(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2010332969 B2**

(54) Title
New CCR2 receptor antagonists and uses thereof

(51) International Patent Classification(s)
C07D 405/14 (2006.01) ***A61P 29/00*** (2006.01)
A61K 31/506 (2006.01) ***C07D 491/10*** (2006.01)

(21) Application No: **2010332969** (22) Date of Filing: **2010.12.13**

(87) WIPO No: **WO11/073154**

(30) Priority Data

(31) Number	(32) Date	(33) Country
09179555.9	**2009.12.17**	**EP**
10162621.6	**2010.05.12**	**EP**

(43) Publication Date: **2011.06.23**
(44) Accepted Journal Date: **2015.02.12**

(71) Applicant(s)
Boehringer Ingelheim International GmbH

(72) Inventor(s)
Ebel, Heiner;Frattini, Sara;Gerlach, Kai;Giovannini, Riccardo;Hoenke, Christoph;Mazzaferro, Rocco;Santagostino, Marco;Scheuerer, Stefan;Tautermann, Christofer;Trieselmann, Thomas

(74) Agent / Attorney
Spruson & Ferguson, L 35 St Martins Tower 31 Market St, Sydney, NSW, 2000

(56) Related Art
WO 2006/004741 A2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2011 (23.06.2011)

PCT

(10) International Publication Number
WO 2011/073154 A1

(51) International Patent Classification:
C07D 405/14 (2006.01) *A61P 29/00* (2006.01) *A61K 31/506* (2006.01) *C07D 491/10* (2006.01)

(21) International Application Number: PCT/EP2010/069549

(22) International Filing Date: 13 December 2010 (13.12.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09179555.9 17 December 2009 (17.12.2009) EP
10162621.6 12 May 2010 (12.05.2010) EP

(71) Applicant (*for all designated States except US*): **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim am Rhein (DE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **EBEL, Heiner** [DE/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **FRATTINI, Sara** [IT/IT]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **GERLACH, Kai** [DE/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **GIOVANNINI, Riccardo** [IT/IT]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **HOENKE, Christoph** [DE/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **MAZZAFERRO, Rocco** [IT/IT]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **SANTAGOSTINO, Marco** [IT/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patent, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **SCHEUERER, Stefan** [DE/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **TAUTERMANN, Christofer** [AT/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE). **TRIESELMANN, Thomas** [DE/DE]; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE).

(74) Agents: **HAMMANN, Heinz** et al.; BOEHRINGER INGELHEIM GMBH, Corporate Patents, Binger Str. 173, 55216 Ingelheim am Rhein (DE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

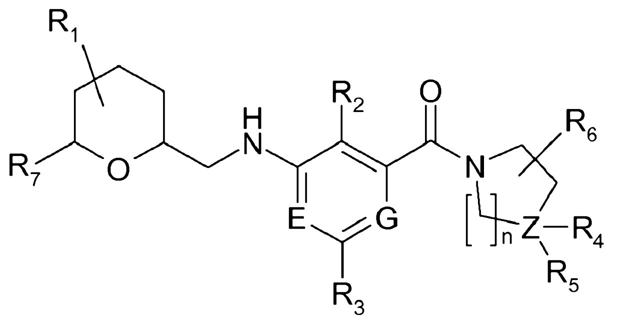
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) **Title**: NEW CCR2 RECEPTOR ANTAGONISTS AND USES THEREOF



(I)

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

WO 2011/073154 A1

Published:

— *with international search report (Art. 21(3))*

New CCR2 receptor antagonists and uses thereof

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 chemotatctic 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).

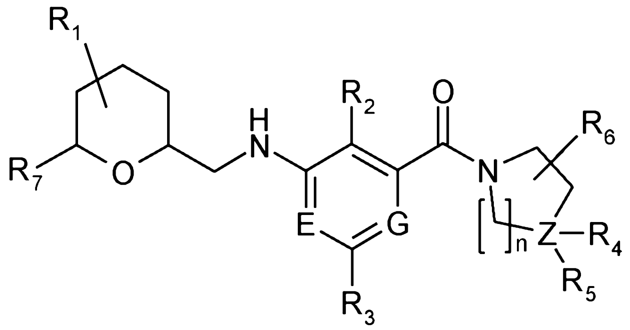
Therefore, in order to reduce macrophage-induced inflammation, it would be desirable to block the monocyte CCR2 by an antagonist, so that the monocytes can be less triggered to move towards an inflammation area for conversion into macrophages.

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

2010332969 23 Jan 2015

Summary of Invention

In a first aspect, the present invention provides a compound of formula (I),



(I)

wherein R_1 is a group selected from among -H, -halogen, -CN, -O-C_1-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_7 is a ring selected from among -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, and -C_5-C_{10}-heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -S-CF_3, -CN, -C_1-C_6-alkyl,–C$(CH_3)_2$-CN, and -halogen,

or wherein the ring R_7 is optionally substituted with one or more groups selected from among -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_2-C_6-alkenyl, and -C_2-C_6-alkynyl, optionally being substituted by one or more groups selected from among -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, -methyl, and =O,

or wherein the ring R_7 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 -C_1-C_6-alkylene, -C_2-C_6-alkenylene and -C_4-C_6-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, and =O;

wherein R_2 is selected from among -H, -halogen, -CN, -O-C_2-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH_3, -CF_3, and –CN;

wherein n is 1, 2 or 3;

wherein G and E are independently selected from among C-H or N;

