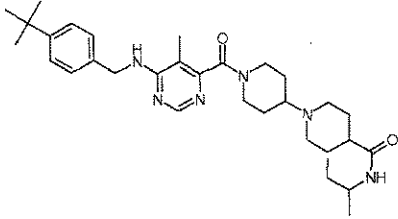
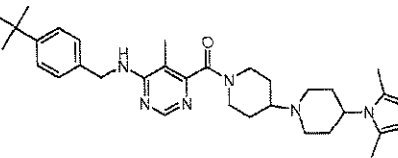
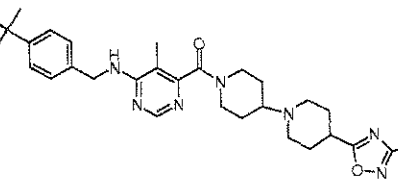
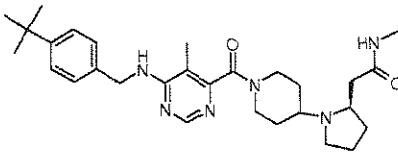
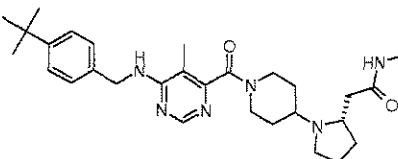
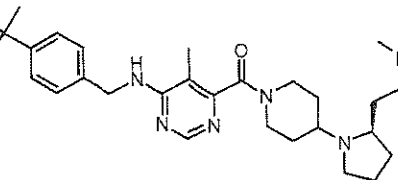
178		28 a	N-Ethyl- N- piperidin- 4-yl- methane- sulfon- amide	597	9.62	1E (Hydro)
179		28 a	(S)- piperidine- 3- carboxylic acid	520	6.60	1E (Fusion)
180		28 b	Methyl-(3- methyl- oxetan- 3-yl- methyl)- amine	492	8.05	1E (Hydro)
181		28 b	2- (methoxy- ethyl)- methyl- amine	466	7.72	1E (Hydro)
182		28 b	Methyl- amino- aceto- nitrile	447	8.00	1E (Hydro)
183		28 b	2,3- dihydro- 1H- isoindole	496	9.52	1E (Hydro)

184		28 b	4-trifluoro-methyl-piperidine	530	9.60	1E (Hydro)
185		28 b	18	585	7.33	1E (Hydro)
186		28 b	Piperidin-4-carboxylic acid methyl-amide	519	7.42	1E (Hydro)
187		28 b	Piperidin-4-yl-urea	520	7.05	2F
188		28 b	2-methanesulfonyl-2,8-diazaspiro[4.5]-decane	595	8.32	1E (Hydro)
189		28 b	4-(1,1-dioxo-2-thiazolidin-2-yl)-piperidine	581	8.23	1E (Hydro)
190		28 b	2,8-diazaspiro[4.5]decan-1-one	531	7.58	1E (Hydro)

191		28 b	16a	585	7.65	1E (Hydro)
192		28 b	1- piperidin- 4-yl- pyrrolidin- 2-one	545	8.08	1E (Hydro)
193		28 b	Azetidin- 3- carboxylic acid methyl- amide	491	7.55	1E (Hydro)
194		28 b	N-methyl- N- piperidin- 4-yl- acetamide	533	7.87	1E (Hydro)
195		28 b	Ethan- sulfonic acid- piperidin- 4-yl-amide	569	8.15	1E (Hydro)
196		28 c	Piperidine -4-sulfonic acid dimethyl- amide	557	9.11	1E (Hydro)

197		28 b	Propan-2-sulfonic acid-piperidin-4-yl-amide	583	8.37	1E (Hydro)
198		28 c	4-ethoxy-piperidine	494	10.75	1E (Hydro)
199		28 c	N-piperidin-4-methyl-methan-sulfon-amide	557	9.45	1E (Hydro)
200		28 c	4-tert-butyl-piperidine	506	7.86	2F
201		28 c	4-(piperidin-4-yl)-pyridine	527	10.88	1E (Hydro)
202		28 c	Piperidine-4-carbonitrile	475	9.77	1E (Hydro)
203		28 c	4-(3,4-difluorophenoxy)-piperidine	578	11.05	1E (Hydro)

204		28 c	2-(piperidin-4-yloxy)-pyridine	543	10.38	1E (Hydro)
205		28 c	Propan-2-sulfonic-acid-piperidin-4-yl-amide	571	9.12	1E (Hydro)
206		28 c	N-Ethyl-N-piperidin-4-yl-methane-sulfon-amide	571	10.18	1E (Hydro)
207		28 g	Piperidine-4-sulfonic acid dimethyl-amide	571	9.67	1E (Hydro)
208		28 c	4-methoxy-piperidine	480	2.21	2G
209		28 c	2-methyl-morpho-line	466	3.46	2F
210		28 c	3-Phenyl-pyrroli-dine	512	9.68	2F

211		28 c	Piperidin-4-carboxylic acid sec-butyl amide	549	9.53	1E (Hydro)
212		28 c	4-(3,5-dimethyl-[1,2,4]-triazol-4-yl)-piperidine	545	8.93	1E (Hydro)
213		28 c	4-(3-methyl-[1,2,4]-oxadiazol-5-yl)-piperidine	532	8.21	2F
214		28 c	N-methyl-2-(R)-(pyrrolidin-2-yl)acetamide	507	9.35	1E (Hydro)
215		28 c	N-methyl-2-(S)-(pyrrolidin-2-yl)acetamide	507	9.24	1E (Hydro)
216		28 c	N,N-dimethyl-2-(R)-(pyrrolidin-2-yl)acetamide	521	9.71	1E (Hydro)

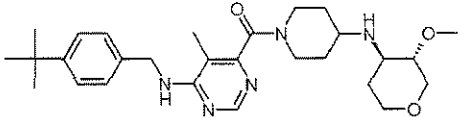
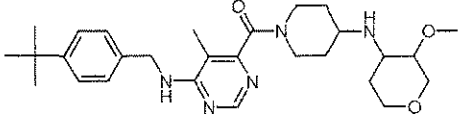
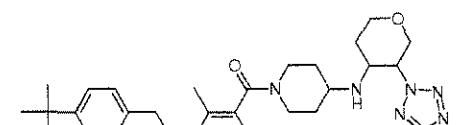
217		28 c	N,N- dimethyl- 2-(S)- (pyrrolidin -2-yl) acetamide	521	9.72	1E (Hydro)
218		28 c	2,6- dimethyl- morpho- line	480	8.92	2F
219		28 c	(R)-3- methoxy- pyrroli- dine	466	7.23	2F
220		28 c	(S)-3- methoxy- pyrroli- dine	466	7.23	2F
221		28 c	Piperidine -4-sulfonic acid methyl- amide	543	8.50	1E (Hydro)
222		28 c	N- azetidin-3- yl-N- methyl- methane- sulfon- amide	529	8.65	1E (Hydro)

223		28 c	N-azetidin-3-yl-methane-sulfonamide	515	8.02	1E (Hydro)
224		28 c	4-methyl-piperidine-4-carboxylic acid methylamide	521	9.00	1E (Hydro)
225		28 c	4-phenyl-piperidine	526	10.83	1E (Hydro)
226		28 b	N-methyl-N-(S)-(pyrrolidin-3-yl)-methane-sulfonamide	555	8.04	1E (Hydro)
227		28 b	16b	599	8.13	1E (Hydro)
228		28 b	Piperidine-4-sulfonic acid amide	541	7.12	1E (Hydro)

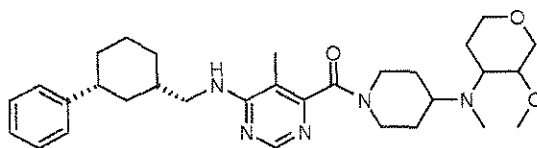
228 a		28 c	Methyl- (tetra- hydro- pyran-3- yl)-amine	480	10,05	1E (Hydro)
228 b		41 b	3- methoxy- tetrahydro -pyran-4- one	522	9,25	1E (Hydro)
228 c		41 a	3- methoxy- tetrahydro -pyran-4- one	496	8,87	1E (Hydro)
228 d		41 a	3-fluoro- tetrahydro -pyran-4- one	484		1E (Hydro)
228 e		41 a	N-carb- ethoxy-3- methoxy- 4- piperidone	567	7,42	2F
228f		41 a	4- chromano ne	514	10,31	1E (Hydro)
228 g		41 a	43	530	9,76	1E (Hydro)

228 ga		28 c	47a	496	5.77	2M
228 gb		28 c	1-(2-Methoxy-ethyl)- 3a,4,5,6,7, 7a- hexahydro -1H- pyrazolo- [3,4- c]pyridine	546	9.55	1E (Hydro)
228 gc		28 c	1-((R)-3-Amino- piperidin- 1-yl)- ethanone	507	8.85	1E (Hydro)
228 gd		28 c	(R)-1-Methanesu- lfonyl- piperidin- 3-ylamine	543	9.11	1E (Hydro)
228 ge		28 c	3- Phenoxym ethyl- pyrrolidin e	542	10.92	1E (Hydro)
228 gf		28 c	3- Pyrrolidin- 3-yl- pyridine	527	10.00	1E (Hydro)

228 gg		28 c	3- Trifluoro methyl- 5,6,7,8- tetrahydro - [1,6]napht hyridine	567	7.69	2F
228 gh		28 c	C- (Tetrahydr opyran-2- yl)methyl- amine	480	2.09	2Cb
228 gi		28 c	56	515	2.18	2Cb
228 gj		28 c	1-Oxa-3,8- diazaspiro[4,5] decan-2-one	521	8.30	1E (Hydro)
228 gk		28 c	4- Piperidin- 4-yl- benzonitril e	551	10.35	1E (Hydro)
228 gl		28 c	4-(3,4- Difluoro- benzyl)- piperidine	576	11.42	1E (Hydro)
228 gm		28 c	8-Aza- bicyclo[3. 2.1]octan- 3-ol	492	9.30	1E (Hydro)

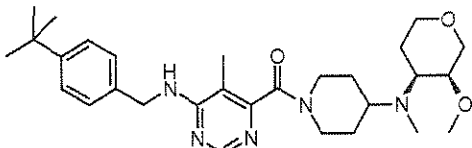
228 gn		28 c	45	496	5.96	2M
228 go		41 a	3-Methoxy-tetrahydro-pyran-4-one	508	5.77	2M
228 gp		41 a	3-Tetrazol-2-yl-tetrahydro-pyran-4-one	534	7.09	2F

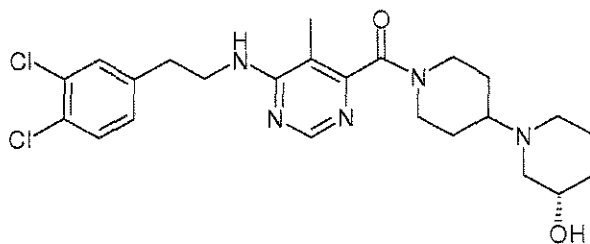
Example 228h



Example 228b (22 mg, 0.032 mmol), formaldehyde (0.003 ml, 0.096 mmol), N,N-diisopropyl-ethylamine (0.008 ml, 0.048 mmol) and trifluoroacetic acid (0.005 ml) in 1.5 ml of methanol were stirred at room temperature for 5 min. Sodium cyanoborohydride (10 mg, 0.160 mmol) was added and the reaction mixture was stirred at room temperature overnight. The organic phase was concentrated under vacuum. The crude product was purified by flash chromatography (Isolute silica gel cartridge 5g, eluent: ethyl acetate/methanol=7:3%). 8.4 mg (0.016 mmol) of the desired product were obtained.

The following examples were synthesized in analogy to the preparation of Example 228h.

Ex #	STRUCTURE	Starting example	[M+H] ⁺	HPLC R _t (min)	Method
228 ha		228ga	510	5.72	2M

Example 229

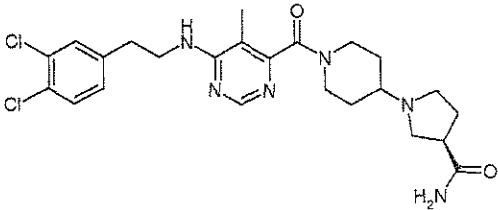
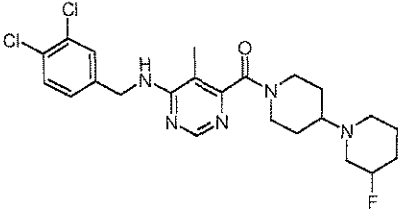
- 5 Intermediate 28a (100 mg, 0.25 mmol), (S)-3-hydroxypiperidine (67 mg, 0.49 mmol) and trimethylorthoformate (1.07 ml, 9.82 mmol) in 5 ml of methanol were stirred at 60°C for 1h. 2-picoline borane complex (26 mg, 0.25 mmol) was added and the reaction mixture was stirred at 60°C overnight. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 64 mg (0.13 mmol) of the desired product were obtained.

HPLC (Method 1E): R_t (min) = 7.18

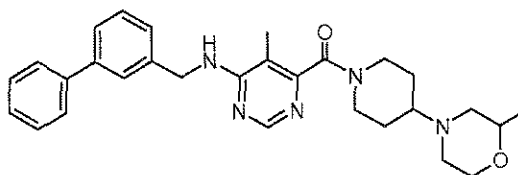
$[M+H]^+ = 492$

- 15 The following examples were synthesized in analogy to the preparation of Example 229.

Ex #	STRUCTURE	Inter-mediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
230		28a	1-piperazin-1-yl-ethanone	519	7.13	2F
231		28a	(R)-piperidin-3-ol	492	7.35	1E (Fusion)

232		28a	(R)-pyrrolidin-3-carboxylic acid amide	505	7.83	1E (Fusion)
233		28b	3-fluoro-piperidine	480	8.32	1E (Hydro)

Example 234

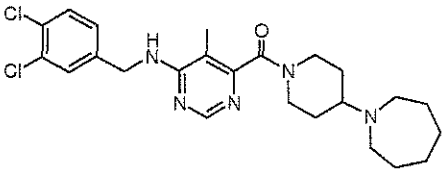


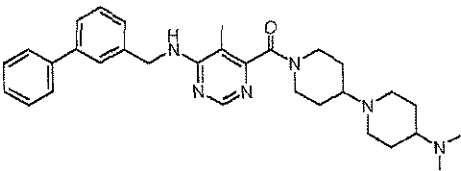
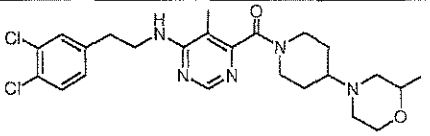
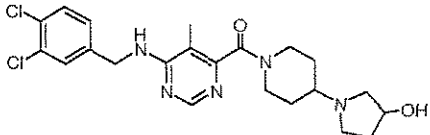
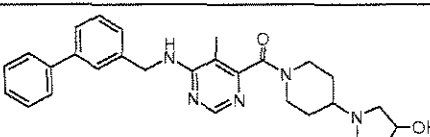
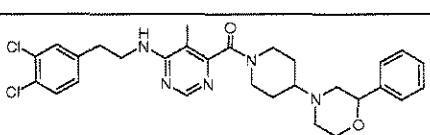
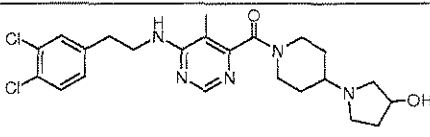
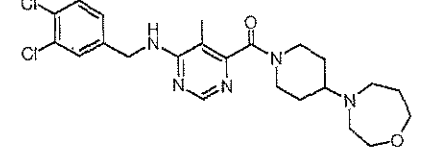
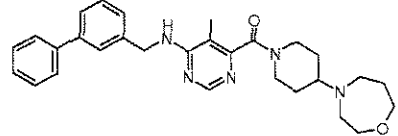
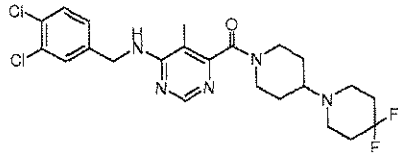
Intermediate 28d (20 mg, 0.05 mmol), 2-methyl-morpholine (0.012 ml, 0.10 mmol), sodium triacetoxyborohydride (43 mg, 0.20 mmol), acetic acid (0.05 ml) and trimethylorthoformate (0.05 ml) in 0.9 ml of DMA were stirred at room temperature for 3h. The reaction mixture was concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 3 mg (0.006 mmol) of the desired product were obtained.

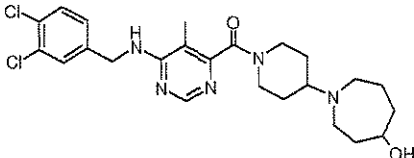
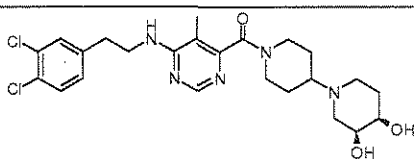
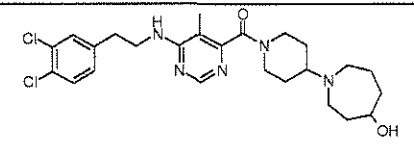
HPLC (Method A): R_t (min) = 1.74

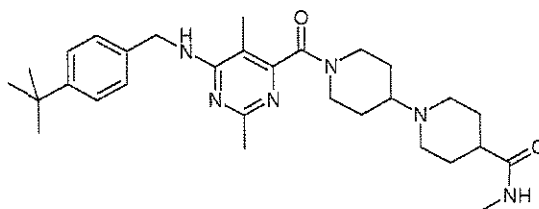
10 $[M+H]^+ = 486$

The following examples were synthesized in analogy to the preparation of Example 234.

Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
235		28b	Azepane	476	1.72	2A

236		28d	Dimethyl - piperidin- 4-yl-amine	513	1.64	2A
237		28a	2-methyl- morpho- line	492	1.72	2A
238		28b	Pyrrolidin -3-ol	464	1.65	2A
239		28d	Pyrrolidin -3-ol	472	1.71	2A
240		28a	2-phenyl- morpho- line	554	1.84	2A
241		28a	Pyrrolidin -3-ol	478	1.68	2A
242		28b	[1,4]-oxa- zepane	478	1.66	2A
243		28d	[1,4]-oxa- zepane	486	1.72	2A
244		28b	4,4- difluoro- piperidine	498	1.72	2A

245		28b	Azepan-4-ol	492	1.65	2A
246		28a	(3S,4R)-piperidine-3,4-diol	508	1.66	2A
247		28a	Azepan-4-ol	506	1.68	2A

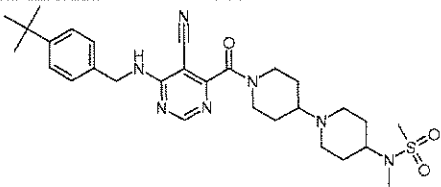
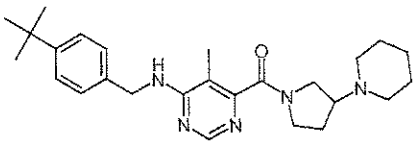
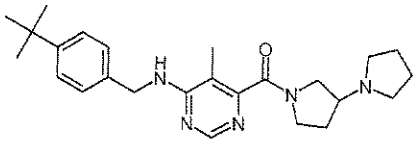
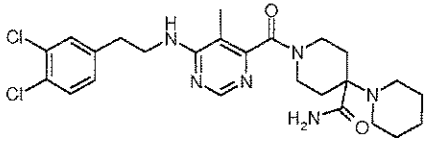
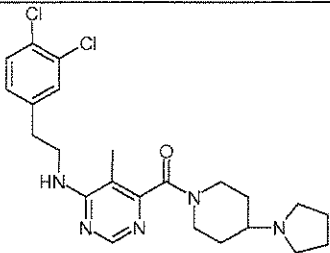
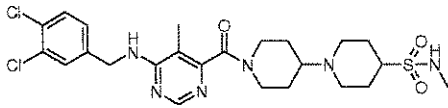
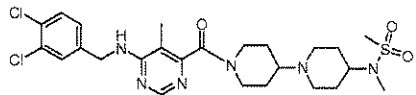
Example 248

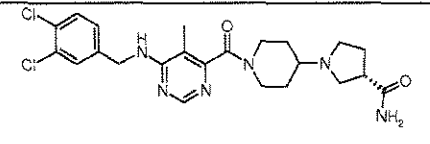
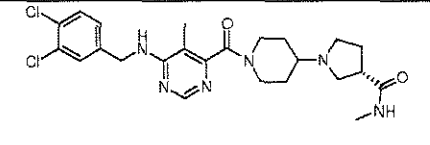
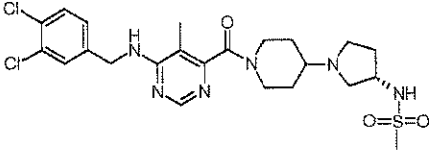
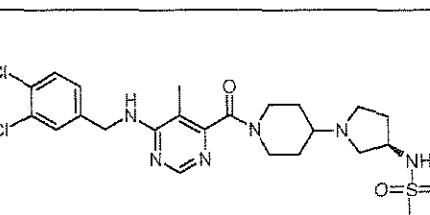
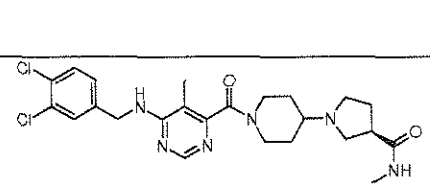
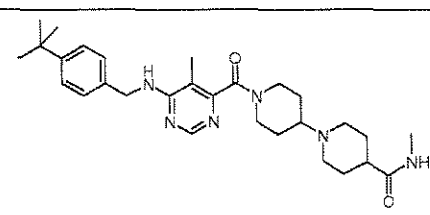
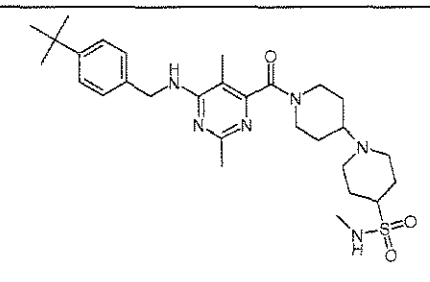
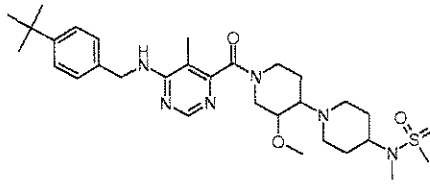
Intermediate 27e (105 mg, 0.33 mmol), TBTU (215 mg, 0.67 mmol) and N,N-diisopropylethylamine (0.12 ml, 0.67 mmol) in 2 ml DMF were stirred at room temperature for 5 min. Intermediate 20f (100 mg, 0.33 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5g); eluent: ethyl acetate/methanol=90/10%). 30 mg (0.057 mmol) of the desired product were obtained.