wherein Z is C,

and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-

$N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,
or wherein Z is N,
and R_4 denotes an electron pair and R_5 is selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-$N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,
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, -CF_3, -CN, -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -O-C_3-C_8-cycloalkyl, -O-C_3-C_8-heterocyclyl, -O-C_5-C_{10}-aryl, -O-C_5-C_{10}-heteroaryl, -C_0-C_6-alkylene-CN, -C_0-C_4-alkylene-O-C_1-C_4-alkyl, -C_0-C_4-alkylene-O-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-O-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-O-C_5-C_{10}-aryl, -C_0-C_4-alkylene-O-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-C_0-C_4-alkyl-$N(R_9,R_{9'})$, -C_0-C_4-alkylene-$N(R_{10})$-Q-C_1-C_4-alkyl, -C_0-C_4-alkylene-$N(R_{10})$-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-$N(R_{10})$-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-$N(R_{10})$-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-$N(R_{10})$-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-$N(R_{11},R_{11'})$, -C_0-C_4-alkylene-$N(R_{12})$-Q-$N(R_{13},R_{13'})$, -C_0-C_4-alkylene-R_{14}, -C_0-C_4-alkylene$(R_{20},R_{20'})$, -C_0-C_4-alkylene-Q-C_1-C_6-alkyl, -C_0-C_4-alkylene-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-O-Q-$N(R_{15},R_{15'})$, and -C_0-C_4-alkylene-$N(R_{16})$-Q-O-(R_{17}),
wherein Q is selected from among -C(O)-, and -SO_2-,
wherein R_{10}, R_{12}, R_{16}, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-cycloalkyl,
wherein R_9, $R_{9'}$, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-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 -C_2-C_6-alkylene group,
wherein R_{14} and R_{17} are independently selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring,
and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -COOH, -OCF_3, -CN, -halogen, -C_1-C_4-alkyl, =O, and -SO_2-C_1-C_4-alkyl,
wherein R_{20} and $R_{20'}$ together form a spiro-C_3-C_8-carbocycle or spiro-C_3-C_8-heterocycle comprising one or more group selected from O in the ring, and wherein

2010332969 23 Jan 2015

said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among -C_1-C_6-alkylene, -C_2-C_6-alkenylene, and -C_4-C_6-alkynylene and wherein said spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -COOH, -OCF_3, -CN, -halogen, or wherein Z is C,

and R_4 denotes –H and R_5 is a group of the structure –L_1-R_{18},

wherein L_1 is selected from among -NH-, -N(C_1-C_4-alkyl)-, and a bond,

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,

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,

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 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;

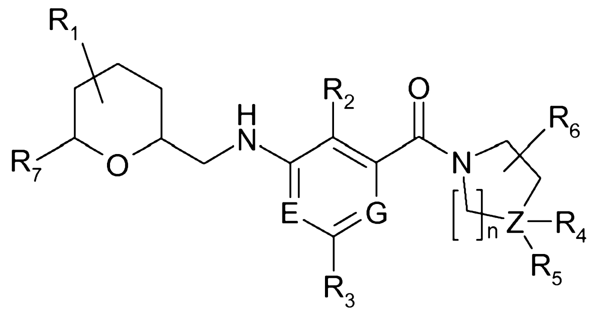
as well as in form of their acid addition salts with pharmacologically acceptable acids.

In a second aspect, the present invention provides the compound according to the first aspect whenever used as a medicament.

In a third aspect, the present invention provides the compound according to the first aspect when used 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),



(I)

wherein R_1 is a group selected from among -H, -halogen, -CN, -O-C_1-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_7 is a ring selected from among -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, and -C_5-C_{10}-heteroaryl,
wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -S-CF_3, -CN, -C_1-C_6-alkyl, –C(CH_3)$_2$-CN, and -halogen,
or wherein the ring R_7 is optionally substituted with one or more groups selected from among -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_2-C_6-alkenyl, and -C_2-C_6-alkynyl, optionally being substituted by one or more groups selected from among -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, -methyl, and =O,
or wherein the ring R_7 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 -C_1-C_6-alkylene, -C_2-C_6-alkenylene and -C_4-C_6-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, and =O;

wherein R_2 is selected from among -H, -halogen, -CN, -O-C_2-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH_3, -CF_3, and –CN;

wherein n is 1, 2 or 3;

wherein G and E are independently selected from among C-H or N;

wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,
or wherein Z is N,
and R_4 denotes an electron pair and R_5 is selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl

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, -CF_3, -CN, -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -O-C_3-C_8-cycloalkyl, -O-C_3-C_8-heterocyclyl, -O-C_5-C_{10}-aryl, -O-C_5-C_{10}-heteroaryl, -C_0-C_6-alkylene-CN, -C_0-C_4-alkylene-O-C_1-C_4-alkyl, -C_0-C_4-alkylene-O-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-O-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-O-C_5-C_{10}-aryl, -C_0-C_4-alkylene-O-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-C_0-C_4-alkyl-N(R_9,$R_{9'}$), -C_0-C_4-alkylene-N(R_{10})-Q-C_1-C_4-alkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-N(R_{11},$R_{11'}$), -C_0-C_4-alkylene-N(R_{12})-Q-N(R_{13},$R_{13'}$), -C_0-C_4-alkylene-R_{14}, -C_0-C_4-alkylene(R_{20},$R_{20'}$), -C_0-C_4-alkylene-Q-C_1-C_6-alkyl, -C_0-C_4-alkylene-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-O-Q-N(R_{15},$R_{15'}$), and -C_0-C_4-alkylene-N(R_{16})-Q-O-(R_{17}),
wherein Q is selected from among -C(O)-, and -SO_2-,
wherein R_{10}, R_{12}, R_{16}, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-cycloalkyl,
wherein R_9, $R_{9'}$, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-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 -C_2-C_6-alkylene group,
wherein R_{14} and R_{17} are independently selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring,
and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -COOH, -OCF_3, -CN, -halogen, -C_1-C_4-alkyl, =O, and -SO_2-C_1-C_4-alkyl,

wherein R_{20} and $R_{20'}$ together form a spiro-C_3-C_8-cycloalkylcycle or spiro-C_3-C_8-heterocycle comprising one or more group selected from O in the ring, and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among -C_1-C_6-alkylene, -C_2-C_6-alkenylene, and -C_4-C_6-alkynylene and wherein said spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -COOH, -OCF_3, -CN, -halogen,

or wherein Z is C,
and R_4 denotes –H, and R_5 is selected from a group of the structure –L_1-R_{18},
wherein L_1 is selected from among -NH- and -N(C_1-C_4-alkyl)-, and a bond,
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,
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,
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 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;