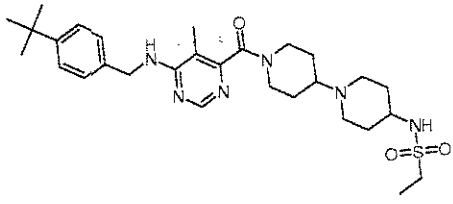
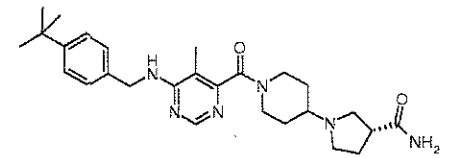
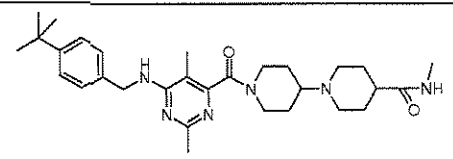
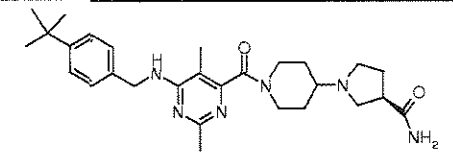
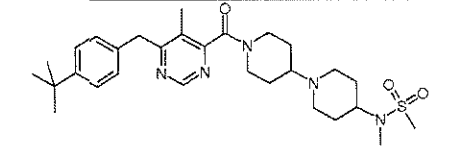
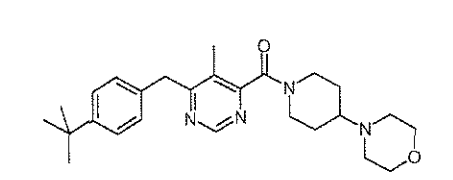
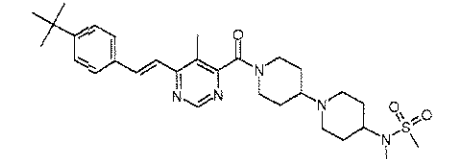
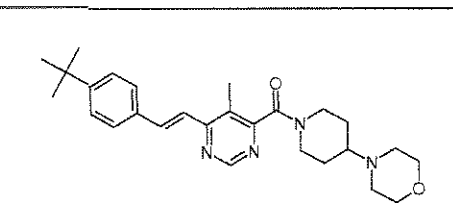
HPLC (Method 1E Hydro): R_t (min) = 9.2

$[M+H]^+ = 521$

The following examples were synthesized in analogy to the preparation of Example 248.

Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
249		27i	20a	568	10.07	1E (Hydro)
250		27c	1- pyrrolidin- 3-yl- piperidine	436	1.5	1E (Hydro)
251		27c	[1,3']- Bipyrro- lidinyl	422	10.35	1E (Hydro)
252		27a	[1,4']- Bipiperidi nyl-4' carboxylic acid amide	519	8.60	1E (Fusion)
253		27a	4-pyrroli- din-1-yl- piperidine	462	7.07	2F
254		27b	20g	555	7.50	1E (Hydro)
255		27b	20a	569	8.15	1E (Hydro)

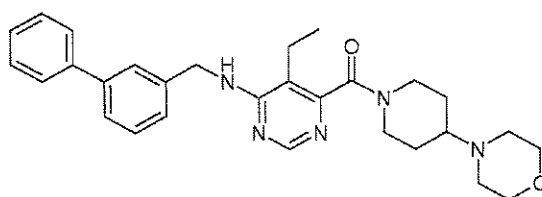
256		27b	20j	491	7.03	1E (Hydro)
257		27b	20i	505	7.43	1E (Hydro)
258		27b	20d	541	7.50	1E (Hydro)
259		27b	20c	541	7.48	1E (Hydro)
260		27b	20h	505	7.85	1E (Hydro)
261		27c	20f	507	8.70	1E (Hydro)
262		27e	20g	557	9.11	1E (Hydro)
263		27c	20m	587	8.79	2F

264		27c	20e	557	8.85	1E (Hydro)
265		27c	20l	479	8.37	1E (Hydro)
266		27e	20f	521	9.2	1E (Hydro)
267		27e	20l	493	8.93	1E (Hydro)
268		39b	20a	542	3.54	2F
269		39b	4- piperidin- 4-yl- morpho- line	436	7.46	2F
270		39a	20a	553	8.28	2F
271		39a	4- piperidin- 4-yl- morpho- line	449	7.60	2F

272		39c	20a	556	7.98	2F
273		39c	4- piperidin- 4-yl- morpho- line	450	7.29	2F
274		39d	24	554	8.28	1E (Hydro)
275		39d	[1,4']- bipiperidin yl-4-ol	477	7.77	1E (Hydro)
275 a		27c	20la	480	10,03	1E (Hydro)
275 b		27c	20lb	510	9,48	1E (Hydro)
275 c		27c	20lc	508	10,27	1E (Hydro)
275 d		27c	20ld	514	10.13	1E (Hydro)
275 da		27h c	20lg	526	9.16	1E (Hydro)

275 db		27h d	20lg	526	9.18	1E (Hydro)
275 dc		27h s	20lg	508	7.25	1F
275 dd		27hf	20lf	494	6.53	2F
275 de		27h r	20lg	508	8.55	1E (Hydro)
275 df		27h e	20lg	494	8.07	1E (Hydro)
275 dg		27hf	20lg	494	8.10	1E (Hydro)
275 dh		27h a	20lf	522	9.03	1E (Hydro)
275 di		27h a	20lg	522	9.00	1E (Hydro)
275 dj		27h a	20la	536	9.76	1E (Hydro)

275 dk		27ib	20a	595	2.16	2Cb
275 dl		27ic	20a	593	2.20	2Cb

Example 276

Intermediate 27g (50 mg, 0.14 mmol), HATU (55 mg, 0.14 mmol) and N,N-diisopropylethylamine (0.05 ml, 0.28 mmol) in 2 ml DMF were stirred at room temperature for 5 min. 4-piperidin-4-yl-morpholine (24 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature 3h. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 80 mg (0.13 mmol) of the desired product were obtained.

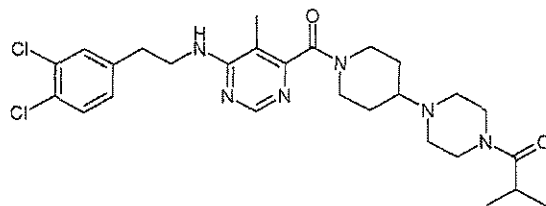
HPLC (Method C): R_t (min) = 1.57

$[M+H]^+ = 486$

The following examples were synthesized in analogy to the preparation of Example 276.

Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
277		27h	4-piperidin-4-yl-morpholine	536	1.69	2C

278		27h	[1,4']- Bipiperidin yl-4-ol	550	1.65	2C
279		27a	4-piperidin- 4-yl- morpholine	478	1.52	2C
280		27f	[1,4']- Bipiperidin yl-4-ol	506	1.52	2C
281		27f	4-piperidin- 4-yl- morpholine	492	1.53	2C
282		27g	[1,4']- Bipiperidin yl-4-ol	500	1.55	2C
283		39e	[1,4']- Bipiperidin yl-4-ol	484	1.66	2C

Example 284

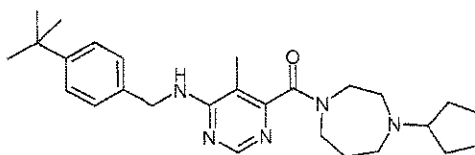
Intermediate 30 (45 mg, 0.088 mmol) and N,N-diisopropylethylamine (0.05 ml, 0.27 mmol) were dissolved in 5 ml of dichloromethane. The reaction mixture was stirred at 0°C and isobutyrylchloride (0.01 ml, 0.09 mmol) was added. The reaction mixture was stirred at 0°C for 20 min, then it was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was suspended and stirred in diisopropyl ether, the solid filtered off to obtain 30 mg (0.05 mmol) of the desired compound.

HPLC (Method 1E): R_t (min) = 7.02

$$[M+H]^+ = 547$$

The following examples were synthesized in analogy to the preparation of Example 284.

Ex #	STRUCTURE	Intermediate	Chloride	$[M+H]^+$	HPLC R_t (min)	Method
285		30	Methane-sulfonyl chloride	555	6.91	2F

Example 286

Intermediate 32 (100 mg, 0.26 mmol) and cyclopentanone (0.02 ml, 0.26 mmol) in 2 ml of dichloromethane were stirred at room temperature for 10 min. Sodium triacetoxyborohydride

(132 mg, 0.62 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 31 mg (0.07 mmol) of the desired product were obtained.

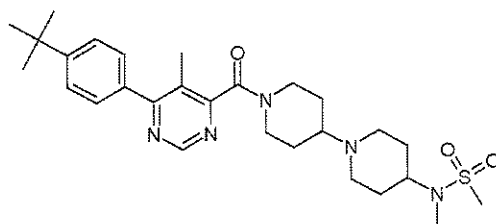
HPLC (Method 2F): R_t (min) = 7.52

$[M+H]^+ = 450$

The following examples were synthesized in analogy to the preparation of Example 286.

Ex #	STRUCTURE	Intermediate	Ketone	$[M+H]^+$	HPLC R_t (min)	Method
287		32	Acetone	424	7.24	2F
288		32	Tetrahydro-pyran-4-one	466	7.18	2F

Example 289



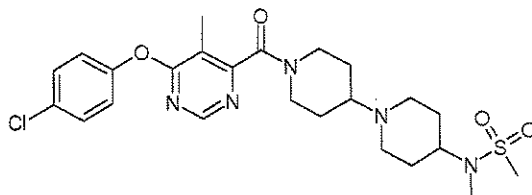
Intermediate 25b (200 mg, 0.46 mmol) 4-tert-butylphenylboronic acid (99 mg, 0.56 mmol), tetrakis(triphenylphosphine)palladium (53 mg, 0.05 mmol) and 0.56 ml of a 2M aqueous solution of sodium carbonate in 2 ml of 1,2-dimethoxyethane were stirred at 80°C overnight. After cooling to room temperature, water was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude

product was purified by flash chromatography (Si Isolute cartridge (5g); eluent: ethyl acetate/methanol=95/5%). 41 mg (0.08 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t (min) = 9.93

5 $[M+H]^+ = 528$

Example 290



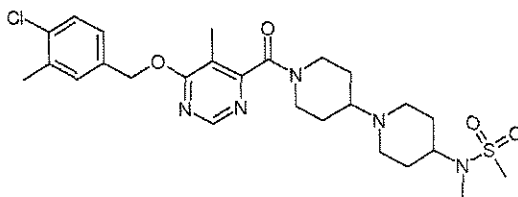
Intermediate 25b (60 mg, 0.14 mmol) and 4-chlorophenol (0.014 ml, 0.14 mmol) were dissolved in 2 ml of DMF. Cesium carbonate (45 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum, the crude product was dissolved in dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5g); eluent: dichloromethane/ethyl acetate=90/1%). 50 mg (0.09 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t (min) = 8.9

$[M+H]^+ = 522$

20 The following example was synthesized in analogy to the preparation of Example 290.

Ex #	STRUCTURE	Intermediate	Phenol	$[M+H]^+$	HPLC R_t (min)	Method
291		25b	4-tertbutyl-phenol	544	7.64	2F

Example 292

Sodium hydride (19 mg, 0.46 mmol) and 4-chloro-3-methylbenzylalcohol (44mg, 0.28 mmol) were suspended in 5 ml of dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 10 min, then Intermediate 25b (100 mg, 0.23 mmol) was added. The reaction mixture was stirred at 50°C overnight. The solvent was concentrated under vacuum, the crude product was dissolved in dichloromethane and the organic phase was washed with water, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5g); eluent: dichlorometane/methanol =95/5%). 40 mg (0.07 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t (min) = 9.95

$[M+H]^+ = 550$

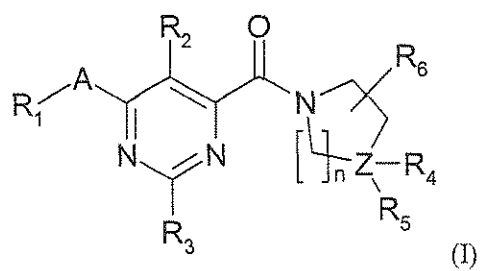
The following examples were synthesized in analogy to the preparation of Example 292.

Ex #	STRUCTURE	Intermediate	Phenol	$[M+H]^+$	HPLC R_t (min)	Method
293		25b	4-hydroxy-methyl-benzonitrile	527	8.17	1E (Hydro)
294		25b	(3-fluoro-4-methyl-phenyl)-methanol	534	9.12	1E (Hydro)
295		25b	(1-phenyl-pyrrolydin-3-yl)-methanol	571	10.2	1E (Hydro)

296		25b	(4-tert-butyl-phenyl)-methanol	558	2.71	1F
297		25f	(4-tert-butyl-phenyl)-methanol	466	9.50	1E (Hydro)
298		25h	(4-tert-butyl-phenyl)-methanol	453	8.01	2F
299		25a	(4-tert-butyl-phenyl)-methanol	544	9.68	1E (Hydro)
300		25d	(4-tert-butyl-phenyl)-methanol	508	10.25	1E (Hydro)
301		25n	(4-tert-butyl-phenyl)-methanol	588	2.20	2Ca
302		25n	(3-Phenyl-cyclohexyl)-methanol	614	2.18	2Ca

Claims

1. Compounds according to formula (I),



wherein

R_1 is $-L_1-R_7$,

and wherein L_1 is a bond or a group selected from among methylene, ethylene, and ethenylene,

and wherein R_4 and R_5 if different from an electron pair or -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R_9 , R_9 '), -C₀-C₄-alkylene-N(R_{10})-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R_{10})-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R_{11} , R_{11} '), -C₀-C₄-alkylene-N(R_{12})-Q-N(R_{13} , R_{13} '), -C₀-C₄-alkylene- R_{14} , -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R_{15} , R_{15} '), and -C₀-C₄-alkylene-N(R_{16})-Q-O-(R_{17}), wherein Q is selected from among -C(O)-, and -SO₂-, wherein R_{12} , R_{16} , are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl, wherein R_9 , R_9 ', R_{10} , R_{11} , R_{11} ', R_{13} , R_{13} ', R_{15} , R_{15} ', are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl, or wherein R_9 and R_9 ', R_{11} and R_{11} ', R_{13} and R_{13} ', R_{15} and R_{15} ', together form a -C₂-C₆-alkylene group, wherein R_{14} and R_{17} are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring, and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl,

or wherein R_4 and / or R_5 are independently a group of the structure -L₂- R_{18} , wherein L₂ is selected from among -NH- and -N(C₁-C₄-alkyl)-, wherein R_{18} is selected from among -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein R_{18} is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl, -NH-C(O)-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-C(O)-C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, -NH-S(O)₂-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-S(O)₂-C₁-C₆-alkyl, and -C(O)-O-C₁-C₆-alkyl, and wherein R_4 , R_5 and R_{18} are optionally further substituted by spiro-C₃-C₈-cycloalkyl or spiro-C₃-C₈-heterocyclyl such that together with R_4 , R_5 and/or R_{18} a spirocycle is formed, wherein said spiro-C₃-C₈-heterocyclyl optionally comprises one or more groups selected from among nitrogen, -C(O)-, -SO₂-, and -N(SO₂-C₁-C₄-alkyl)- in the ring,

or wherein R_4 , R_5 and R_{18} are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among $-C_1-C_6$ -alkylene, $-C_2-C_6$ -alkenylene, and $-C_4-C_6$ -alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among $-OH$, $-NH_2$, $-C_1-C_3$ -alkyl, $O-C_1-C_6$ -alkyl, $-CN$, $-CF_3$, $-OCF_3$, and halogen;

wherein R_6 is selected from among $-H$, $-C_1-C_4$ -alkyl, $-OH$, $-O-C_1-C_4$ -alkyl, $-halogen$, $-CN$, $-CF_3$, and $-OCF_3$;

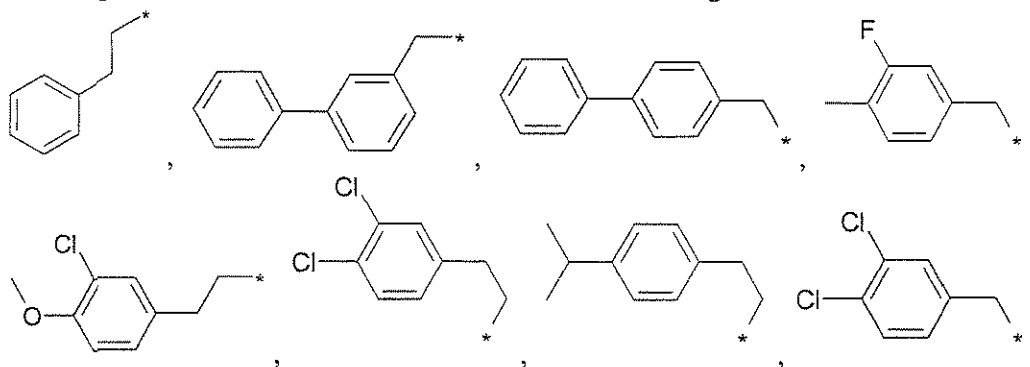
wherein A is selected from among a single bond, $-CH_2-$, $-O-$, $-S-$, and $-NH-$;

wherein n is 1, 2 or 3;

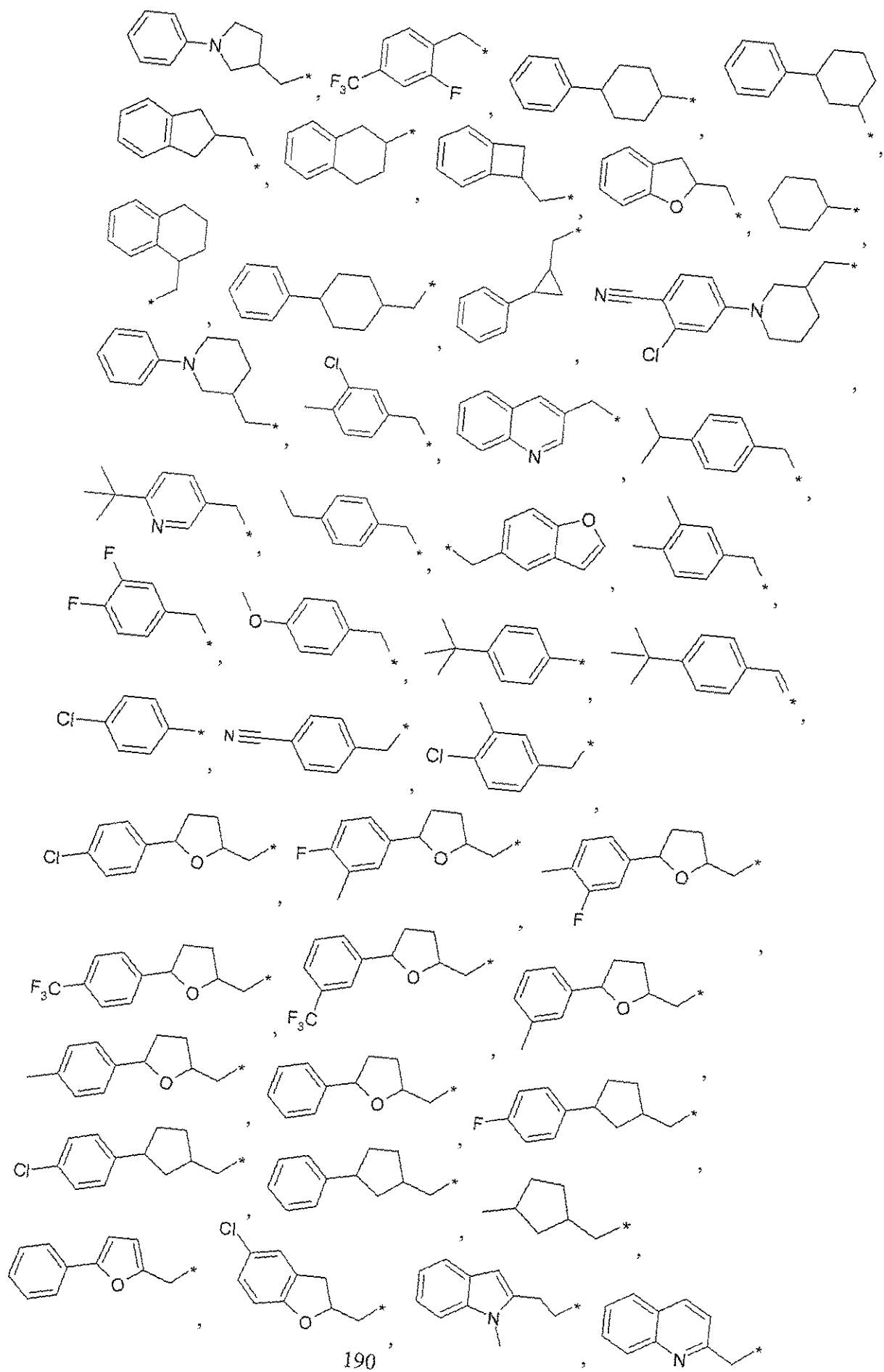
wherein Z is C or N,

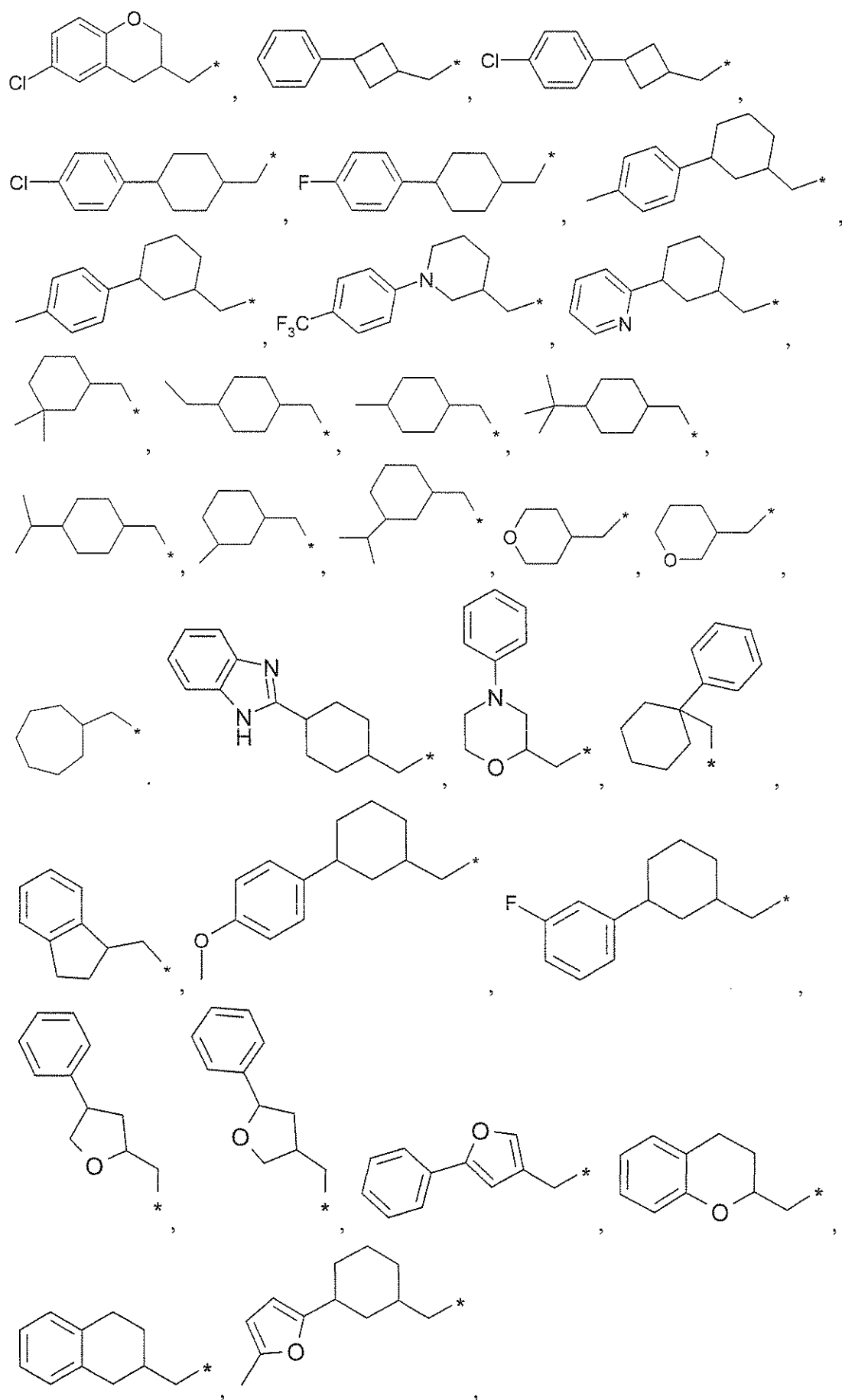
as well as in form of their acid addition salts with pharmacologically acceptable acids.

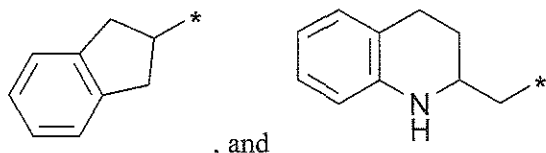
2. The compounds of claim 1, wherein R_1 is selected from among





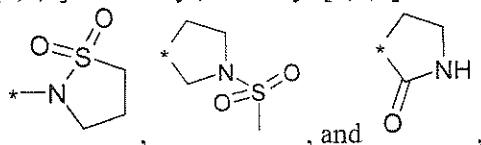






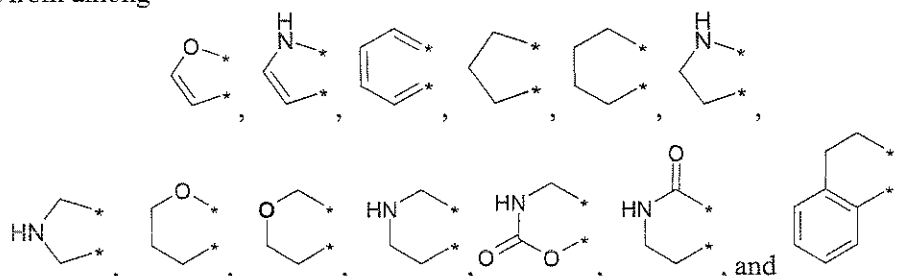
3. The compounds of any of the preceding claims, wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH₂, -C≡CH, and -OCH₃.
4. The compounds of any of the preceding claims, wherein R_2 is selected from among -H, -Methyl, -Ethyl, -Br, and -OCH₃.
5. The compounds of any of the preceding claims, wherein R_3 is selected from among -H, and -methyl.
6. The compounds of any of the preceding claims, wherein R_4 and R_5 are independently selected from among an electron pair, -H, and a group selected from among -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8 , R_8'), with R_8 and R_8' independently being selected from among -H and -C₁-C₆-alkyl, wherein R_4 and R_5 if different from an electron pair, and -H are optionally independently substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃,

-CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



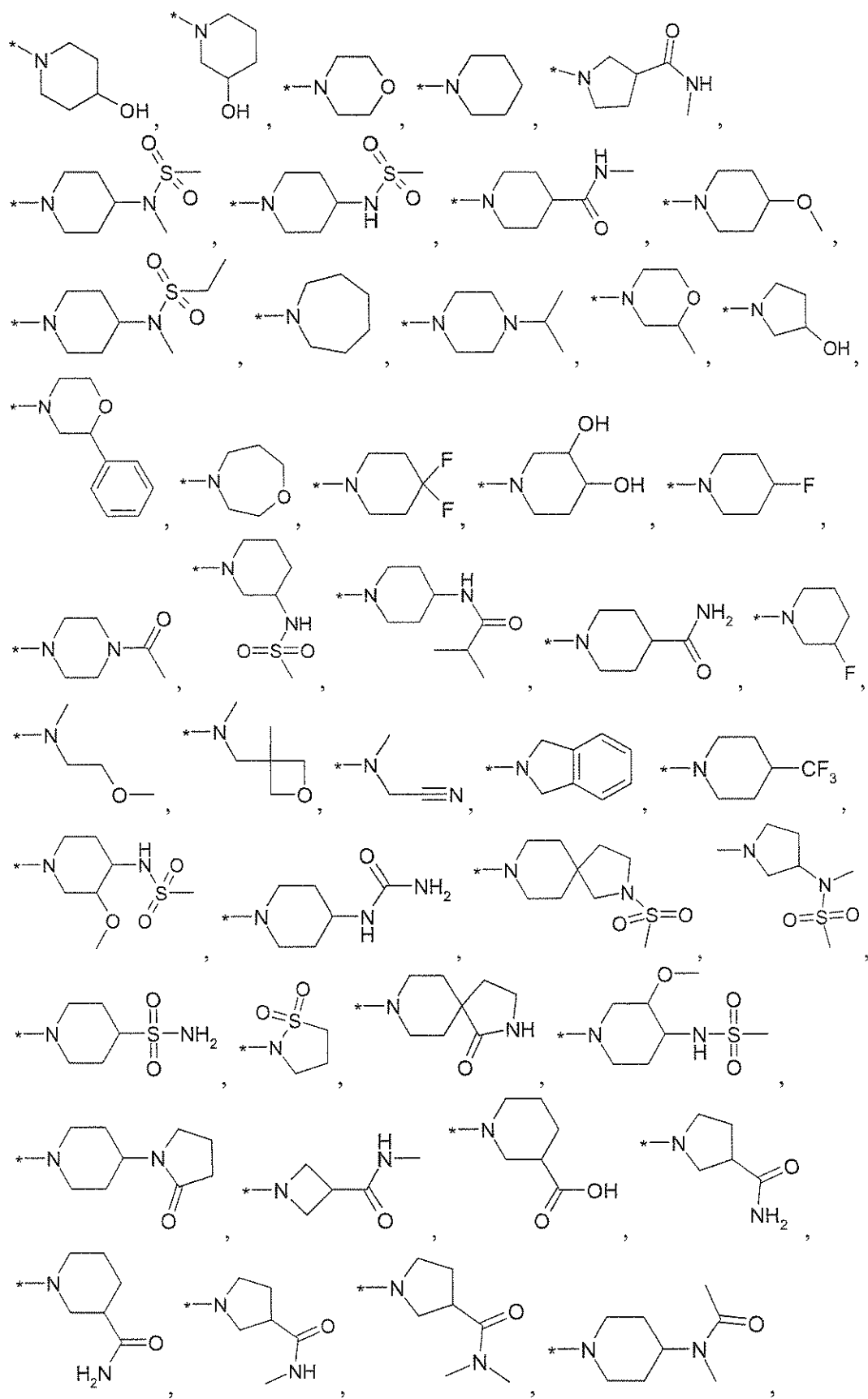
or wherein R₄ and R₅ are independently a group of the structure -L₂-R₁₈, wherein L₂ is selected from among -NH-, -N(CH₃)-, and -N(C₂H₅)-, and wherein R₁₈ is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl, -morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl, -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, and -C(O)-O-C₂H₅,

and wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more groups selected from among



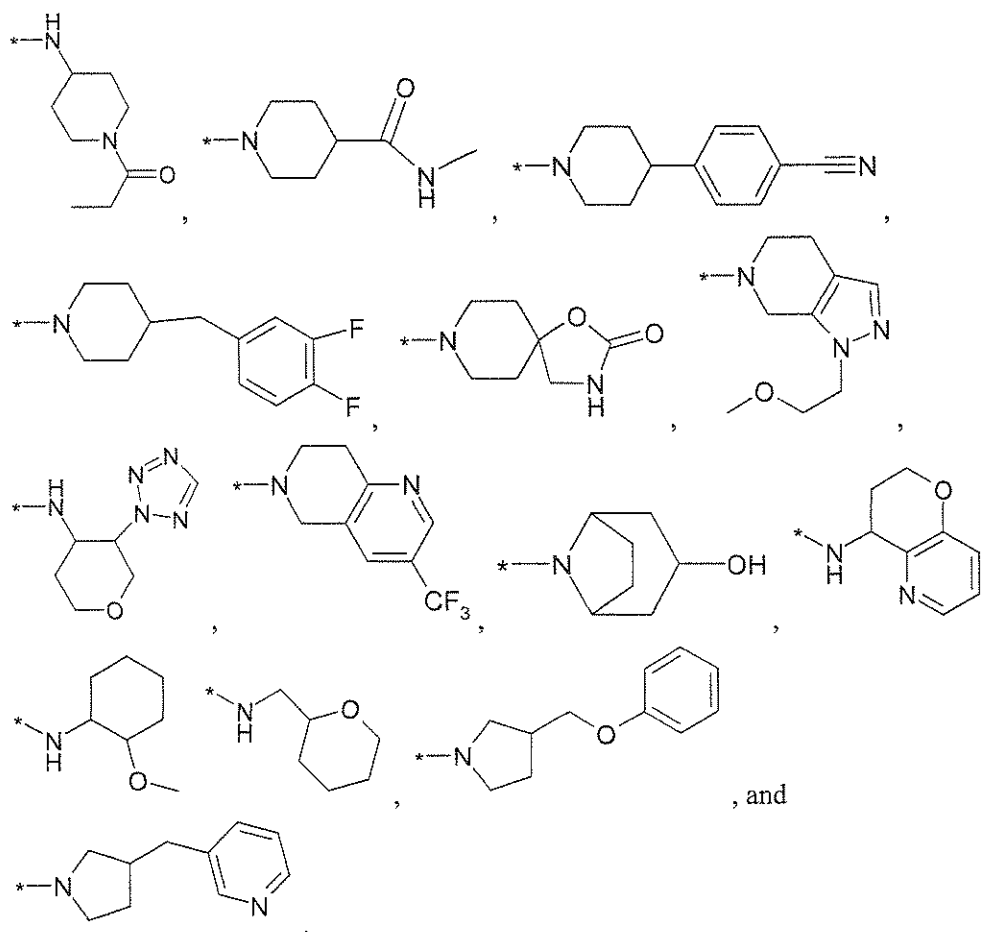
on one ring atom or on two neighboring ring atoms, such that spirocyclic or annellated rings are formed.

7. The compounds of any of the preceding claims, wherein R₄ is selected from among



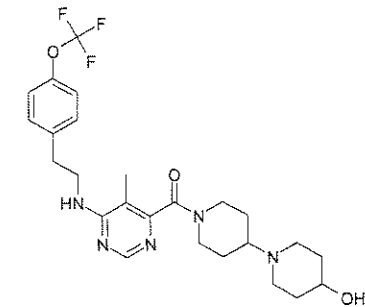
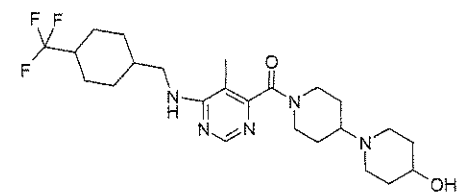
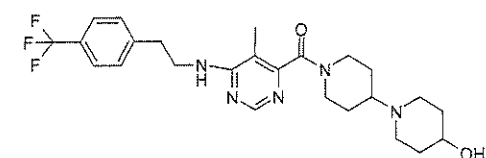
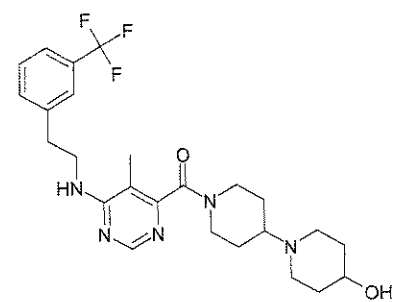
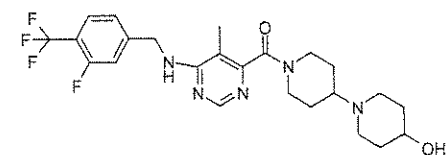
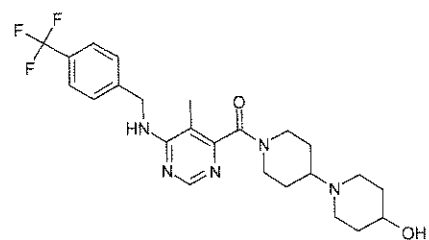
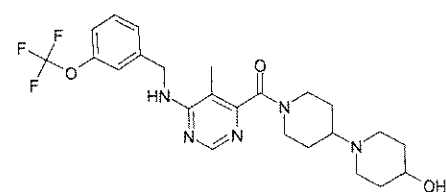
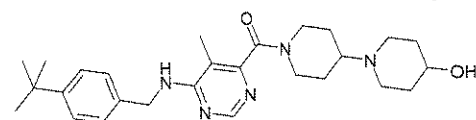
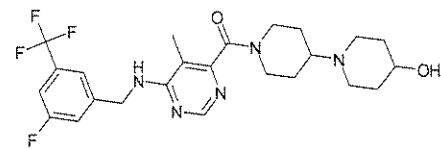
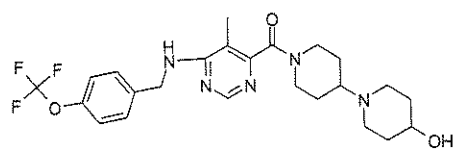
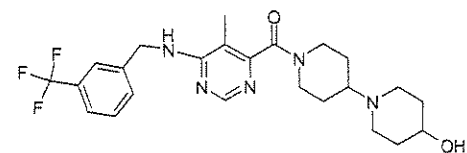
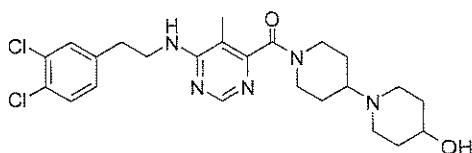
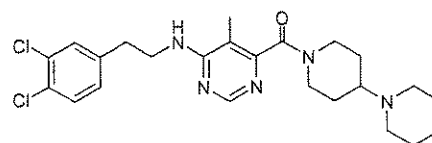
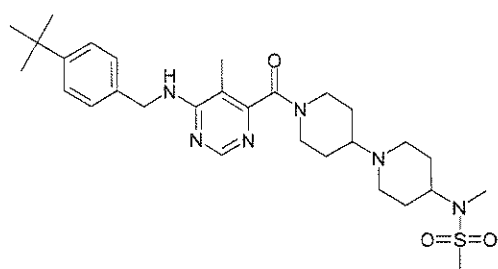


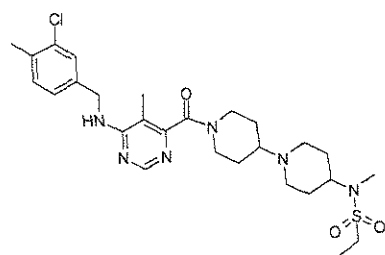
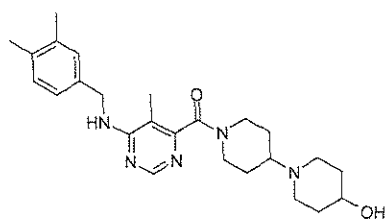
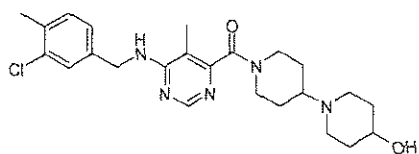
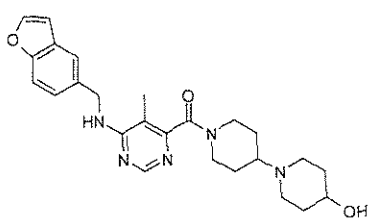
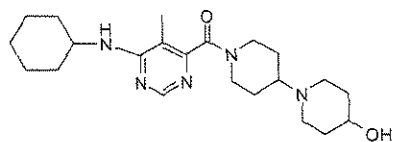
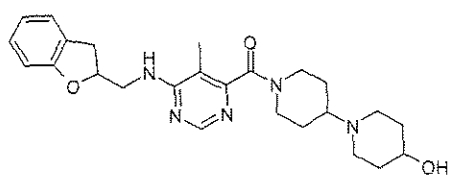
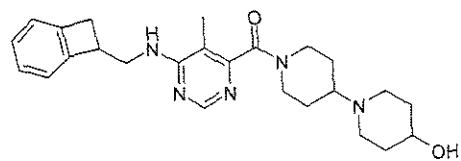
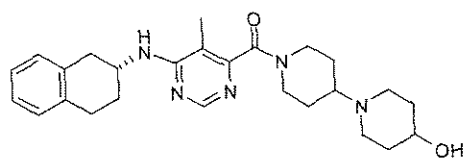
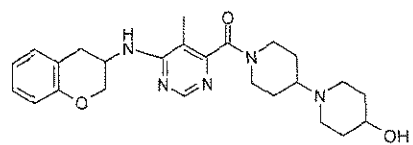
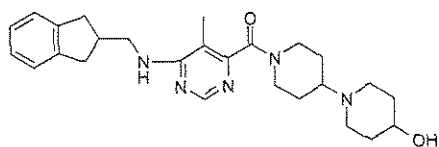
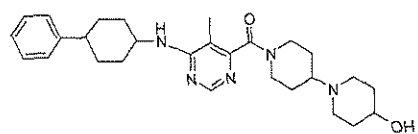
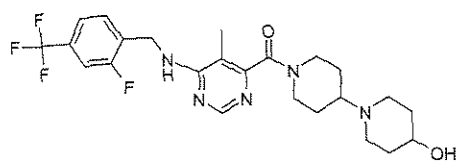
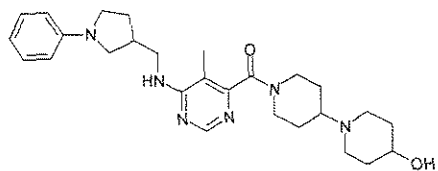
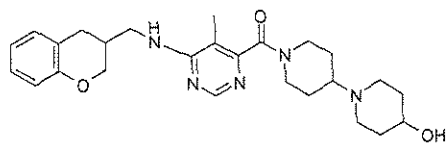
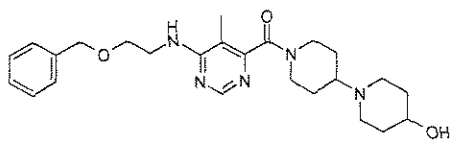
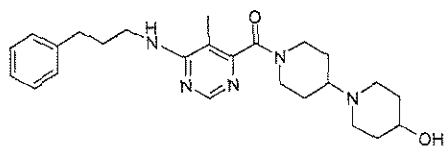
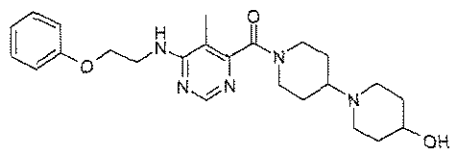
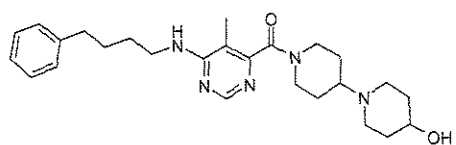