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_1, R_2, R_3, 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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_7 is a ring selected from among -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, and -C_5-C_{10}-heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among $-CF_3$, $-O-CF_3$, -CN, $-C_1-C_6$-alkyl,$–C(CH_3)_2$-CN, and -halogen,
or wherein the ring R_7 is optionally substituted with one or more groups selected from among $-C_1-C_6$-alkyl, $-O-C_1-C_6$-alkyl, $-C_5-C_{10}$-aryl, $-C_5-C_{10}$-heteroaryl, $-C_3-C_8$-cycloalkyl, $-C_3-C_8$-heterocyclyl, $-C_2-C_6$-alkenyl, and $-C_2-C_6$-alkynyl, optionally being substituted by one or more groups selected from among -OH, $-NH_2$, $-C_1-C_3$-alkyl, $-O-C_1-C_6$-alkyl, -CN, $-CF_3$, $-OCF_3$, halogen, -methyl, and =O,
or wherein the ring R_7 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 $-C_1-C_6$-alkylene, $-C_2-C_6$-alkenylene and $-C_4-C_6$-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, $-NH_2$, $-C_1-C_3$-alkyl, $-O-C_1-C_6$-alkyl, -CN, $-CF_3$, $-OCF_3$, halogen, and =O.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_{19}, $R_{19'}$, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from -H, $-C_1-C_6$-alkyl, $-NH_2$, $-C_3-C_8$-cycloalkyl, $-C_3-C_8$-heterocyclyl, $-C_5-C_{10}$-aryl, $-C_5-C_{10}$-heteroaryl, and $-C(O)-N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H, and $-C_1-C_6$-alkyl,
and wherein R_4 and R_5 if different from -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, $-CF_3$, -CN, $-C_1-C_6$-alkyl, $-O-C_1-C_6$-alkyl, $-O-C_3-C_8$-cycloalkyl, $-O-C_3-C_8$-heterocyclyl, $-O-C_5-C_{10}$-aryl, $-O-C_5-C_{10}$-heteroaryl, $-C_0-C_6$-alkylene-CN, $-C_0-C_4$-alkylene-$O-C_1-C_4$-alkyl, $-C_0-C_4$-alkylene-$O-C_3-C_8$-cycloalkyl, $-C_0-C_4$-alkylene-$O-C_3-C_8$-heterocyclyl, $-C_0-C_4$-alkylene-$O-C_5-C_{10}$-aryl, $-C_0-C_4$-alkylene-$O-C_5-C_{10}$-heteroaryl, $-C_0-C_4$-alkylene-$Q-C_0-C_4$-alkyl-$N(R_9,R_{9'})$, $-C_0-C_4$-alkylene-$N(R_{10})-Q-C_1-C_4$-alkyl, $-C_0-C_4$-alkylene-$N(R_{10})-Q-C_3-C_8$-cycloalkyl, $-C_0-C_4$-alkylene-$N(R_{10})-Q-C_3-C_8$-heterocyclyl, $-C_0-C_4$-alkylene-$N(R_{10})-Q-C_5-C_{10}$-aryl, $-C_0-C_4$-alkylene-$N(R_{10})-Q-C_5-C_{10}$-heteroaryl, $-C_0-C_4$-alkylene-$Q-N(R_{11},R_{11'})$, $-C_0-C_4$-alkylene-$N(R_{12})-Q-N(R_{13},R_{13'})$, $-C_0-C_4$-alkylene-R_{14}, $-C_0-C_4$-alkylene-$Q-C_1-C_6$-alkyl, $-C_0-C_4$-alkylene-$Q-C_3-C_8$-cycloalkyl, $-C_0-C_4$-alkylene-$Q-C_3-C_8$-heterocyclyl, $-C_0-C_4$-alkylene-$Q-C_5-C_{10}$-aryl, $-C_0-C_4$-alkylene-$Q-C_5-C_{10}$-heteroaryl, $-C_0-C_4$-alkylene-$O-Q-N(R_{15},R_{15'})$, and $-C_0-C_4$-alkylene-$N(R_{16})-Q-O-(R_{17})$,
wherein Q is selected from among -C(O)-, and $-SO_2$-,
wherein R_{10}, R_{12}, R_{16}, are independently selected from among -H, $-C_1-C_6$-alkyl, and $-C_3-C_6$-cycloalkyl,
wherein R_9, $R_{9'}$, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from among -H, $-C_1-C_6$-alkyl, and $-C_3-C_6$-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 -C_2-C_6-alkylene group,
wherein R_{14} and R_{17} are independently selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring,
and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -OCF_3, -CN, -halogen, -C_1-C_4-alkyl, =O, and -SO_2-C_1-C_4-alkyl,
or wherein Z is C,
and R_4 denotes –H and R_5 is selected from a group of the structure –L_1-R_{18},
wherein L_1 is selected from among -NH-, -N(C_1-C_4-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,
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,
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 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.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_{19}, $R_{19'}$, E, G, Q, and n as herein before or below defined, wherein
Z is N, and R_4 denotes an electron pair, and R_5 is a group selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,
and wherein R_5 if different from an -H is optionally substituted with one or more groups selected from among -halogen, -OH, -CF_3, -CN, -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -O-C_3-C_8-cycloalkyl, -O-C_3-C_8-heterocyclyl, -O-C_5-C_{10}-aryl, -O-C_5-C_{10}-heteroaryl, -C_0-C_6-alkylene-CN, -C_0-C_4-alkylene-O-C_1-C_4-alkyl, -C_0-C_4-alkylene-O-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-O-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-O-C_5-C_{10}-aryl, -C_0-C_4-alkylene-O-