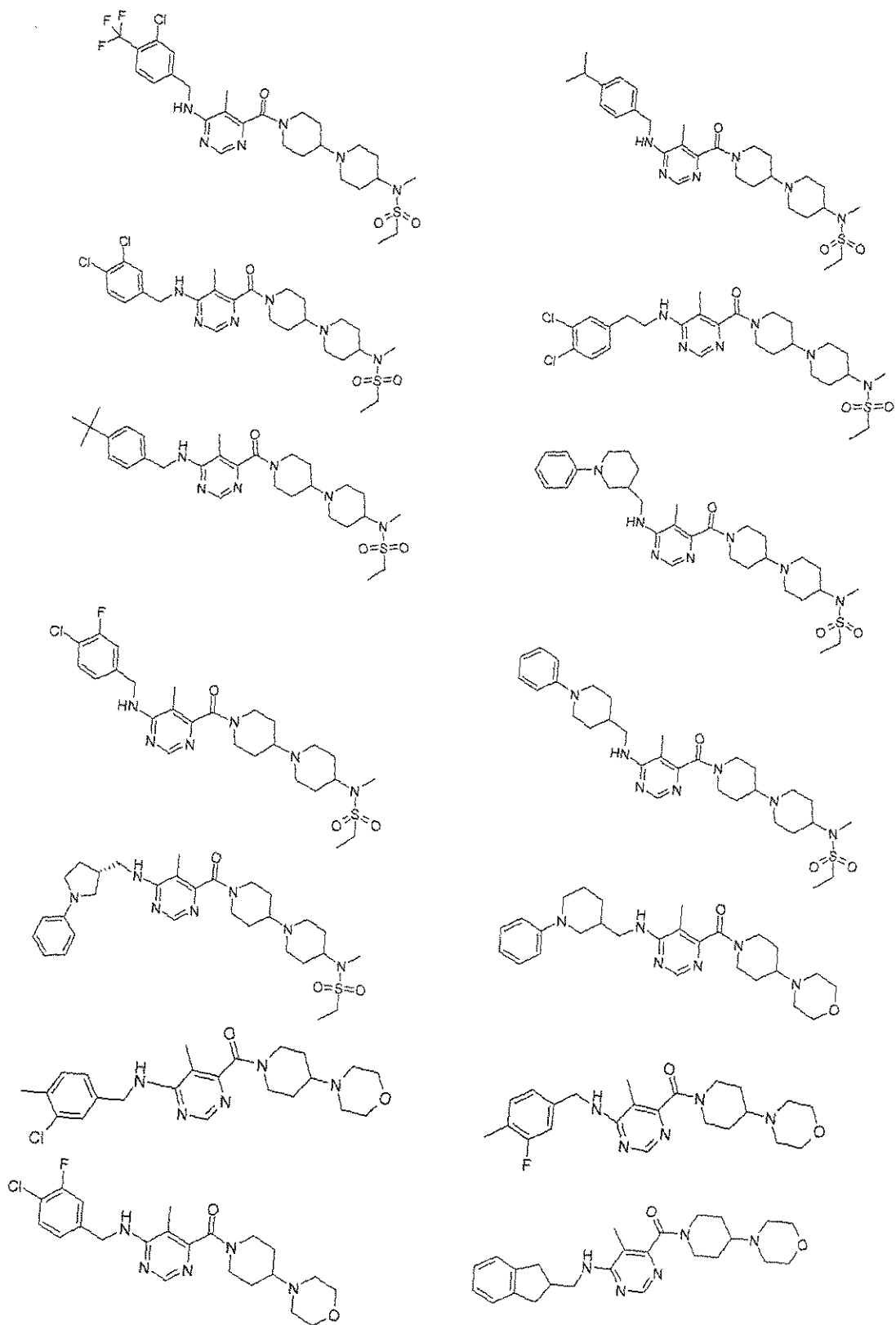


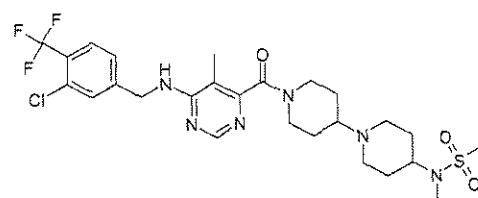
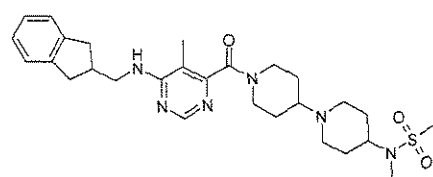
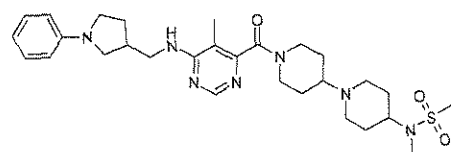
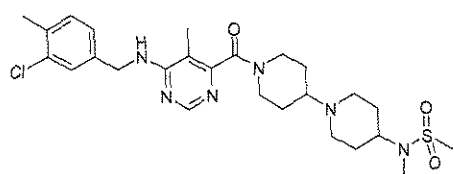
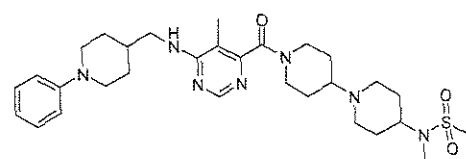
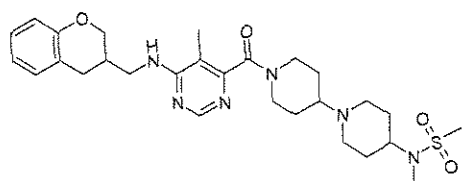
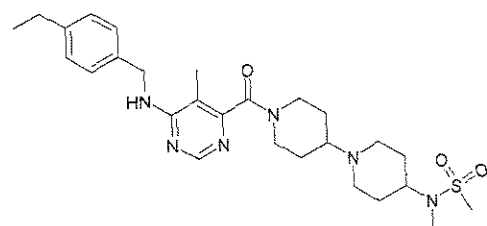
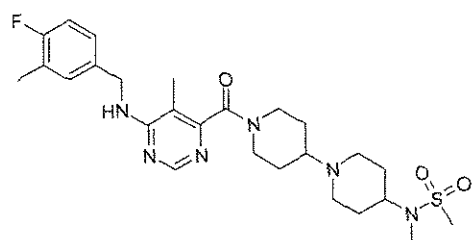
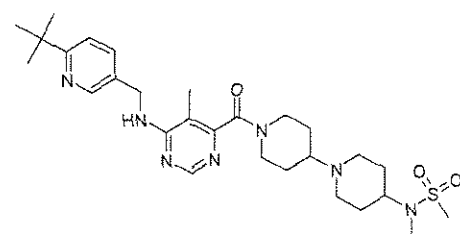
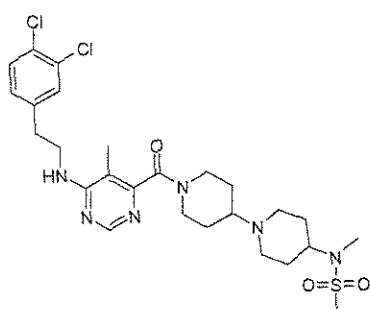
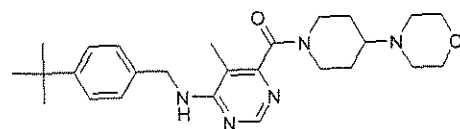
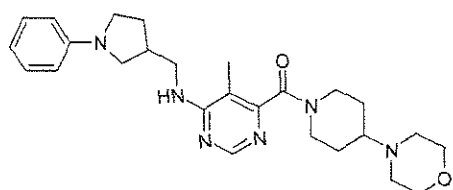
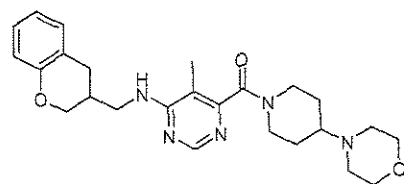
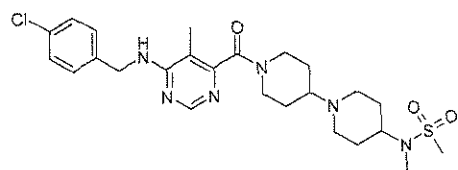
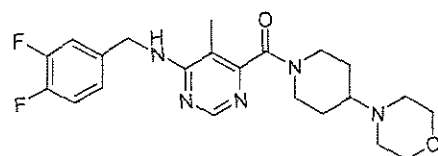
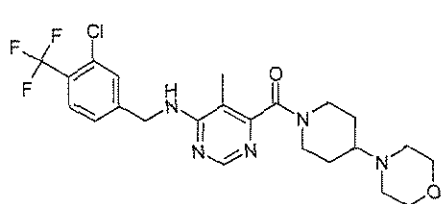
8. The compounds of any of the preceding claims, wherein R_5 is selected from among an electron pair, -H, and -C(O)-NH₂.
9. The compounds of any of the preceding claims, wherein R_6 is selected from among -H, -CH₃, -C₂H₅, -O-CH₃, -O-C₂H₅, -F, -CF₃, and -OCF₃.
10. The compounds of any of the preceding claims, wherein R_6 is H or -O-CH₃.
11. The compounds of any of the preceding claims, wherein A is -O- or -NH-.

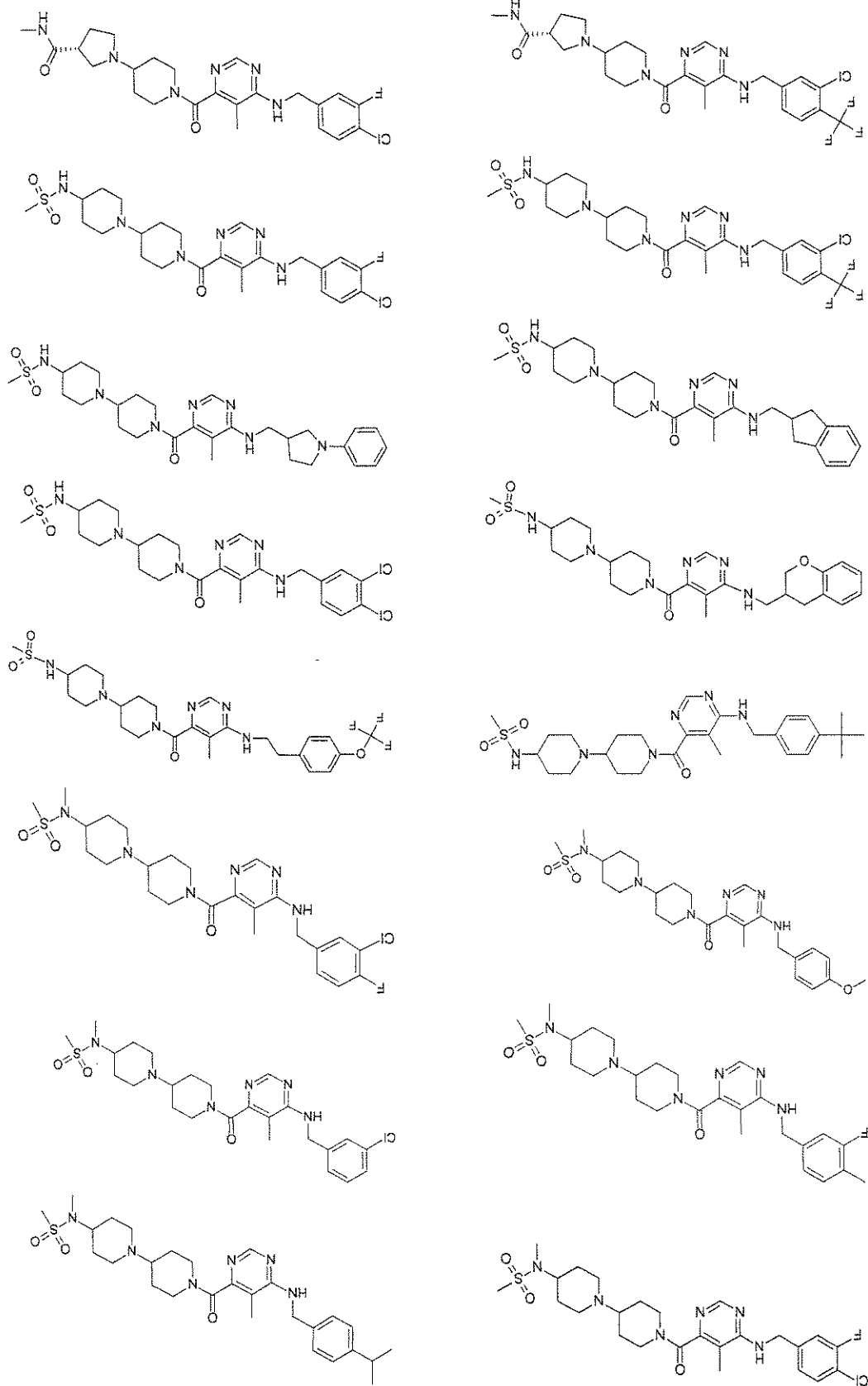
12. The compound according to any of the preceeding claims chosen from the group consisting of

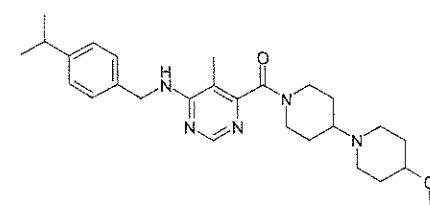
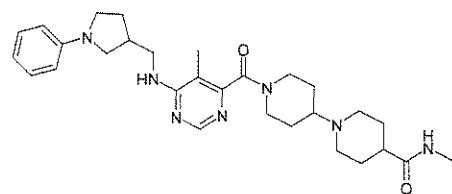
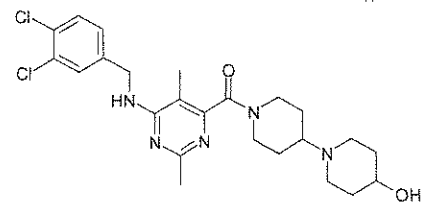
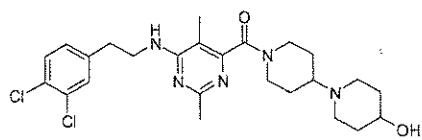
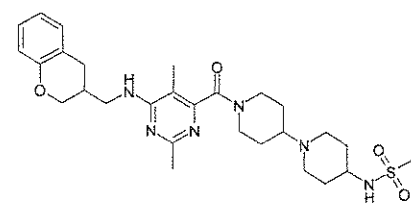
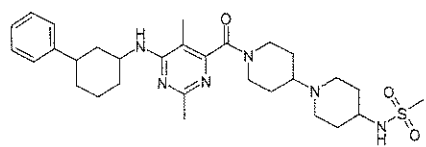
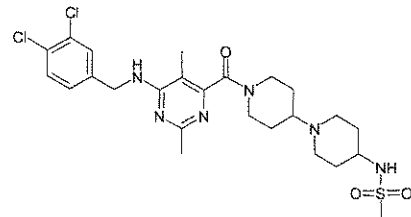
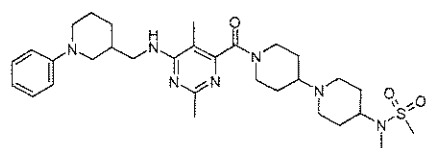
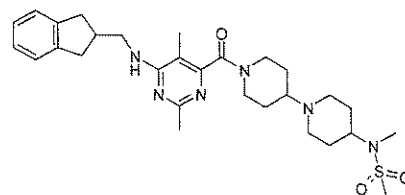
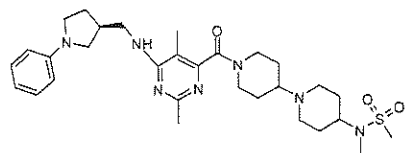
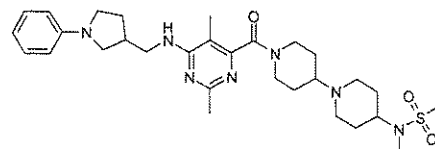
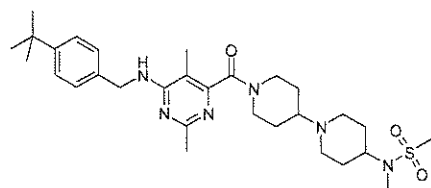
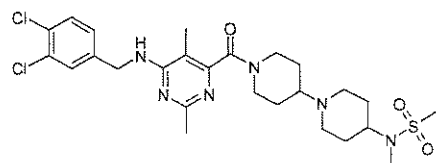
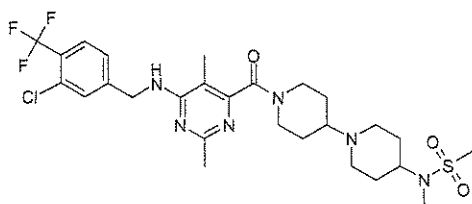
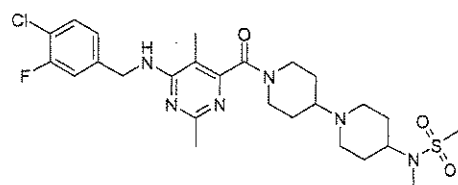
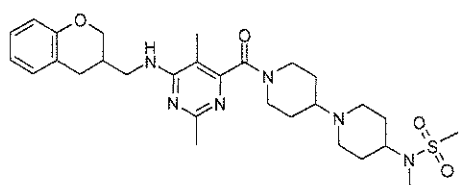


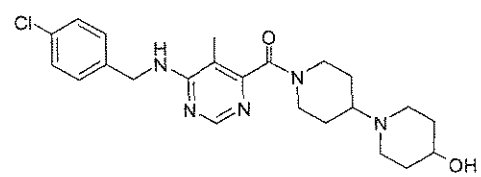
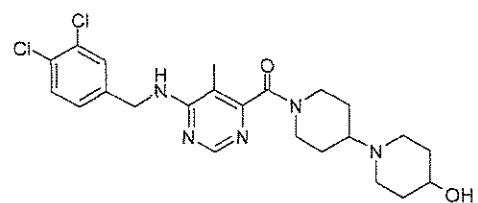
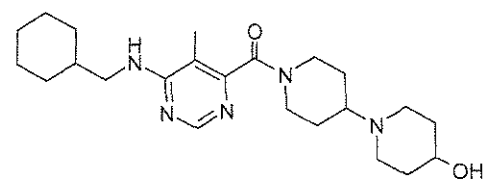
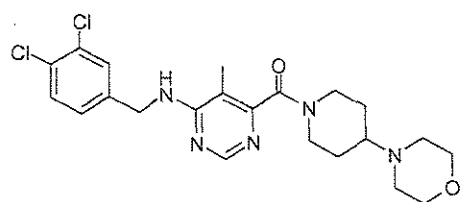
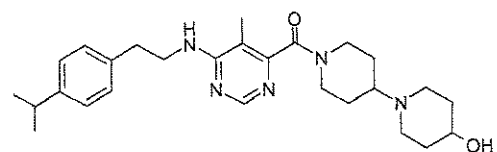
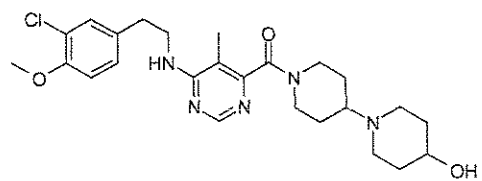
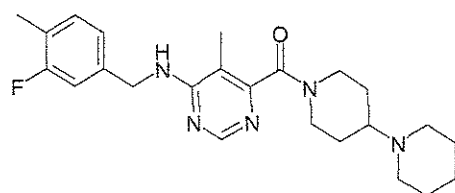
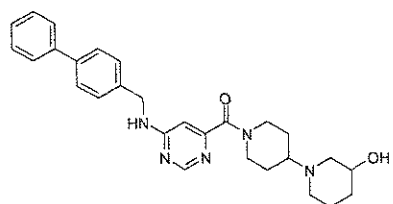
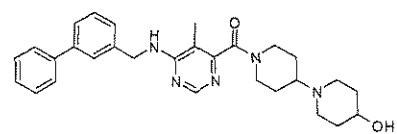
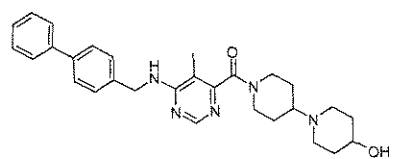
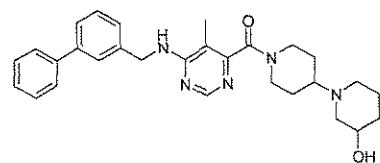
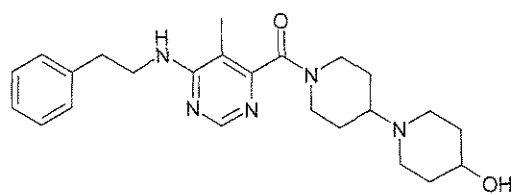
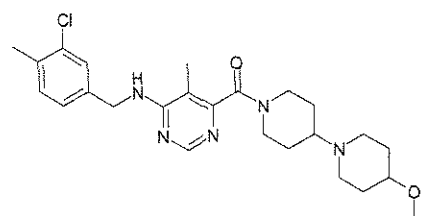
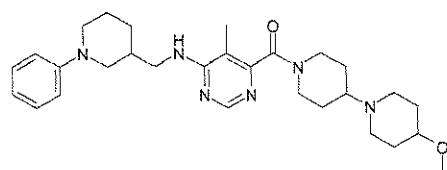
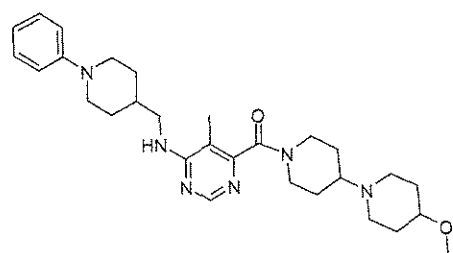
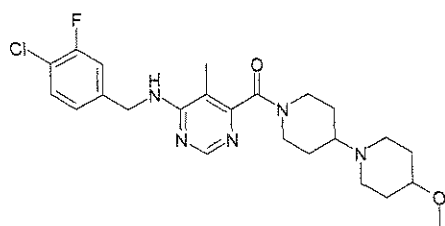


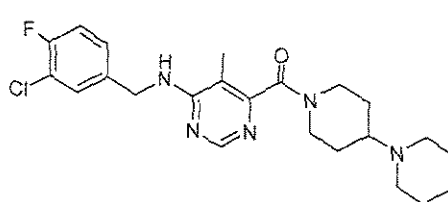
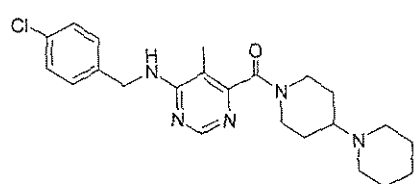
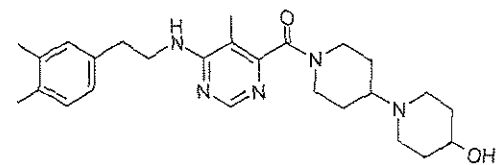
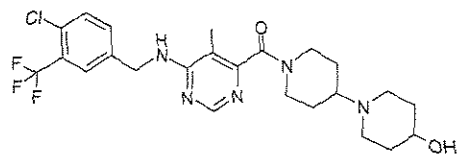
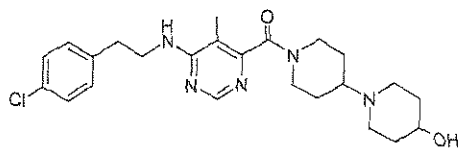
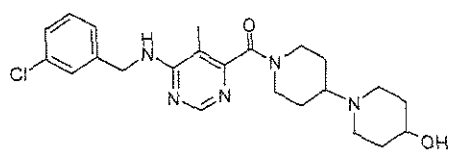
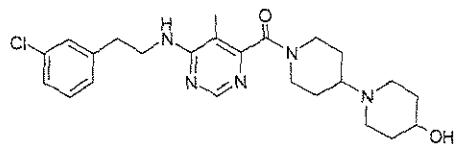
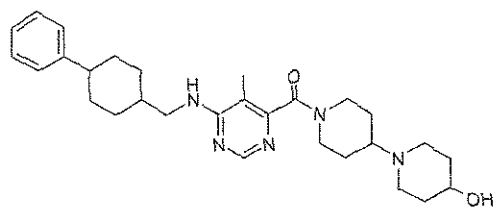
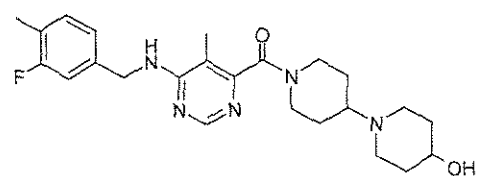
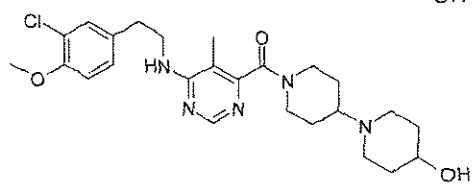
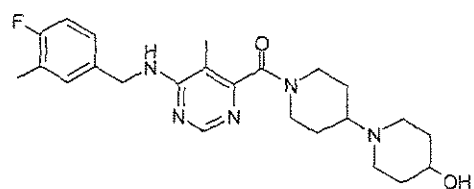
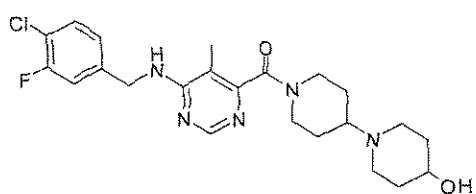
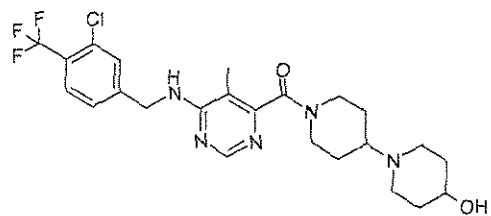
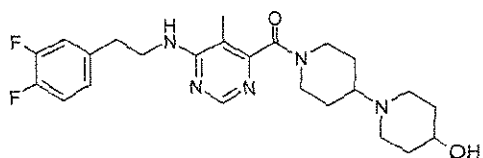
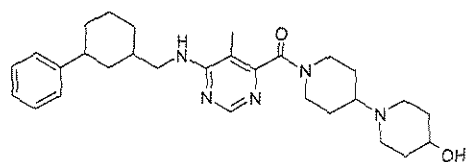
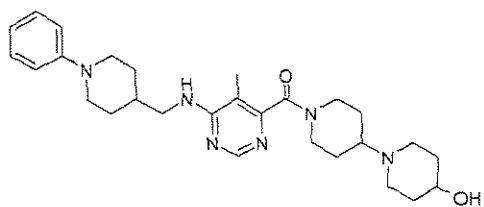
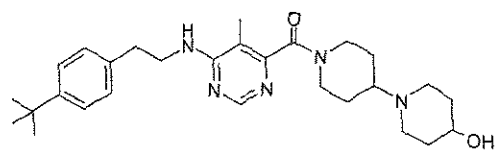
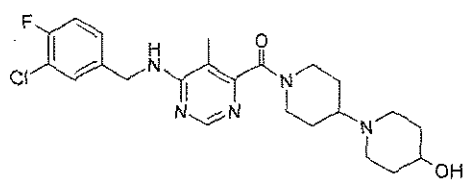


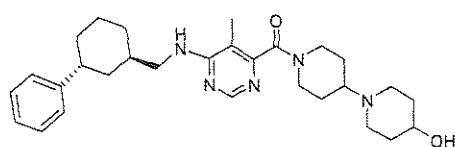
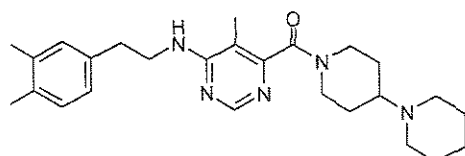
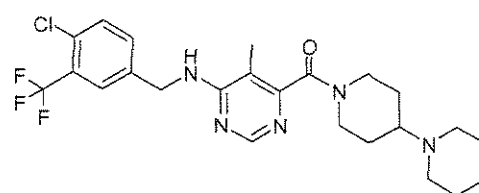
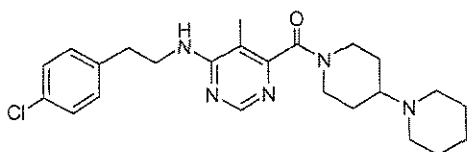
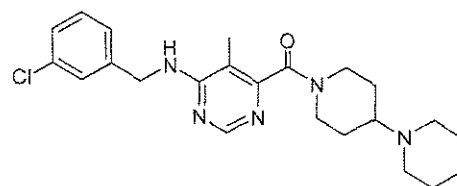
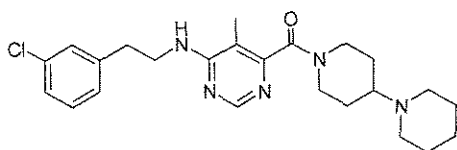
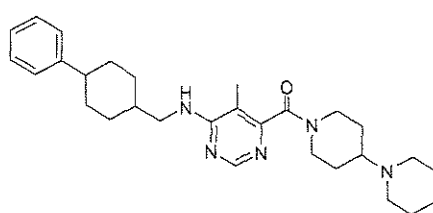
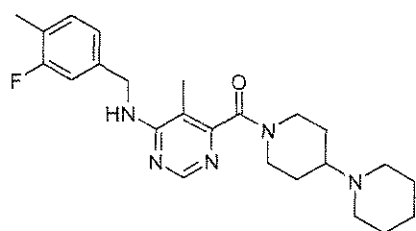
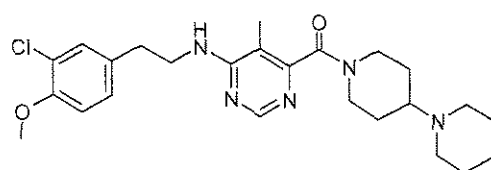
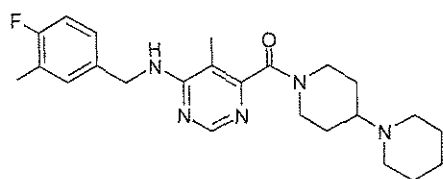
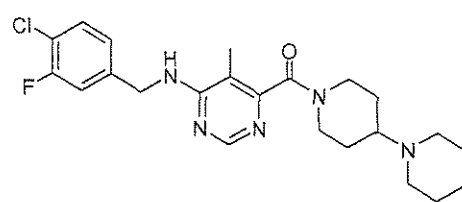
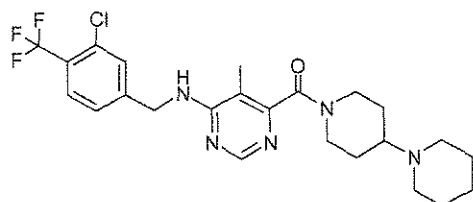
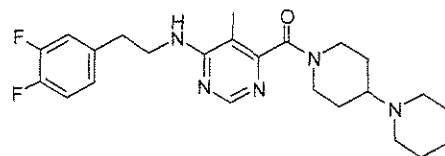
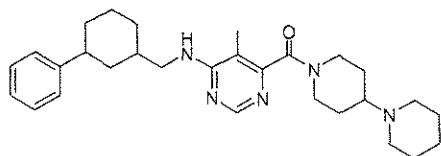
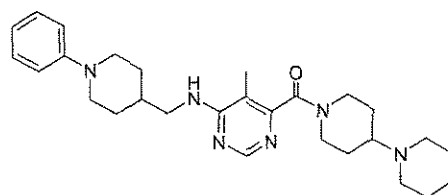
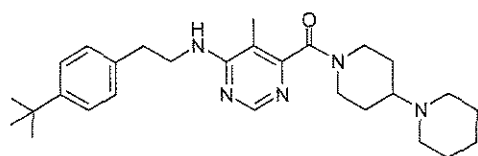


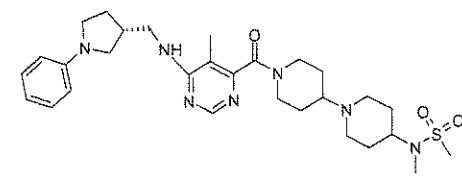
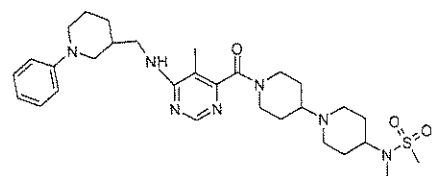
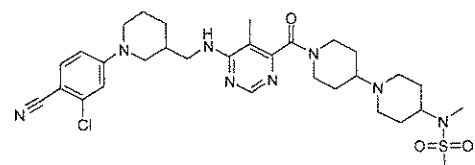
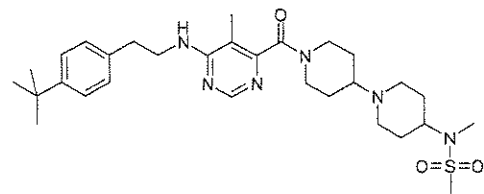
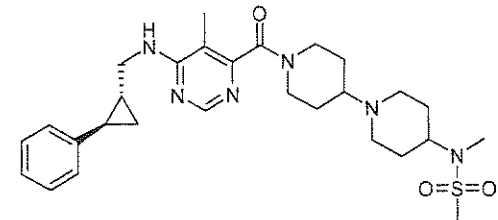
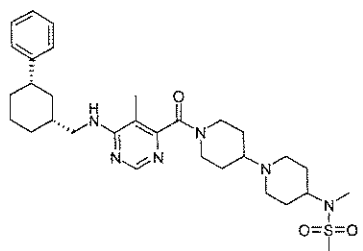
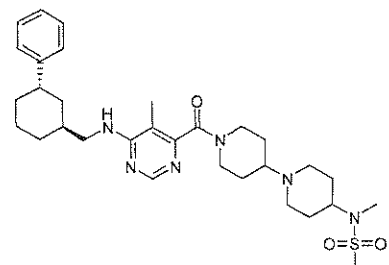
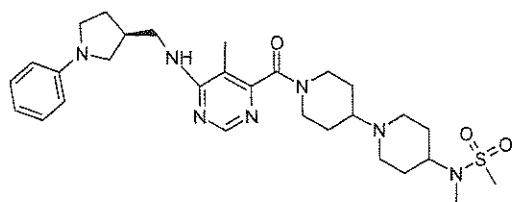
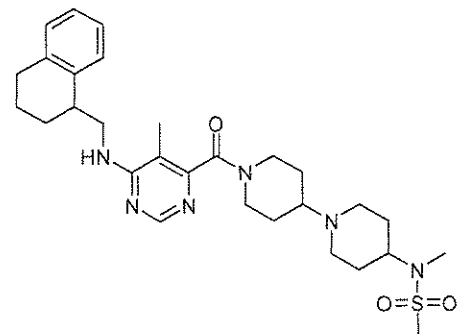
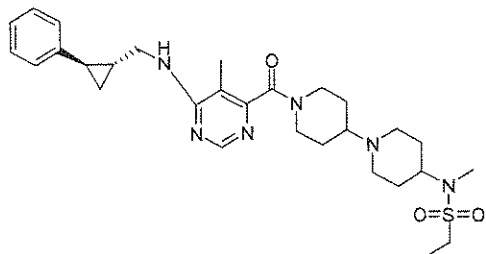
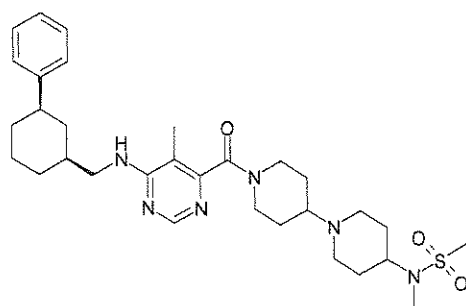
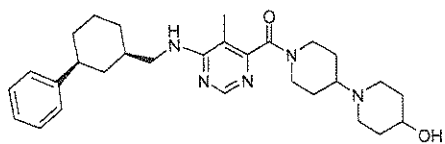


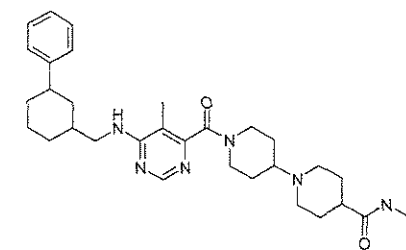
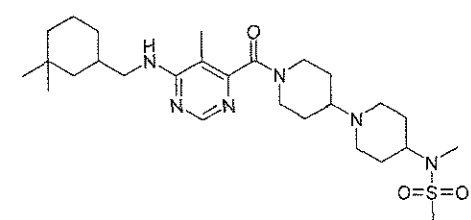
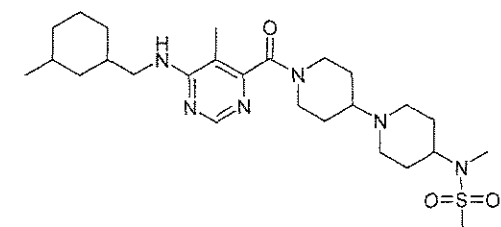
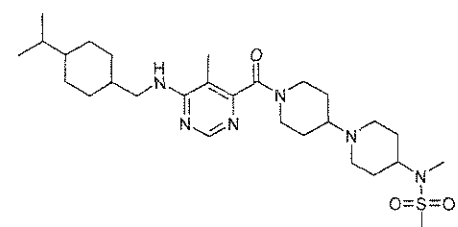
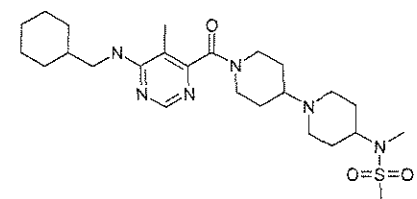
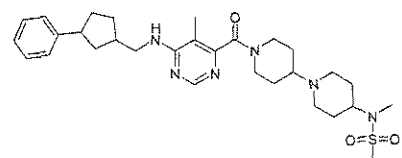
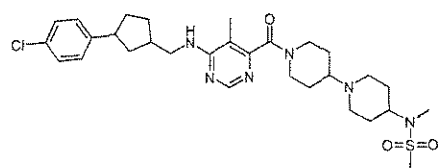
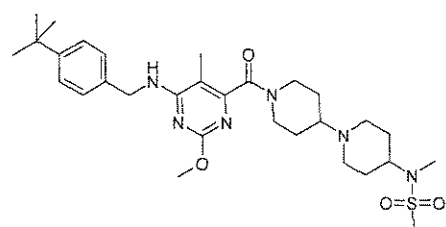
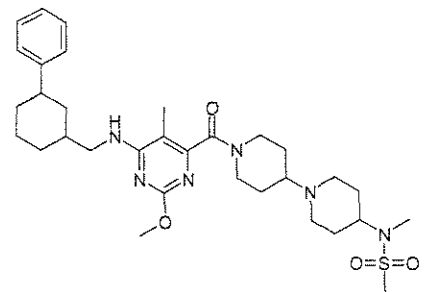
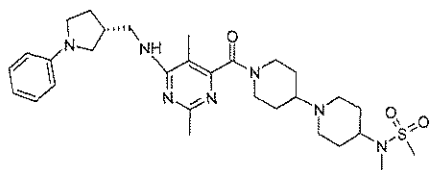
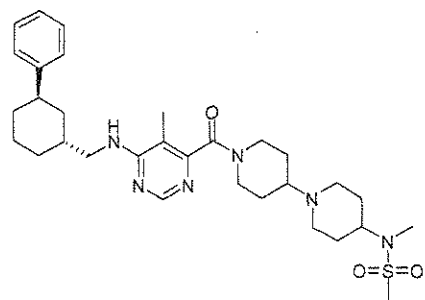
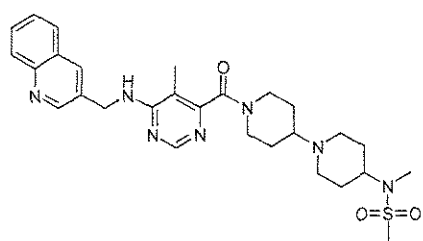


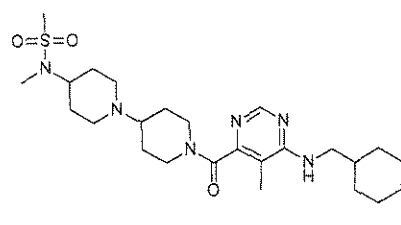
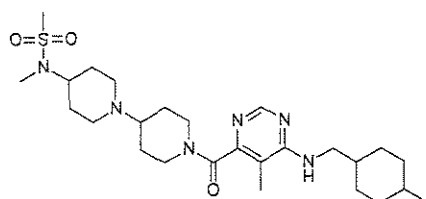
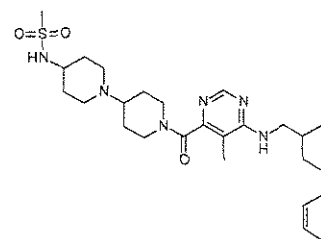
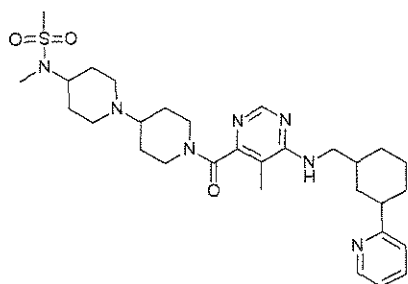
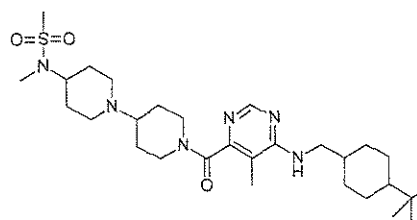
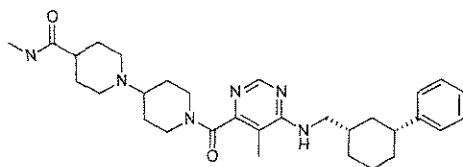
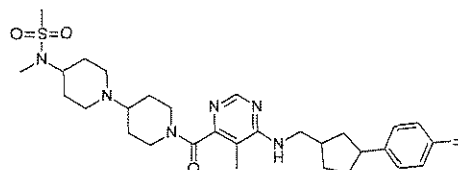
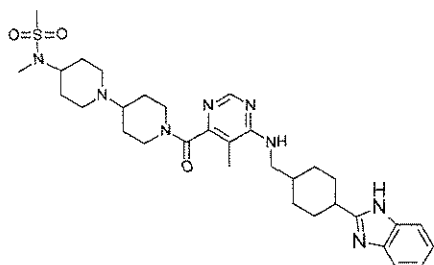
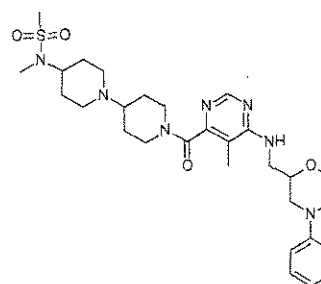
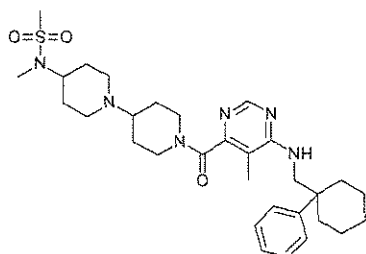
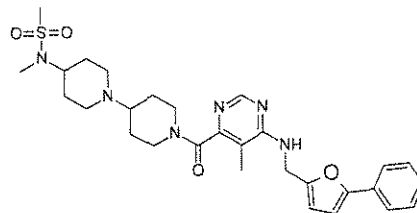
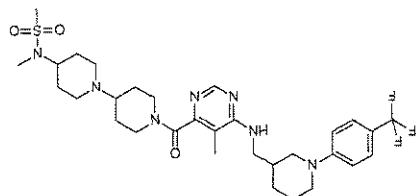
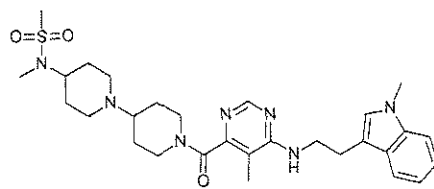
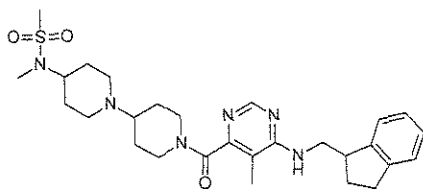