C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-C_0-C_4-alkyl-N(R_9,$R_{9'}$), -C_0-C_4-alkylene-N(R_{10})-Q-C_1-C_4-alkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-N(R_{11},$R_{11'}$), -C_0-C_4-alkylene-N(R_{12})-Q-N(R_{13},$R_{13'}$), -C_0-C_4-alkylene-R_{14}, -C_0-C_4-alkylene-Q-C_1-C_6-alkyl, -C_0-C_4-alkylene-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-O-Q-N(R_{15},$R_{15'}$), and -C_0-C_4-alkylene-N(R_{16})-Q-O-(R_{17}),

wherein Q is selected from among -C(O)-, and -SO_2-,

wherein R_{10}, R_{12}, R_{16}, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-cycloalkyl,

wherein R_9, $R_{9'}$, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-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 -C_2-C_6-alkylene group,

wherein R_{14} and R_{17} are independently selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring,

and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, -OCH_3, -CF_3, -OCF_3, -CN, -halogen, -C_1-C_4-alkyl, =O, and -SO_2-C_1-C_4-alkyl.

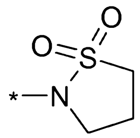
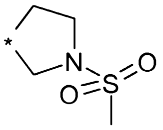
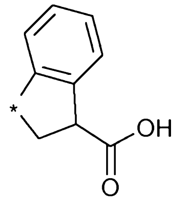
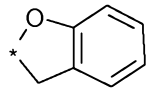
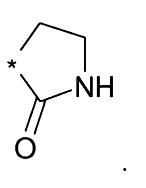
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,

wherein Z is C,

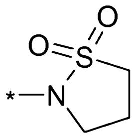
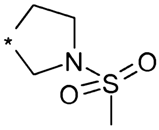
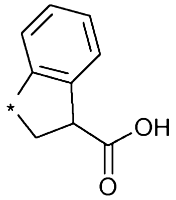
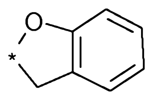
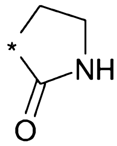
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,

wherein R_4 and R_5 if different from -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, -CF_3, -OCF_3, -CN, -O-CH_3, -O-C_2H_5, -O-C_3H_7, -CH_2-CN, -CH_2-O-CH_3, -$(CH_2)_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-N$(CH_3)_2$, -NH-C(O)-CH_3, -N(CH_3)C(O)-CH_3, -NH-C(O)-C_2H_5, -N(CH_3)-C(O)-C_2H_5, -NH-C(O)-C_3H_7, -N(CH_3)-C(O)-C_3H_7, -NH-SO_2-CH_3, -N(CH_3)-SO_2-CH_3, -N(C_2H_5)-SO_2-CH_3, -N(C_3H_7)-SO_2-CH_3, -NH-SO_2-C_2H_5, -N(CH_3)-SO_2-C_2H_5, -N(C_2H_5)-SO_2-C_2H_5, -N(C_3H_7)-SO_2-C_2H_5, -NH-SO_2-C_3H_7, -N(CH_3)-SO_2-C_3H_7, -N(C_2H_5)-SO_2-C_3H_7, -N(C_3H_7)-SO_2-C_3H_7, -NH-SO_2-C_3H_5, -N(CH_3)-SO_2-C_3H_5, -N(C_2H_5)-SO_2-C_3H_5, -N(C_3H_7)-SO_2-C_2H_5, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5,

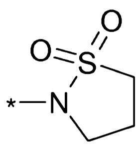
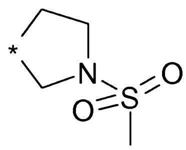
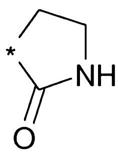
-NH-C(O)-NH_2, -N(CH_3)-C(O)-NH_2, -NH-C(O)-NH-CH_3, -N(CH_3)-C(O)-NH-CH_3, -NH-C(O)-N(CH_3)$_2$, -N(CH_3)-C(O)-N(CH_3)$_2$, -SO_2-NH_2, -SO_2-NH(CH_3), -SO_2-N(CH_3)$_2$, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-N(CH_3)$_2$, –N(CH_3)-SO_2-N(CH_3)$_2$, -(C_6-aryl)-COOH, -phenyl, -pyridin-4-yl, -CH_2-3-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,


,

,

,

, and

.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,
wherein Z is N,
and R_4 denotes an electron pair, and R_5 is a group selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,
wherein R_5 if different from -H is optionally substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF_3, -OCF_3, -CN, -O-CH_3, -O-C_2H_5, -O-C_3H_7, -CH_2-CN, -CH_2-O-CH_3, -(CH_2)$_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-N(CH_3)$_2$, -NH-C(O)-CH_3, -N(CH_3)C(O)-CH_3, -NH-C(O)-C_2H_5, -N(CH_3)-C(O)-C_2H_5, -NH-C(O)-C_3H_7, -N(CH_3)-C(O)-C_3H_7, -NH-SO_2-CH_3, -N(CH_3)-SO_2-CH_3, -N(C_2H_5)-SO_2-CH_3, -N(C_3H_7)-SO_2-CH_3, -NH-SO_2-C_2H_5, -N(CH_3)-SO_2-C_2H_5, -N(C_2H_5)-SO_2-C_2H_5, -N(C_3H_7)-SO_2-C_2H_5, -NH-SO_2-C_3H_7, -N(CH_3)-SO_2-C_3H_7, -N(C_2H_5)-SO_2-C_3H_7, -N(C_3H_7)-SO_2-C_3H_7, -NH-SO_2-C_3H_5, -N(CH_3)-SO_2-C_3H_5, -N(C_2H_5)-SO_2-C_3H_5, -N(C_3H_7)-SO_2-C_2H_5, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5, -NH-C(O)-NH_2, -N(CH_3)-C(O)-NH_2, -NH-C(O)-NH-CH_3, -N(CH_3)-C(O)-NH-CH_3, -NH-C(O)-N(CH_3)$_2$, -N(CH_3)-C(O)-N(CH_3)$_2$, -SO_2-NH_2, -SO_2-NH(CH_3), -SO_2-N(CH_3)$_2$, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-N(CH_3)$_2$, –N(CH_3)-SO_2-N(CH_3)$_2$, -(C_6-aryl)-COOH, -phenyl, -pyridin-4-yl, -CH_2-3-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,

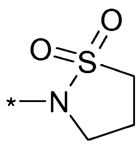
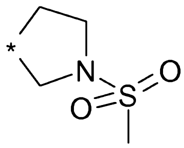
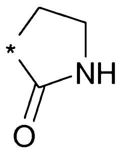
, , , , and .