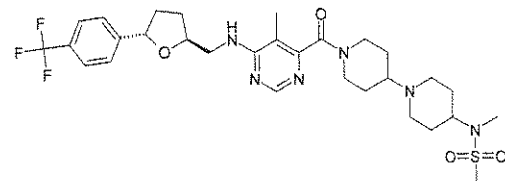
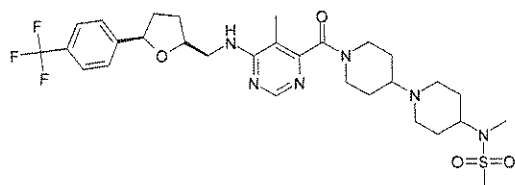
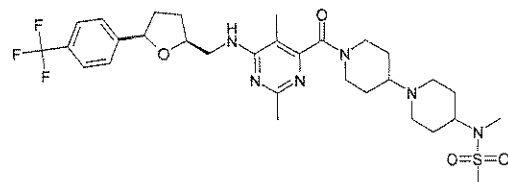
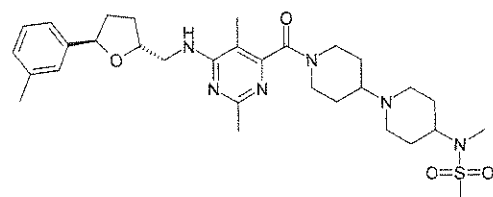
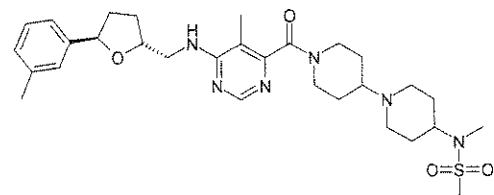
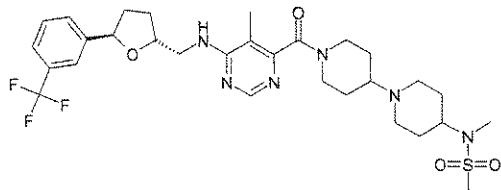
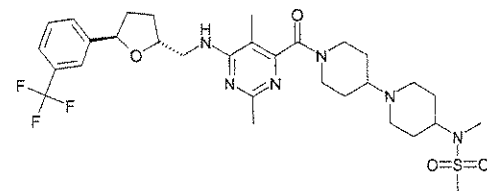
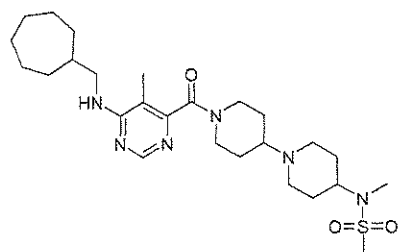
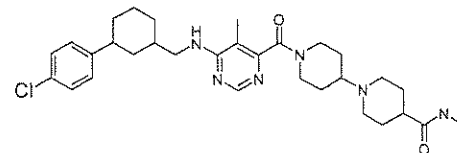
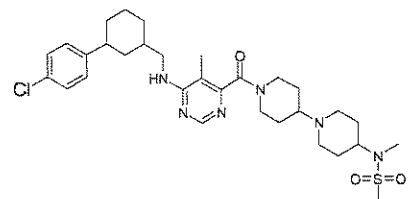
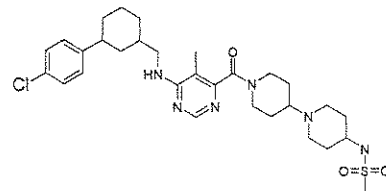
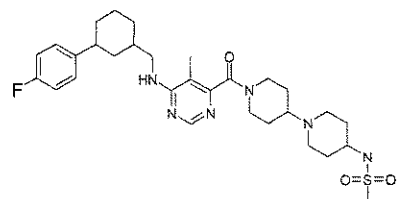
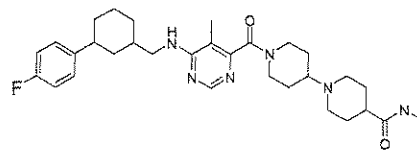
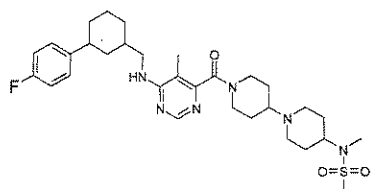


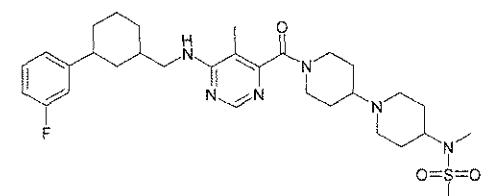
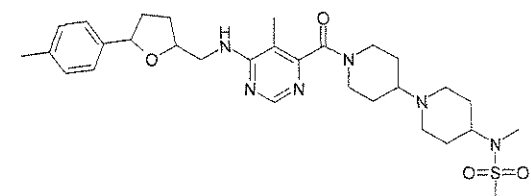
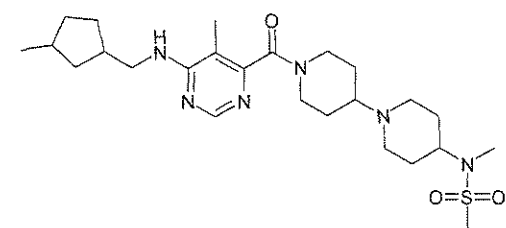
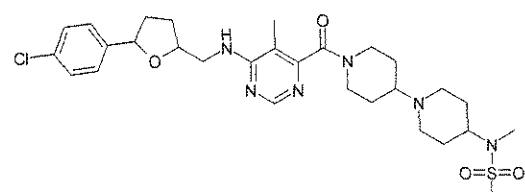
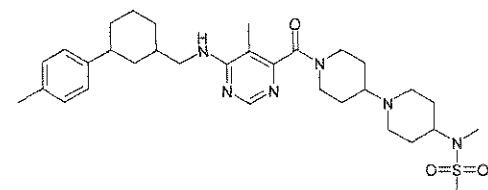
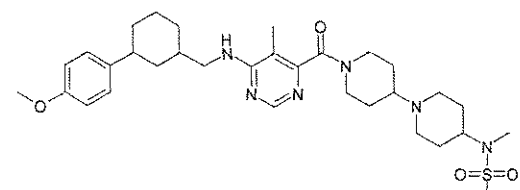
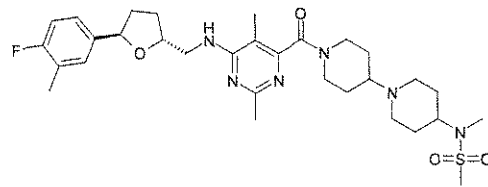
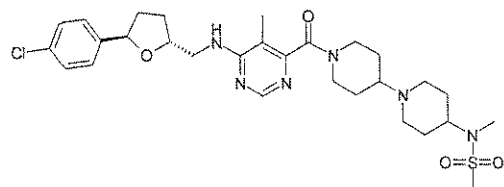
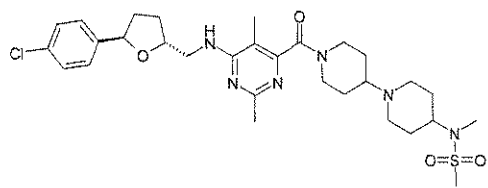
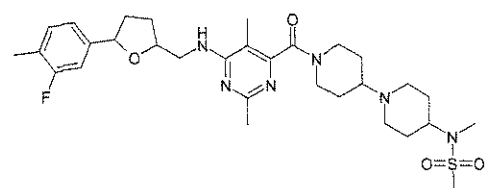
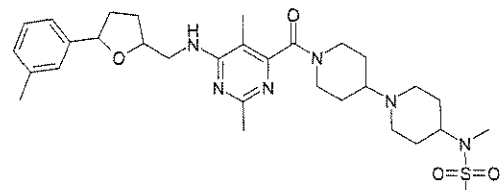
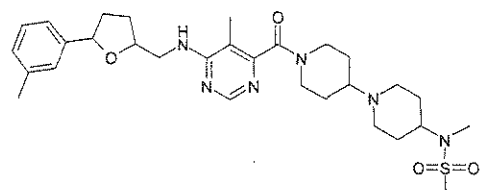
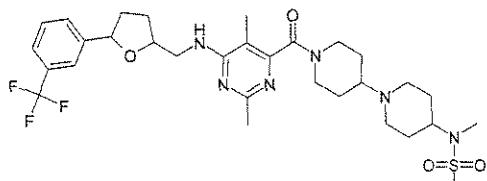
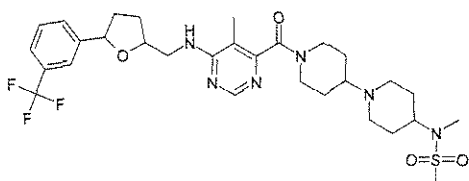
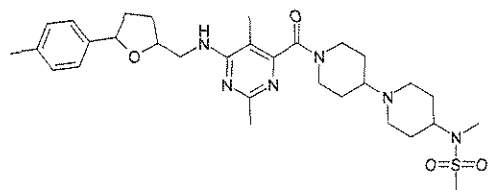
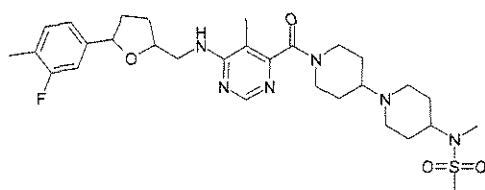


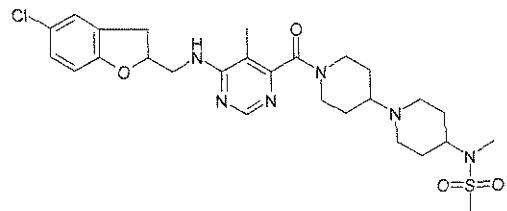
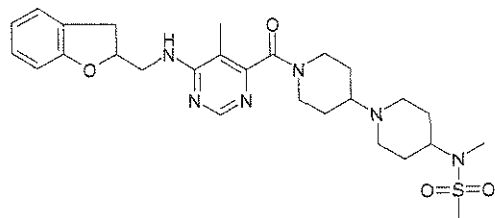
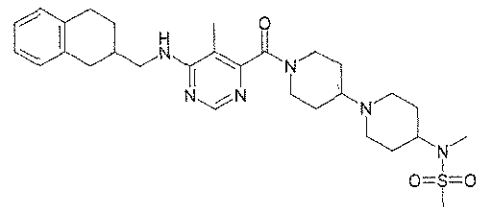
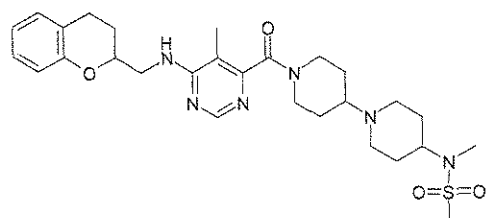
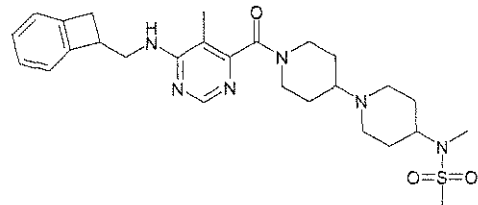
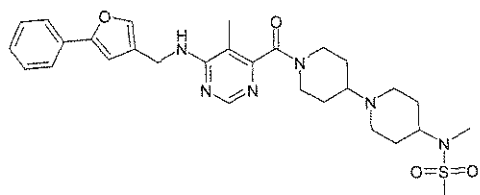
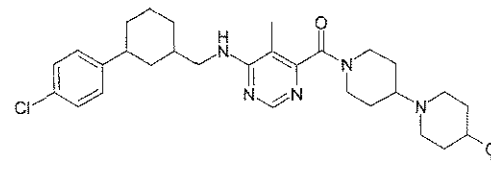
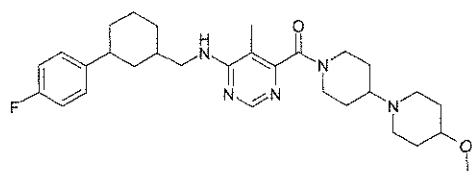
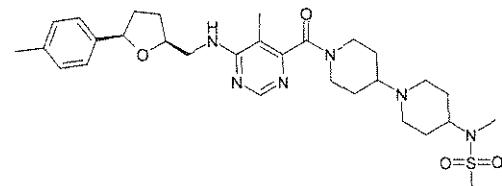
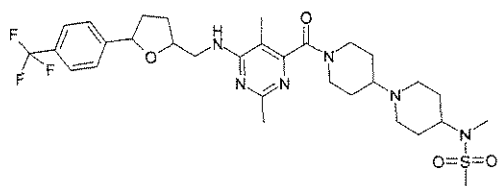
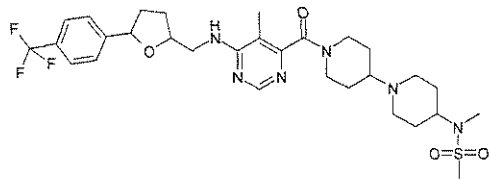
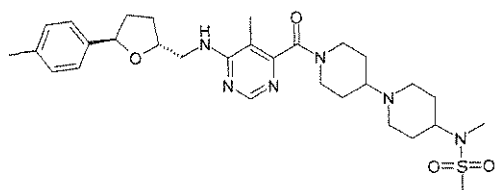
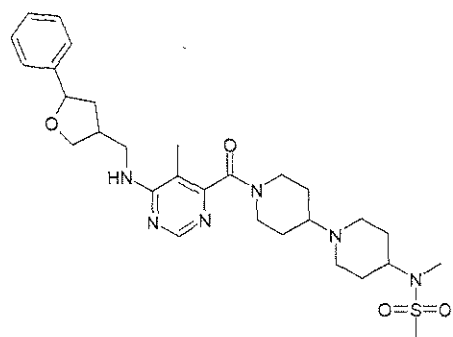
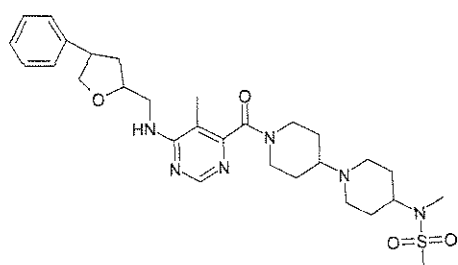


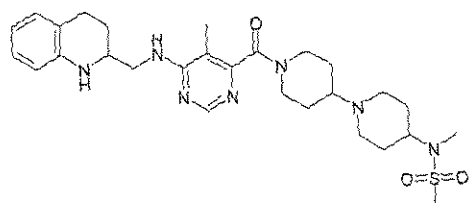
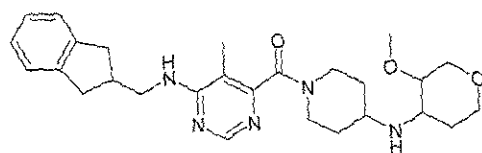
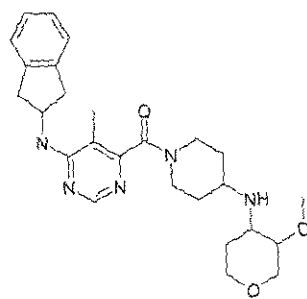
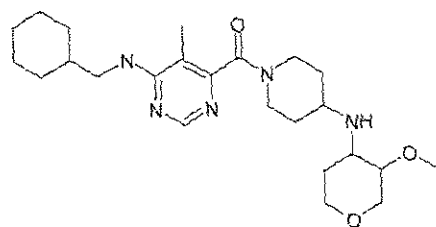
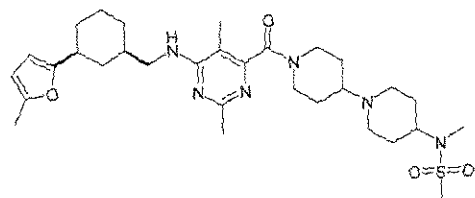
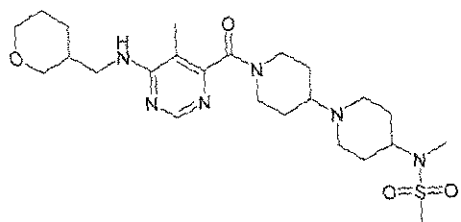
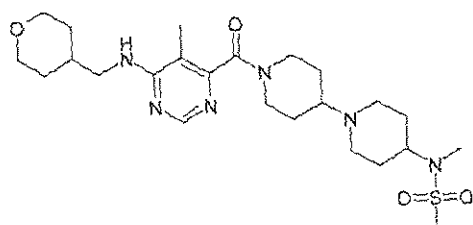
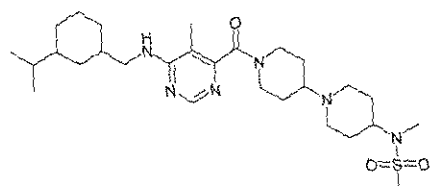
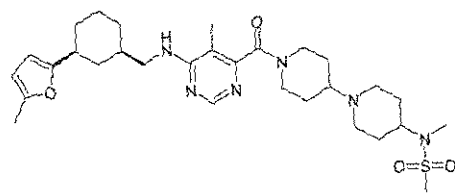
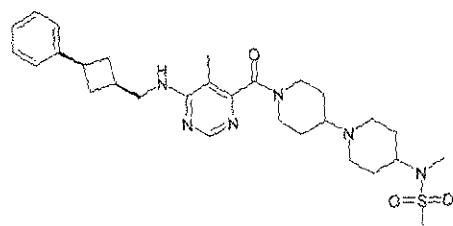
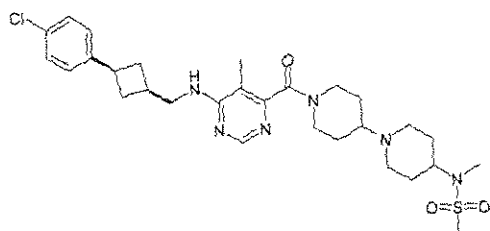
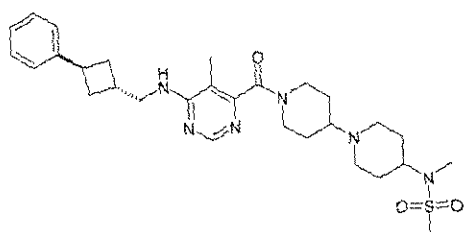
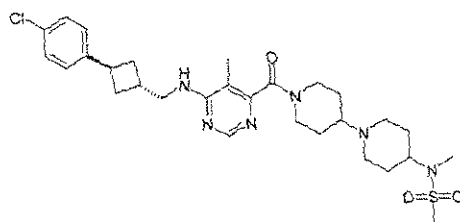
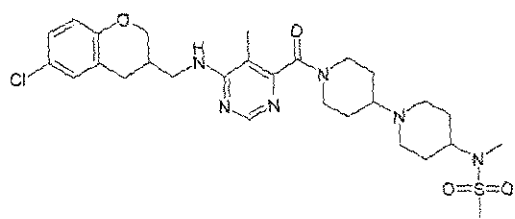


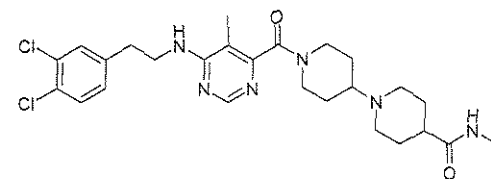
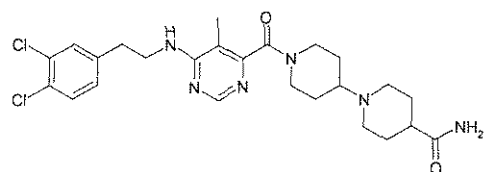
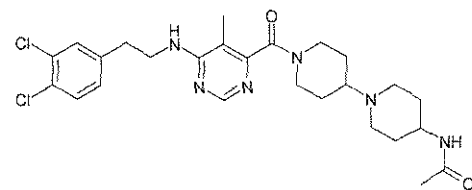
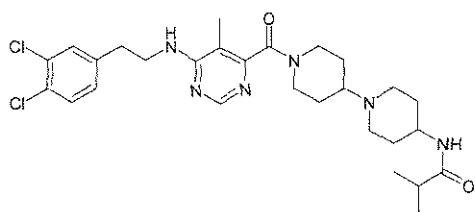
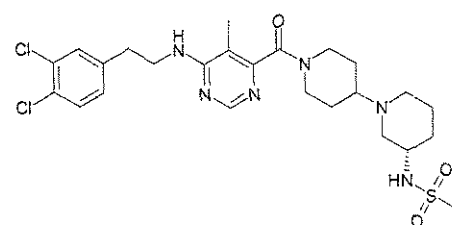
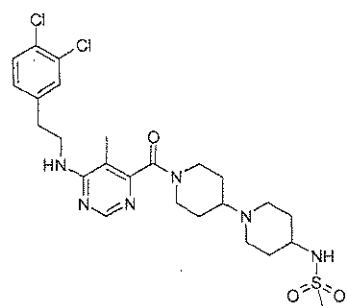
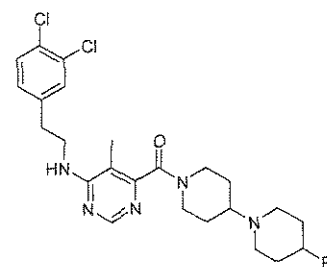
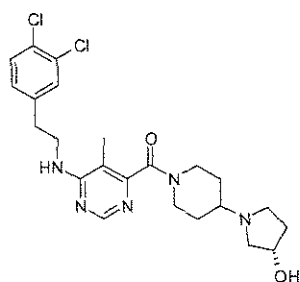
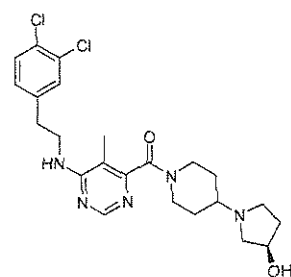
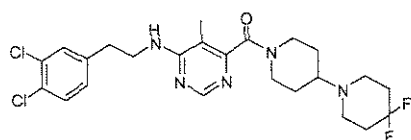
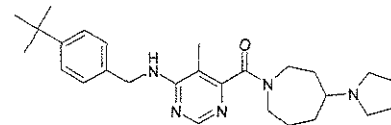
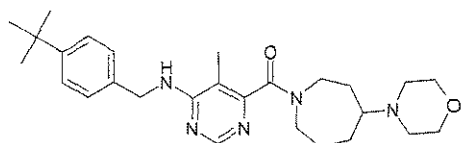
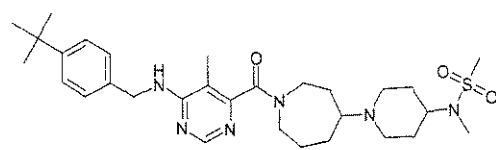
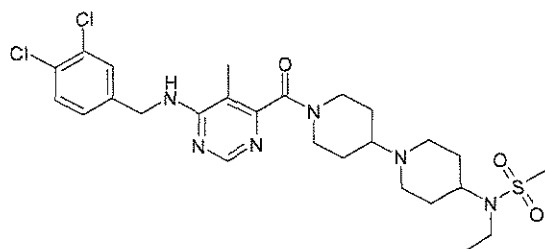