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}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,
wherein R_4 and R_5 if different from -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, -CF_3, -OCF_3, -CN, -O-CH_3, -O-C_2H_5, -O-C_3H_7, -CH_2-CN, -CH_2-O-CH_3, -$(CH_2)_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-$N(CH_3)_2$, -NH-C(O)-CH_3, -$N(CH_3)$C(O)-CH_3, -NH-C(O)-C_2H_5, -$N(CH_3)$-C(O)-C_2H_5, -NH-C(O)-C_3H_7, -$N(CH_3)$-C(O)-C_3H_7, -NH-SO_2-CH_3, -$N(CH_3)$-SO_2-CH_3, -$N(C_2H_5)$-SO_2-CH_3, -$N(C_3H_7)$-SO_2-CH_3, -NH-SO_2-C_2H_5, -$N(CH_3)$-SO_2-C_2H_5, -$N(C_2H_5)$-SO_2-C_2H_5, -$N(C_3H_7)$-SO_2-C_2H_5, -NH-SO_2-C_3H_7, -$N(CH_3)$-SO_2-C_3H_7, -$N(C_2H_5)$-SO_2-C_3H_7, -$N(C_3H_7)$-SO_2-C_3H_7, -NH-SO_2-C_3H_5, -$N(CH_3)$-SO_2-C_3H_5, -$N(C_2H_5)$-SO_2-C_3H_5, -$N(C_3H_7)$-SO_2-C_2H_5, -CH_2-NH-SO_2-CH_3, -CH_2-$N(CH_3)$-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-$N(CH_3)$-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-$N(CH_3)$-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-$N(CH_3)$-SO_2-C_3H_5, -NH-C(O)-NH_2, -$N(CH_3)$-C(O)-NH_2, -NH-C(O)-NH-CH_3, -$N(CH_3)$-C(O)-NH-CH_3, -NH-C(O)-$N(CH_3)_2$, -$N(CH_3)$-C(O)-$N(CH_3)_2$, -SO_2-NH_2, -SO_2-$NH(CH_3)$, -SO_2-$N(CH_3)_2$, -C(O)-NH-C_2H_5, -C(O)-$N(CH_3)$-C_2H_5, -C(O)-$N(CH_3)$-C_3H_7, -C(O)-$N(CH_3)$-C_4H_9, -C(O)-NH-$CH(CH_3)$-C_2H_5, -C(O)-$N(CH_3)$-$CH(CH_3)$-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-$N(CH_3)_2$, –$N(CH_3)$-SO_2-$N(CH_3)_2$, -phenyl, -pyridin-4-yl, -CH_2-3-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,

, , and .

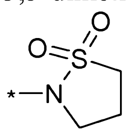
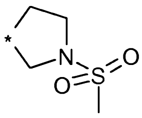
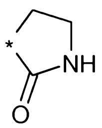
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Q, and n as herein before or below defined,

wherein Z is N,
and R_4 denotes an electron pair, and R_5 is a group selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and $-C(O)-N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H and $-C_1-C_6$-alkyl,
wherein R_5 if different from an -H is optionally substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, $-CF_3$, $-OCF_3$, -CN, $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$, $-CH_2-CN$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)-C_2H_5$, $-C(O)-C_3H_7$, -COOH, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$, $-N(CH_3)C(O)-CH_3$, $-NH-C(O)-C_2H_5$, $-N(CH_3)-C(O)-C_2H_5$, $-NH-C(O)-C_3H_7$, $-N(CH_3)-C(O)-C_3H_7$, $-NH-SO_2-CH_3$, $-N(CH_3)-SO_2-CH_3$, $-N(C_2H_5)-SO_2-CH_3$, $-N(C_3H_7)-SO_2-CH_3$, $-NH-SO_2-C_2H_5$, $-N(CH_3)-SO_2-C_2H_5$, $-N(C_2H_5)-SO_2-C_2H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-NH-SO_2-C_3H_7$, $-N(CH_3)-SO_2-C_3H_7$, $-N(C_2H_5)-SO_2-C_3H_7$, $-N(C_3H_7)-SO_2-C_3H_7$, $-NH-SO_2-C_3H_5$, $-N(CH_3)-SO_2-C_3H_5$, $-N(C_2H_5)-SO_2-C_3H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-CH_3$, $-CH_2-N(CH_3)-SO_2-CH_3$, $-CH_2-NH-SO_2-C_2H_5$, $-CH_2-N(CH_3)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-C_3H_7$, $-CH_2-N(CH_3)-SO_2-C_3H_7$, $-CH_2-NH-SO_2-C_3H_5$, $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-NH-C(O)-NH_2$, $-N(CH_3)-C(O)-NH_2$, $-NH-C(O)-NH-CH_3$, $-N(CH_3)-C(O)-NH-CH_3$, $-NH-C(O)-N(CH_3)_2$, $-N(CH_3)-C(O)-N(CH_3)_2$, $-SO_2-NH_2$, $-SO_2-NH(CH_3)$, $-SO_2-N(CH_3)_2$, $-C(O)-NH-C_2H_5$, $-C(O)-N(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-C_3H_7$, $-C(O)-N(CH_3)-C_4H_9$, $-C(O)-NH-CH(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-C(O)-NH_2$, $-CH_2-C(O)-NH-CH_3$, $-CH_2-C(O)-N(CH_3)_2$, $–N(CH_3)-SO_2-N(CH_3)_2$, -phenyl, -pyridin-4-yl, $-CH_2$-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,

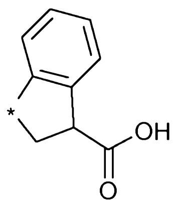
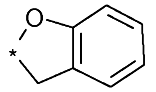

,

, and

.

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}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group selected from among , -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and $-C(O)-N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H and $-C_1-C_6$-alkyl,
wherein R_5 is optionally substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, $-CF_3$, $-OCF_3$, -CN, $-O-CH_3$, $-O-C_2H_5$, $-O-C_3H_7$, $-CH_2-CN$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-C(O)-CH_3$, -C(O)-

C_2H_5, $-C(O)-C_3H_7$, -COOH, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$, $-N(CH_3)C(O)-CH_3$, $-NH-C(O)-C_2H_5$, $-N(CH_3)-C(O)-C_2H_5$, $-NH-C(O)-C_3H_7$, $-N(CH_3)-C(O)-C_3H_7$, $-NH-SO_2-CH_3$, $-N(CH_3)-SO_2-CH_3$, $-N(C_2H_5)-SO_2-CH_3$, $-N(C_3H_7)-SO_2-CH_3$, $-NH-SO_2-C_2H_5$, $-N(CH_3)-SO_2-C_2H_5$, $-N(C_2H_5)-SO_2-C_2H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-NH-SO_2-C_3H_7$, $-N(CH_3)-SO_2-C_3H_7$, $-N(C_2H_5)-SO_2-C_3H_7$, $-N(C_3H_7)-SO_2-C_3H_7$, $-NH-SO_2-C_3H_5$, $-N(CH_3)-SO_2-C_3H_5$, $-N(C_2H_5)-SO_2-C_3H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-CH_3$, $-CH_2-N(CH_3)-SO_2-CH_3$, $-CH_2-NH-SO_2-C_2H_5$, $-CH_2-N(CH_3)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-C_3H_7$, $-CH_2-N(CH_3)-SO_2-C_3H_7$, $-CH_2-NH-SO_2-C_3H_5$, $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-NH-C(O)-NH_2$, $-N(CH_3)-C(O)-NH_2$, $-NH-C(O)-NH-CH_3$, $-N(CH_3)-C(O)-NH-CH_3$, $-NH-C(O)-N(CH_3)_2$, $-N(CH_3)-C(O)-N(CH_3)_2$, $-SO_2-NH_2$, $-SO_2-NH(CH_3)$, $-SO_2-N(CH_3)_2$, $-C(O)-NH-C_2H_5$, $-C(O)-N(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-C_3H_7$, $-C(O)-N(CH_3)-C_4H_9$, $-C(O)-NH-CH(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-C(O)-NH_2$, $-CH_2-C(O)-NH-CH_3$, $-CH_2-C(O)-N(CH_3)_2$, $–N(CH_3)-SO_2-N(CH_3)_2$, -phenyl, -pyridin-4-yl, $-CH_2$-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,

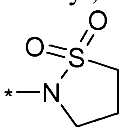
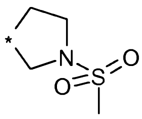
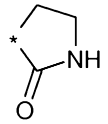

,

,


or wherein R_5 is optionally substituted with one or more groups selected from among $-(C_6$-aryl)-COOH,

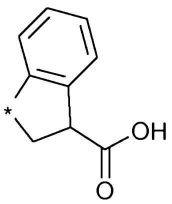
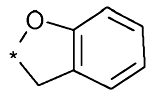

, and

.

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}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and $-C(O)-N(R_8,R_{8'})$, with R_8 and $R_{8'}$ independently being selected from among -H and $-C_1-C_6$-alkyl,
wherein R_4 and R_5 if different from -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, $-CF_3$, -CN, $-CH_2-CN$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)-C_2H_5$, $-C(O)-C_3H_7$, -COOH, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$, $-N(CH_3)C(O)-CH_3$, $-NH-C(O)-C_2H_5$, $-N(CH_3)-C(O)-C_2H_5$, $-NH-C(O)-C_3H_7$, $-N(CH_3)-C(O)-$

C_3H_7, -NH-SO_2-CH_3, -N(CH_3)-SO_2-CH_3, -N(C_2H_5)-SO_2-CH_3, -N(C_3H_7)-SO_2-CH_3, -NH-SO_2-C_2H_5, -N(CH_3)-SO_2-C_2H_5, -N(C_2H_5)-SO_2-C_2H_5, -N(C_3H_7)-SO_2-C_2H_5, -NH-SO_2-C_3H_7, -N(CH_3)-SO_2-C_3H_7, -N(C_2H_5)-SO_2-C_3H_7, -N(C_3H_7)-SO_2-C_3H_7, -NH-SO_2-C_3H_5, -N(CH_3)-SO_2-C_3H_5, -N(C_2H_5)-SO_2-C_3H_5, -N(C_3H_7)-SO_2-C_2H_5, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5, -NH-C(O)-NH_2, -N(CH_3)-C(O)-NH_2, -NH-C(O)-NH-CH_3, -N(CH_3)-C(O)-NH-CH_3, -NH-C(O)-N(CH_3)$_2$, -N(CH_3)-C(O)-N(CH_3)$_2$, -SO_2-NH_2, -SO_2-NH(CH_3), -SO_2-N(CH_3)$_2$, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-N(CH_3)$_2$, –N(CH_3)-SO_2-N(CH_3)$_2$, -phenyl, -pyridin-4-yl, -CH_2-3-methyl-oxetan-3-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,