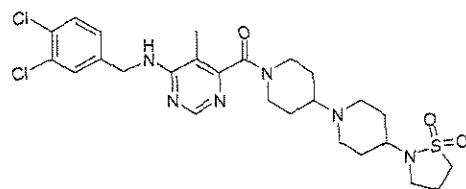
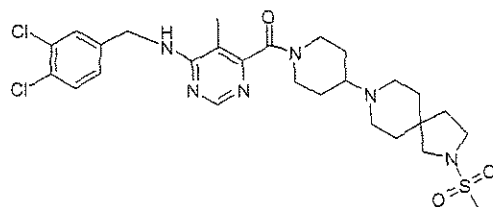
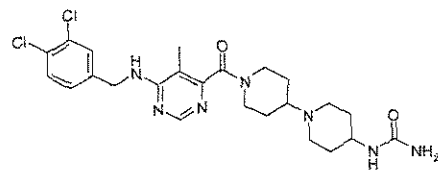
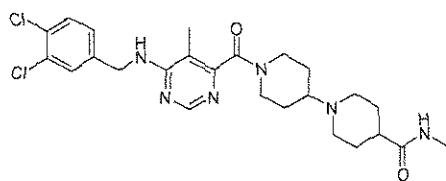
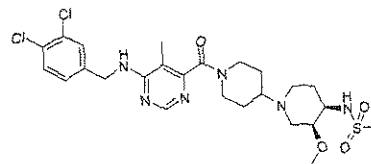
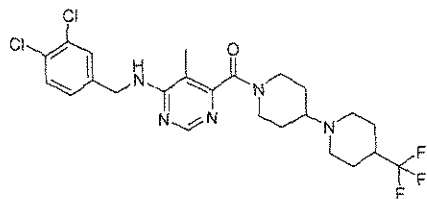
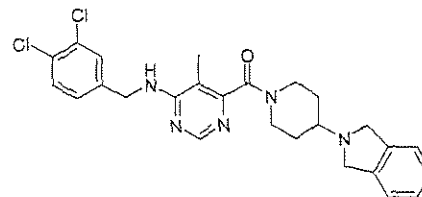
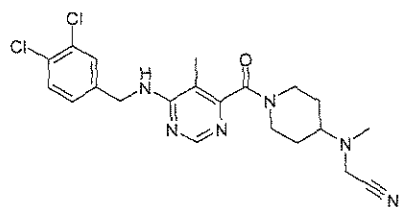
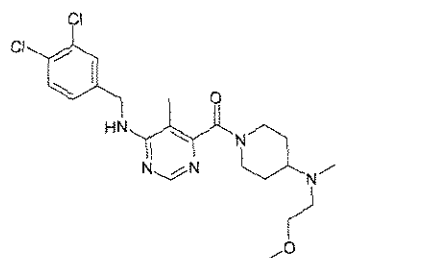
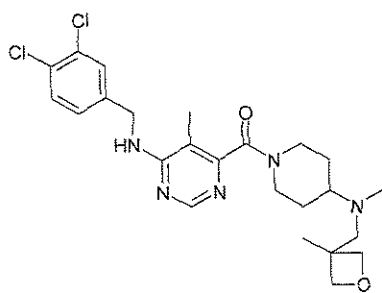
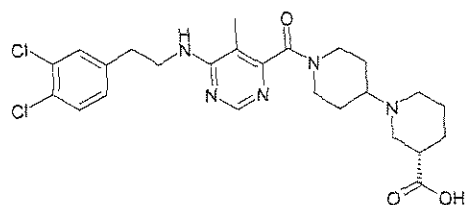
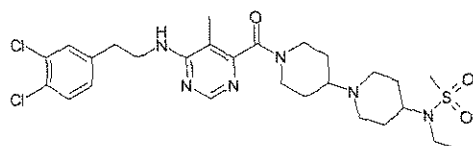
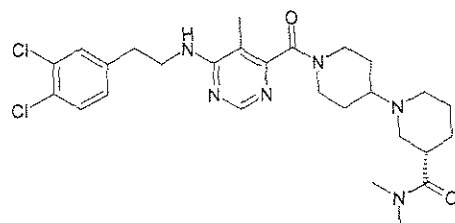
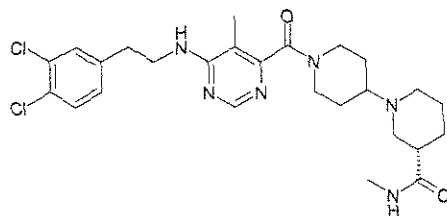
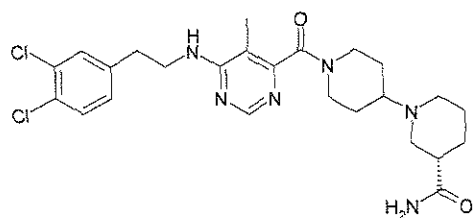
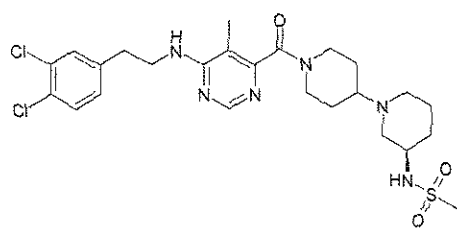


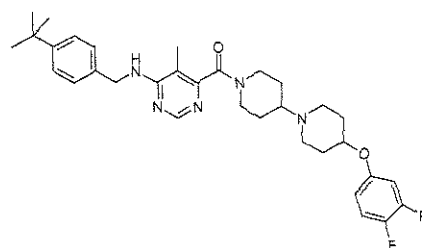
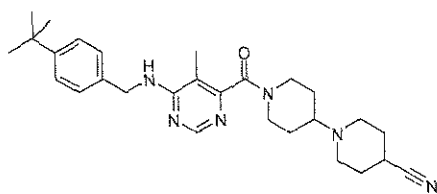
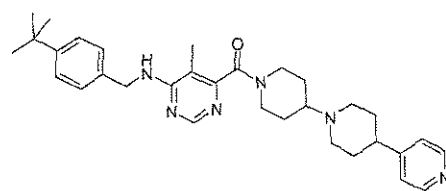
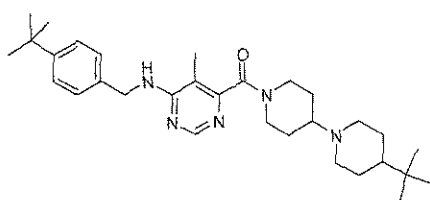
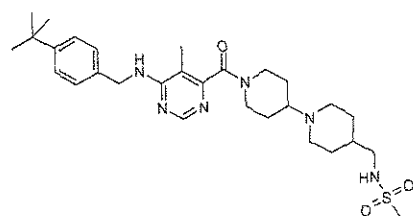
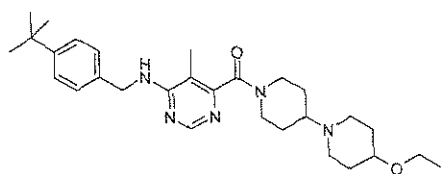
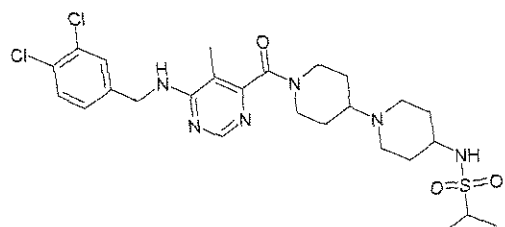
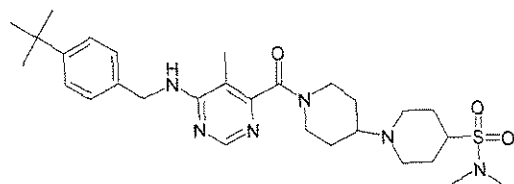
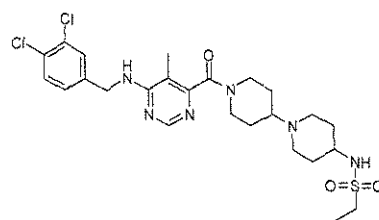
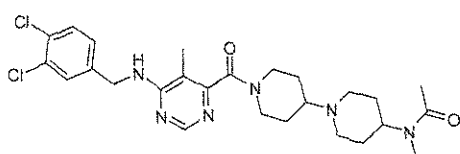
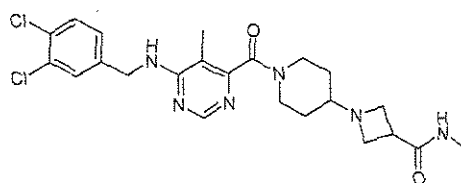
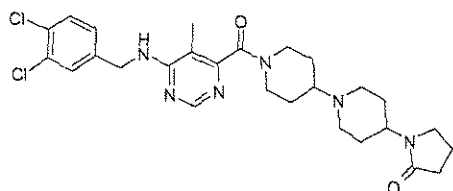
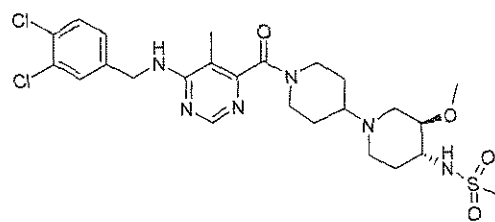
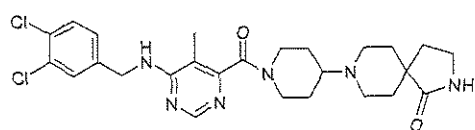


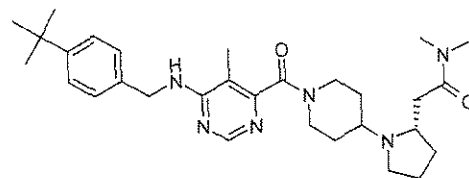
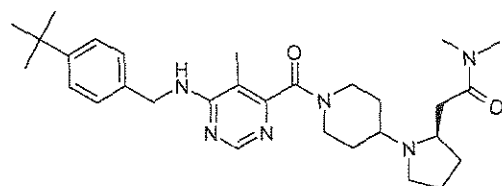
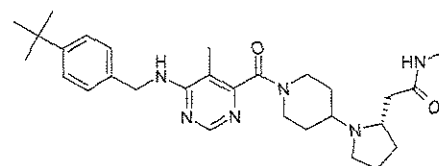
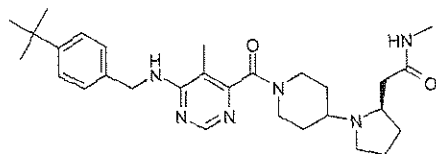
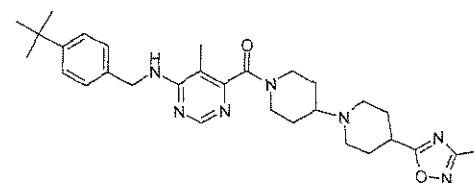
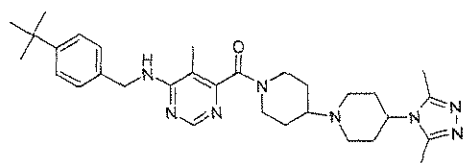
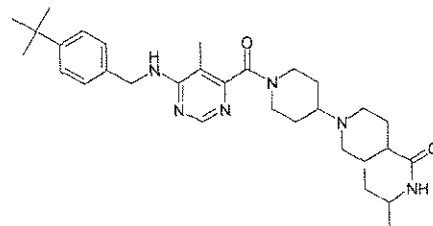
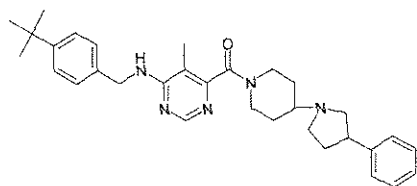
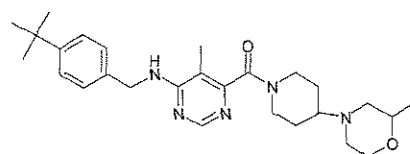
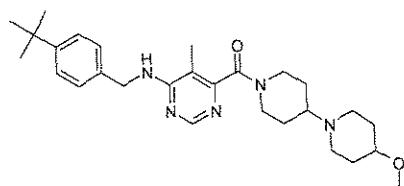
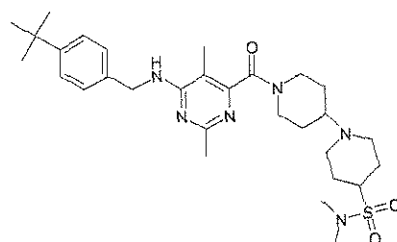
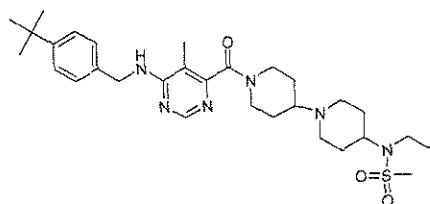
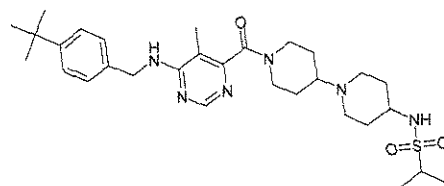
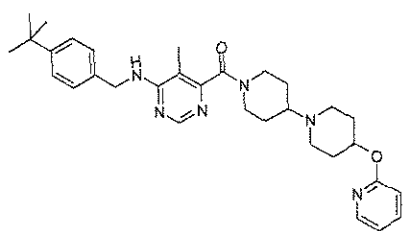


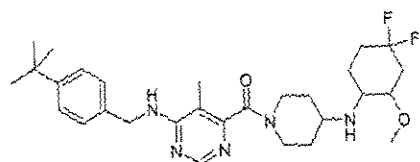
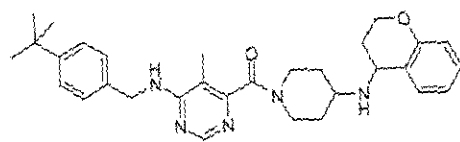
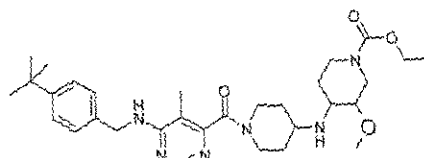
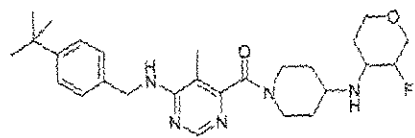
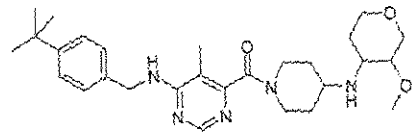
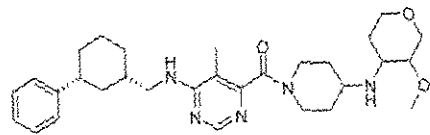
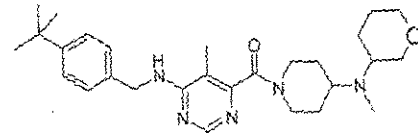
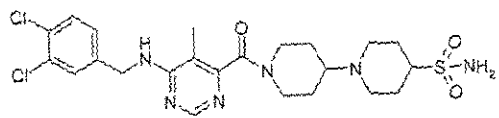
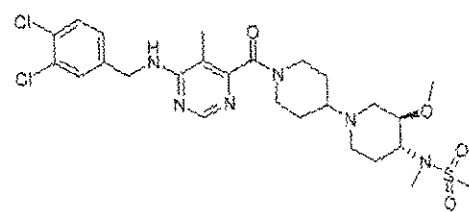
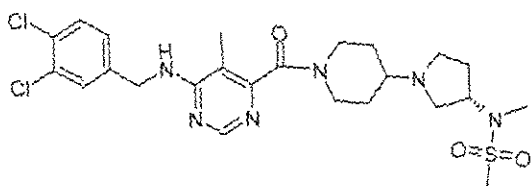
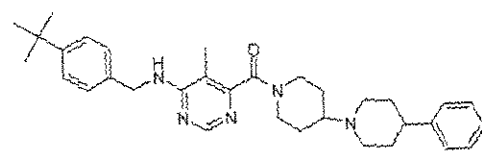
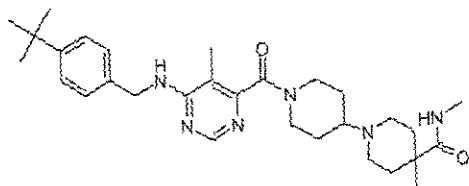
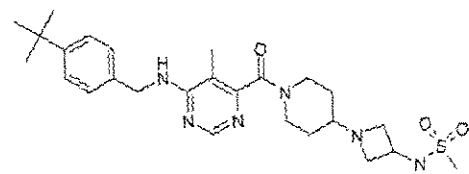
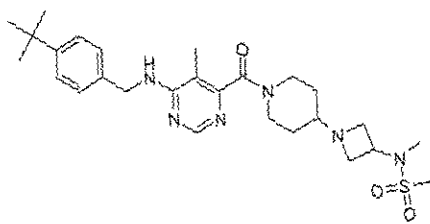
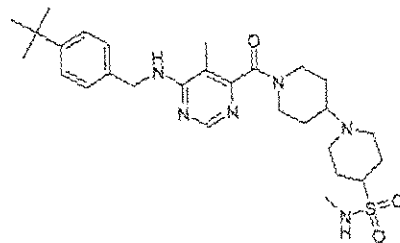
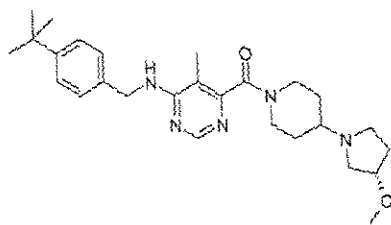
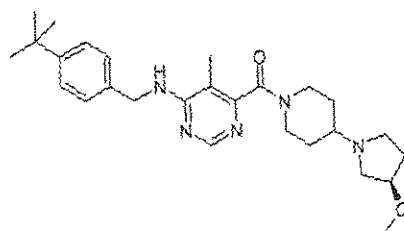
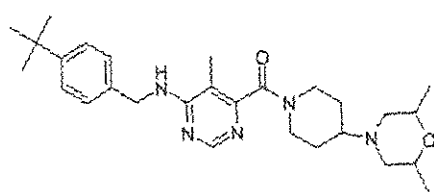


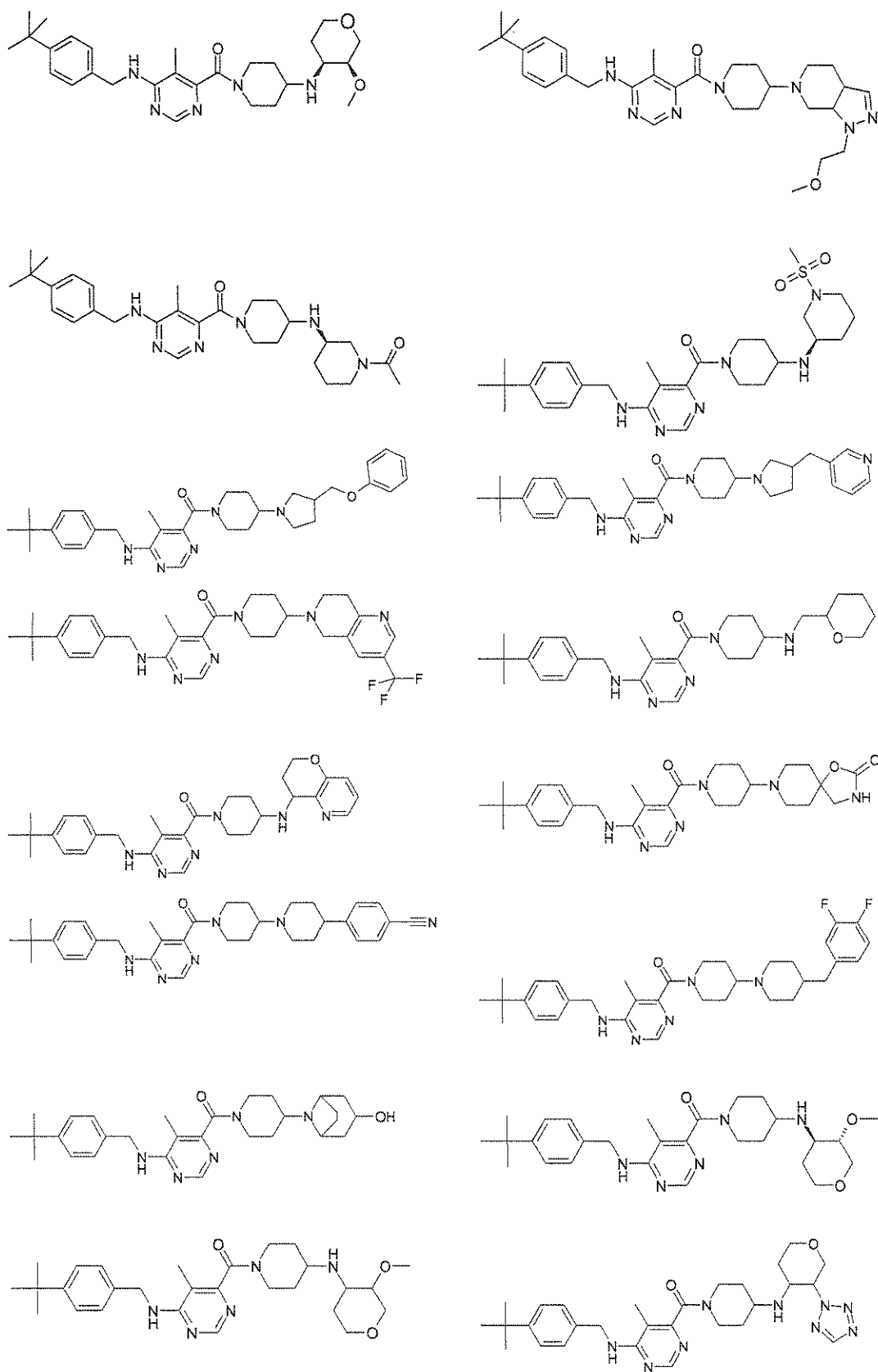


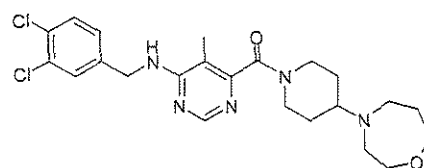
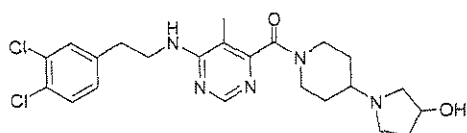
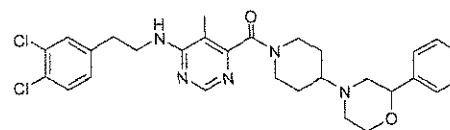
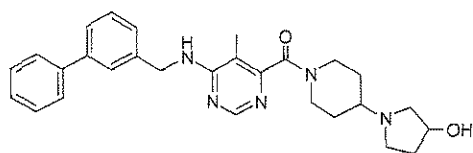
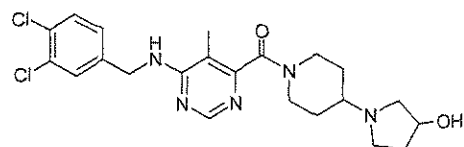
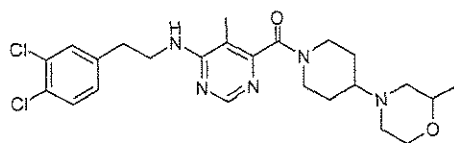
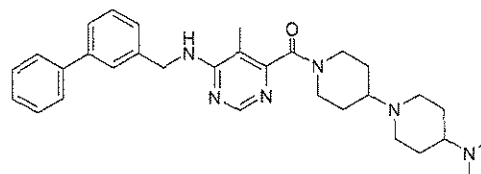
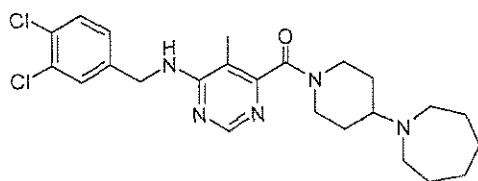
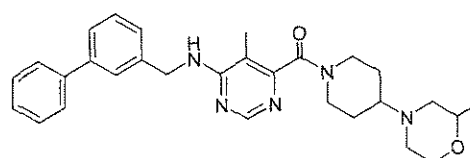
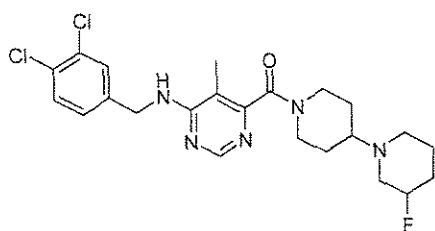
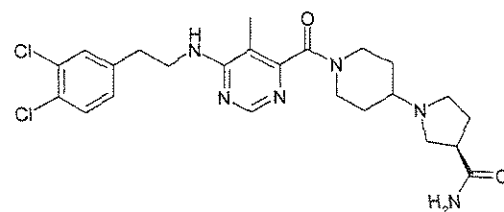
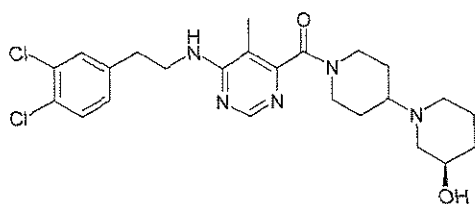
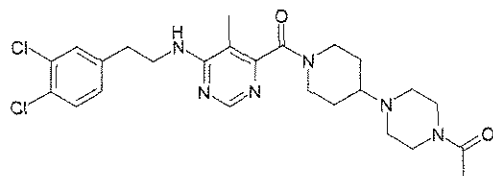
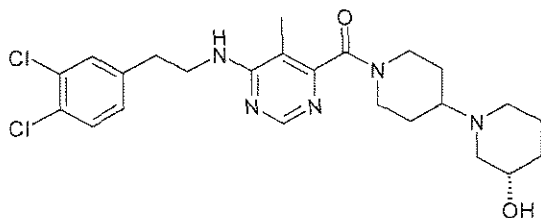
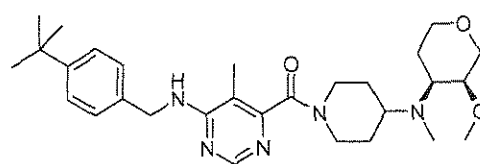
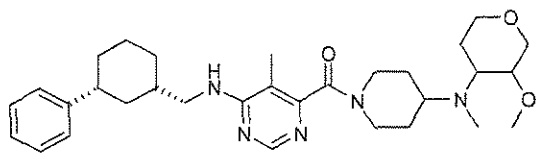