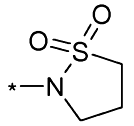
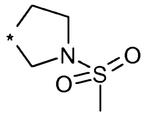
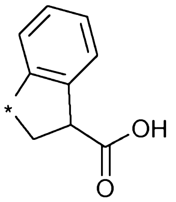
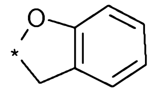
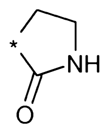

, 
, and 

or wherein R_4 and R_5 if different from -H are optionally independently substituted with one or more groups selected from among -(C_6-aryl)-COOH,

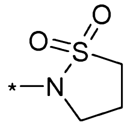
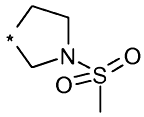
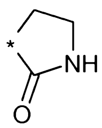

, and 
.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,
wherein R_4 and R_5 if different from -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, -CF_3, -CN, -CH_2-CN, -CH_2-O-CH_3, -(CH_2)$_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-N(CH_3)$_2$, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-N(CH_3)$_2$, –N(CH_3)-SO_2-N(CH_3)$_2$, -(C_6-aryl)-COOH, -phenyl, -pyridin-4-yl,

-CH_2-3-methyl-oxetan-3-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,

, , ,  and .

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}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,
wherein R_4 and R_5 if different from -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, -CF_3, -CN, -CH_2-CN, -CH_2-O-CH_3, -$(CH_2)_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-N$(CH_3)_2$, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-N$(CH_3)_2$, –N(CH_3)-SO_2-N$(CH_3)_2$, -phenyl, -pyridin-4-yl, -CH_2-3-methyl-oxetan-3-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,

, , and .

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure -L_1-R_{18},
wherein L_1 is selected from among -NH-, -N(CH_3)-, -N(C_2H_5)-, and a bond
and wherein R_{18} is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl,

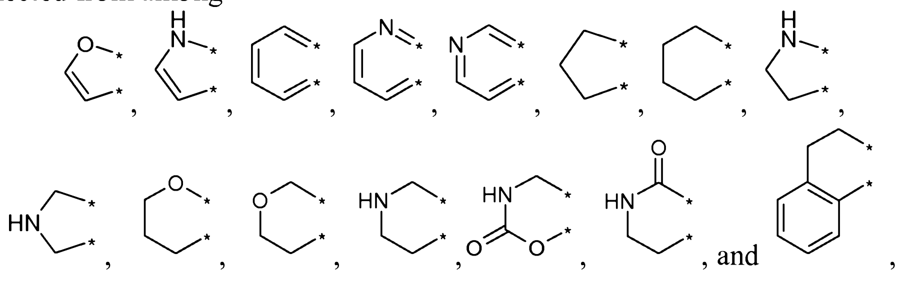
-morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl, -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R_{18} is optionally substituted by one or more groups selected from among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$, more preferred wherein R_{18} is optionally substituted by one or more groups selected from among –F, $-O-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, most preferred wherein R_{18} is optionally substituted by $-O-CH_3$.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_{18} is optionally substituted by one or more groups selected from among –F, and $-O-CH_3$,

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, $-N(C_2H_5)-$, and a bond
and wherein R_{18} 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 R_{18} is optionally substituted by –F.

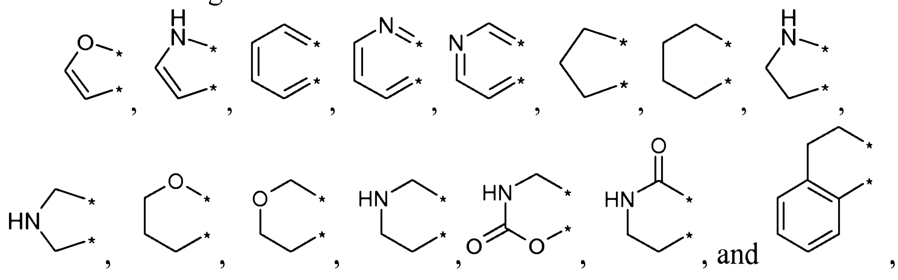
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{19}, $R_{19'}$, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, and $-N(C_2H_5)-$,
and wherein R_{18} 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 R_{18} is optionally substituted by one or more groups selected from among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, $-N(C_2H_5)-$, and a bond,
and 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.

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}, R_{19}, $R_{19'}$, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, and $-N(C_2H_5)-$,
and 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.

Preferred compounds of formula (I) according to the invention are compounds with 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_1 is a group selected from among -H, -halogen, -CN, -C_1-C_3-alkyl, -CH=CH_2, -C≡CH,and -CF_3, more preferred wherein R_1 is a group selected from among -H, -halogen, and –methyl.

Preferred compounds of formula (I) according to the invention are compounds with 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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_1 is a group selected from among -H, -halogen, -CN, -C_1-C_3-alkyl, -CH=CH_2, -C≡CH,and -CF_3, more preferred wherein R_1 is a group selected from among -H, -halogen, and –methyl.

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_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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_7 is selected from among -C_5-C_6-aryl, -C_5-C_6-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl,
and wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -S-CF_3, -CN, -methyl, –C$(CH_3)_2$-CN, and –halogen.

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_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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_7 is selected from among -C_5-C_6-aryl, -C_5-C_6-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl,
and wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -CN, -methyl, –C$(CH_3)_2$-CN, and –halogen.

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_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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_7 is selected from among -C_5-C_6-aryl, and -C_5-C_6-heteroaryl,
wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -S-CF_3, -CN, -methyl, –F, -Cl, –C$(CH_3)_2$-CN, and –Br.