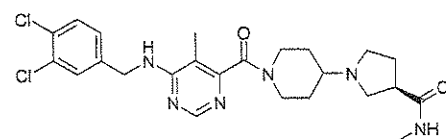
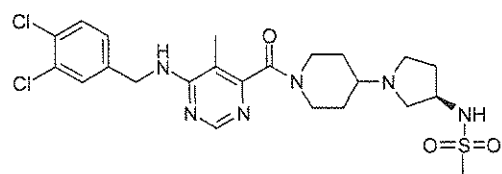
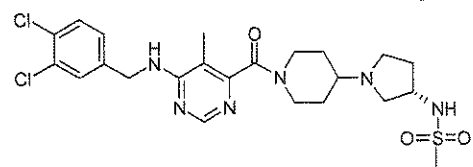
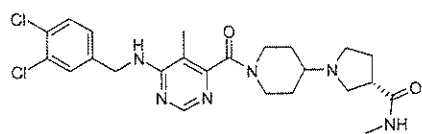
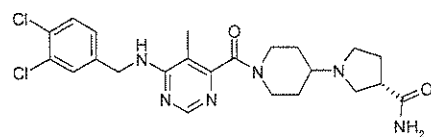
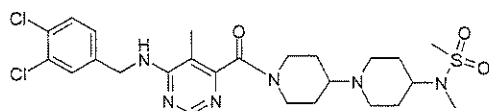
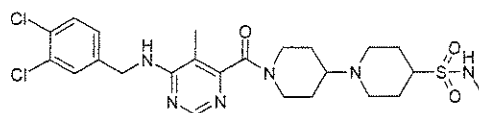
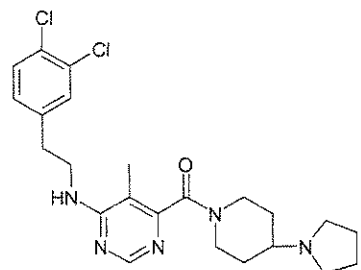
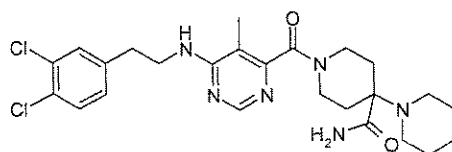
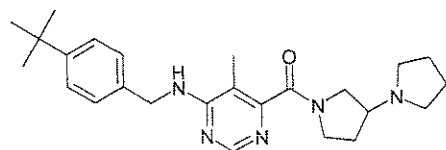
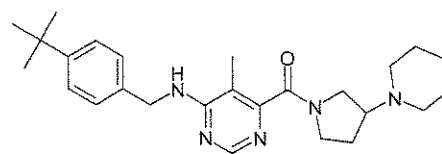
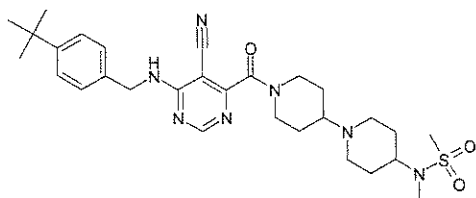
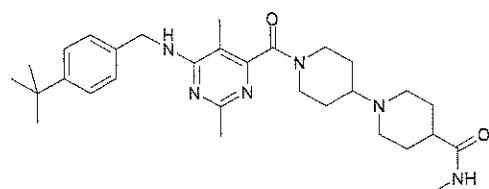
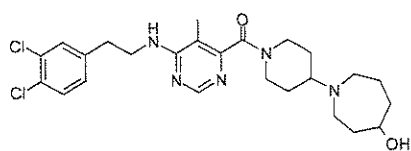
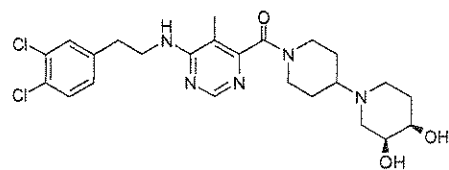
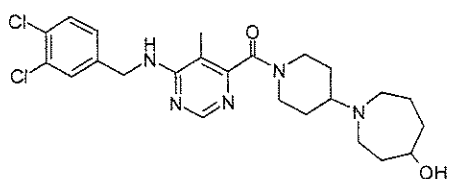
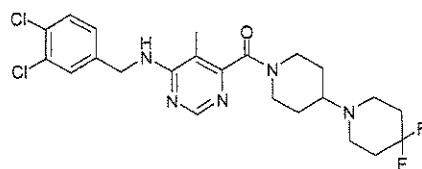
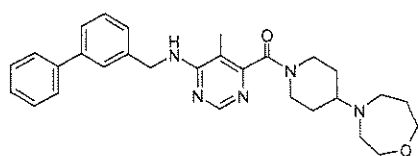


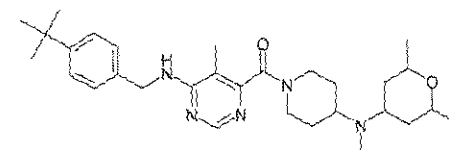
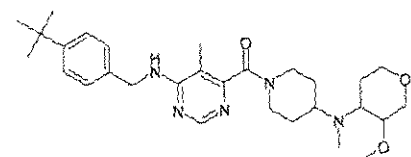
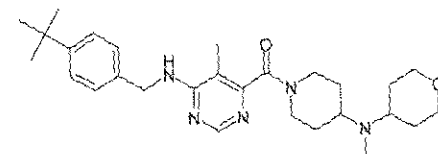
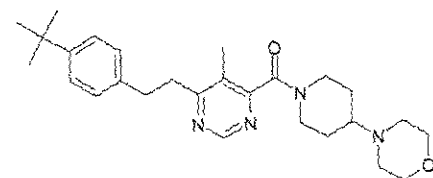
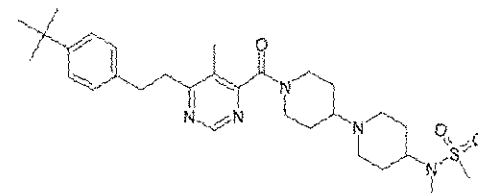
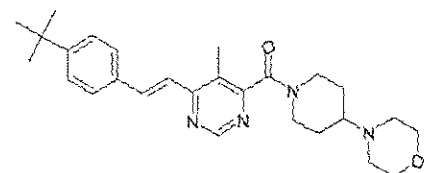
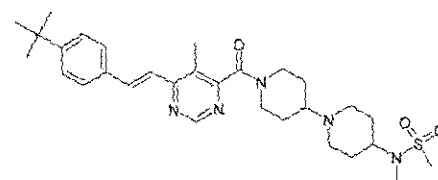
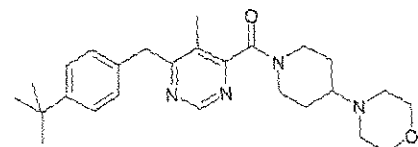
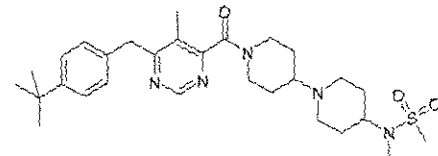
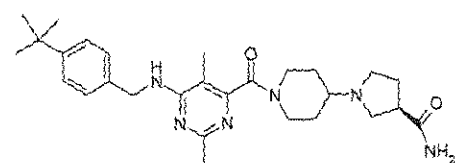
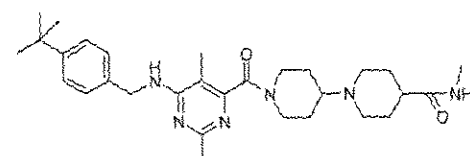
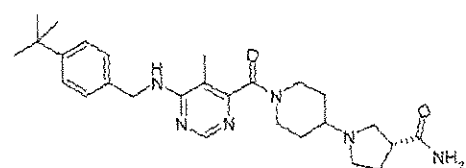
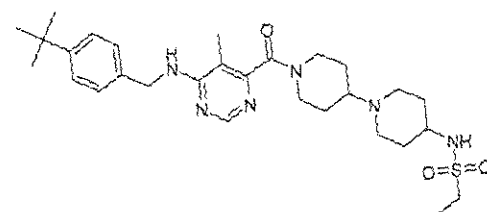
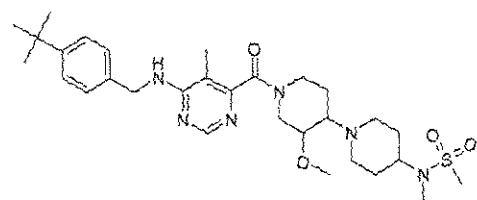
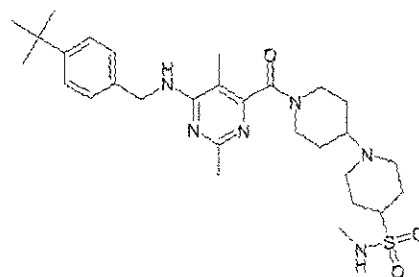
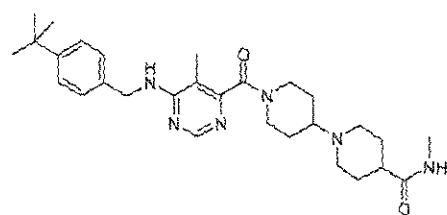


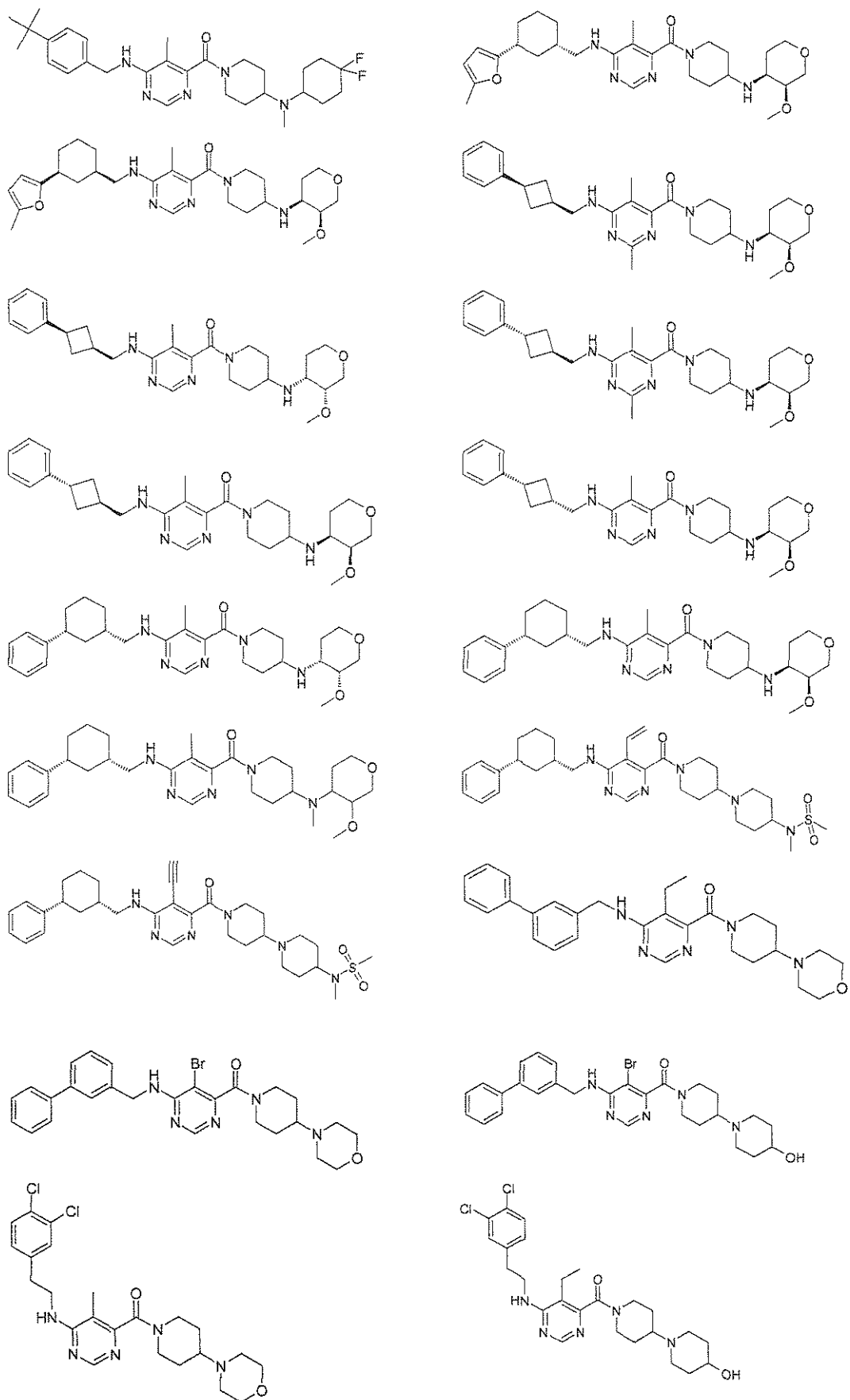


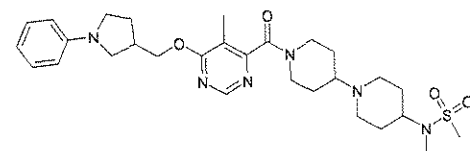
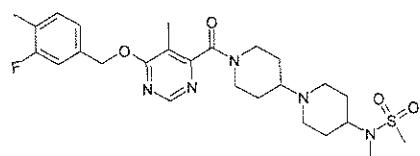
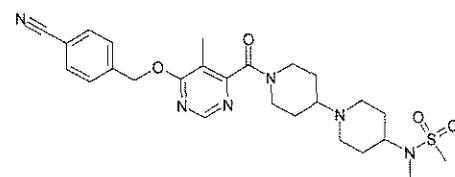
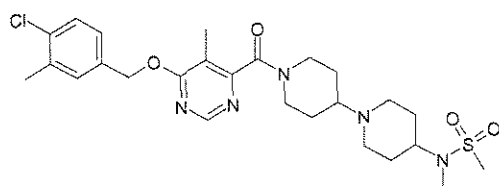
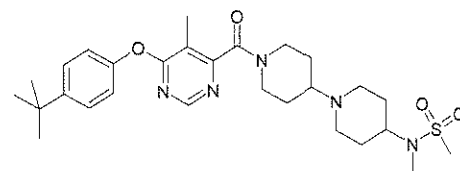
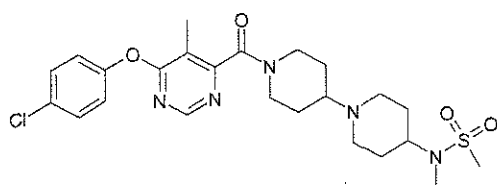
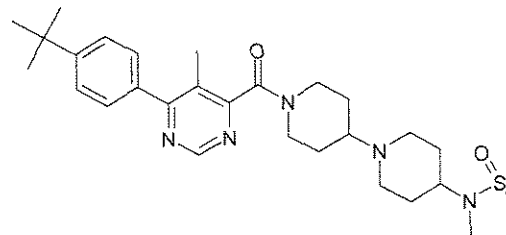
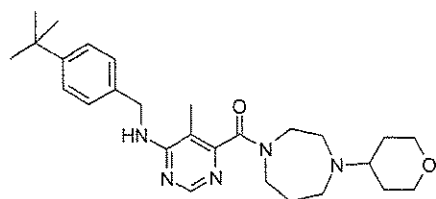
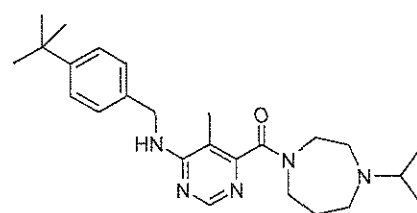
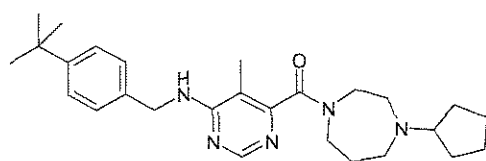
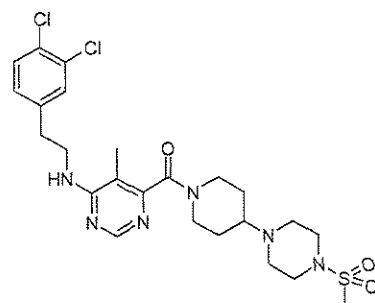
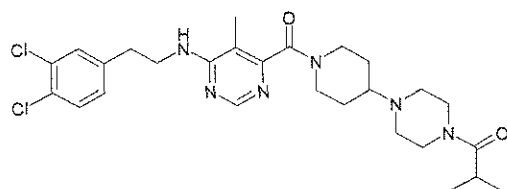
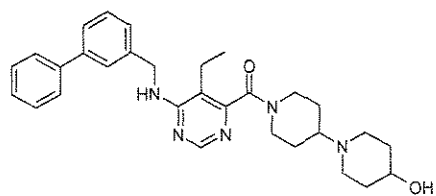
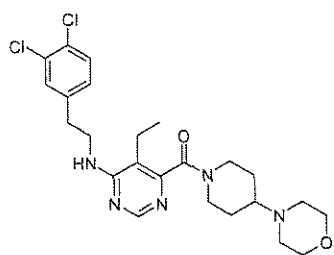


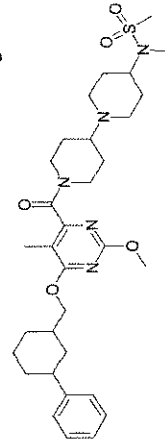
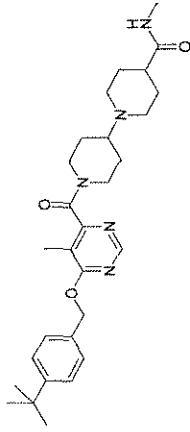
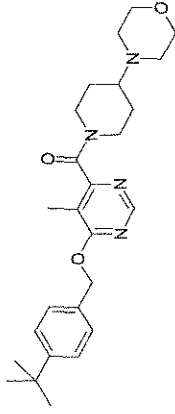
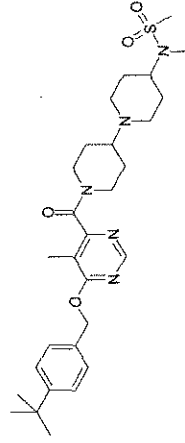
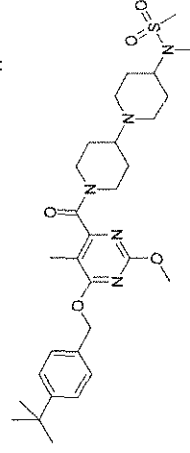
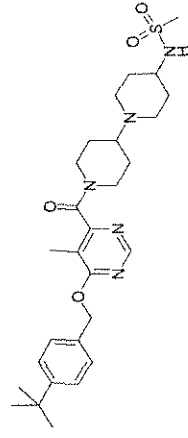
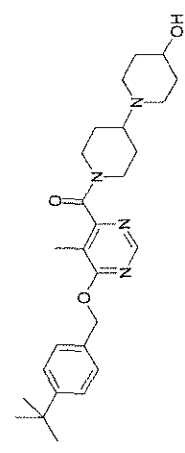












13. A compound according to any of the preceding claims for use as a medicament.
14. The compound according to any of claims 1-12 for use in the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.
15. Use of the compound according to any of claims 1-12 in the manufacture of a medicament for the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.