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_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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_7 is selected from among -C_5-C_6-aryl, and -C_5-C_6-heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among $-CF_3$, $-O-CF_3$, -CN, -methyl, –F, -Cl, $–C(CH_3)_2-CN$, and –Br.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, $-N(C_2H_5)-$, and optionally a bond
and wherein R_{18} is selected from among $–C_6$-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,
and wherein R_{18} is optionally substituted by one or more groups selected from among among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$, more preferred wherein R_{18} is optionally substituted by one or more groups selected from among –F, $-O-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, more preferred wherein R_{18} is optionally substituted by one or more groups selected from among $-O-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, more preferred wherein R_{18} is optionally substituted by one or more groups selected from among -F, and $-O-CH_3$, most preferred wherein R_{18} is optionally substituted by $-O-CH_3$.

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}, R_{19}, $R_{19'}$, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(CH_3)-$, and $-N(C_2H_5)-$,
and wherein R_{18} is selected from among $–C_6$-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,
and wherein R_{18} is optionally substituted by one or more groups selected from among among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$, more preferred wherein R_{18} is optionally substituted by one or more groups selected from among $-O-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, most preferred wherein R_{18} is optionally substituted by $-O-CH_3$.

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}, E, G, Q, and n as herein before or below defined,
wherein Z is C,

and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, and -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group, preferably a -C_4-C_5-alkylene group, more preferably a –C_5-alkylene group such that a ring is formed, wherein such ring is optionally substituted by one or more groups selected from among among -F, -CF_3, -OCF_3, -CN, -OH, -O-CH_3, -CH_3, -NH-C(O)-CH_3, -N(CH_3)-C(O)-CH_3, -C(O)-CH_3, -S(O)$_2$-CH_3, -NH-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_2-CH_3, and -(C_6-aryl)-COOH, -C(O)-O-C_2H_5, more preferred wherein such ring is optionally substituted by one or more groups selected from among -O-CH_3, -NH-S(O)$_2$-CH_3, -(C_6-aryl)-COOH, and -N(CH_3)-S(O)$_2$-CH_3, more preferred wherein such ring is optionally substituted by one or more groups selected from among -O-CH_3, -NH-S(O)$_2$-CH_3, and -N(CH_3)-S(O)$_2$-CH_3, more preferred wherein such ring is optionally substituted by one or more groups selected from among -(C_6-aryl)-COOH, and -N(CH_3)-S(O)$_2$-CH_3, most preferred wherein such ring is optionally substituted by -N(CH_3)-S(O)$_2$-CH_3.

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}, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, and -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group, preferably a -C_4-C_5-alkylene group, more preferably a –C_5-alkylene group such that a ring is formed,
wherein such ring is optionally substituted by -(C_6-aryl)-COOH.

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}, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, and -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group, preferably a -C_5-C_6-alkylene group such that a ring is formed,
wherein such ring is optionally substituted by one or more groups selected from among among -F, -CF_3, -OCF_3, -CN, -OH, -O-CH_3, -CH_3, -NH-C(O)-CH_3, -N(CH_3)-C(O)-CH_3, -C(O)-CH_3, -S(O)$_2$-CH_3, -NH-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_2-CH_3, and -C(O)-O-C_2H_5, more preferred wherein such ring is optionally substituted by one or more groups selected from among -O-CH_3, -NH-S(O)$_2$-CH_3, and -N(CH_3)-S(O)$_2$-CH_3, most preferred wherein such ring is optionally substituted by -N(CH_3)-S(O)$_2$-CH_3.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, $-CH{=}CH_2$, and $-C{\equiv}CH$, more preferred wherein R_2 is selected from among -H, -Methyl, -Ethyl, and -Br, more preferred wherein R_2 is selected from among -H, and -Methyl, most preferred wherein R_2 denotes –Methyl.
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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, $-CH{=}CH_2$, and $-C{\equiv}CH$, more preferred wherein R_2 is selected from among -H, -Methyl, -Ethyl, and -Br, more preferred wherein R_2 is selected from among -H, and -Methyl, most preferred wherein R_2 denotes –Methyl.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_2 denotes –H.
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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_2 denotes –H.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, $-OCH_3$, $-CF_3$, and –CN.
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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, $-OCH_3$, $-CF_3$, and –CN

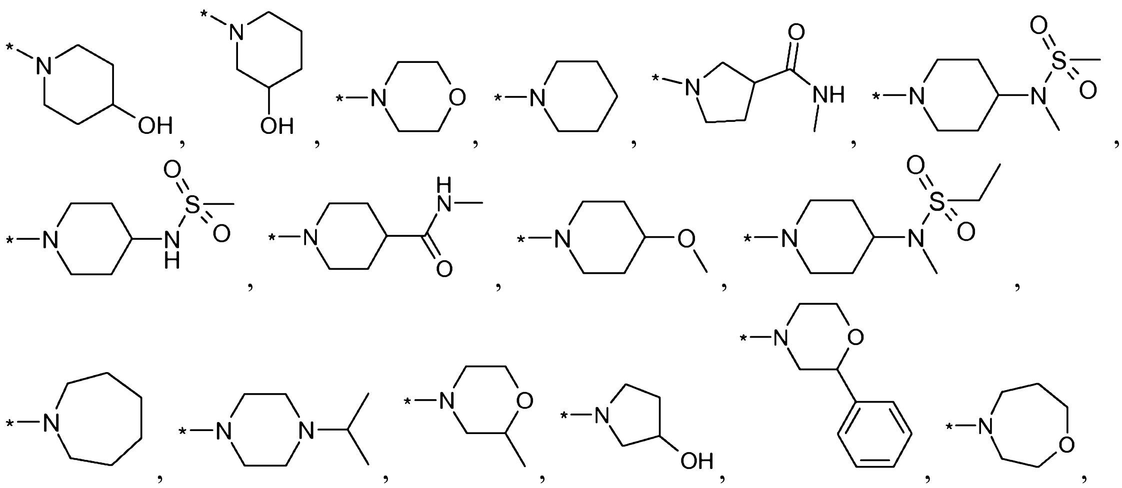
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_3 is selected from among $-OCH_3$, -H, $-CF_3$, and –methyl, more preferred wherein R_3 is selected from among -H, and –methyl, more preferred wherein R_3 denotes -H.

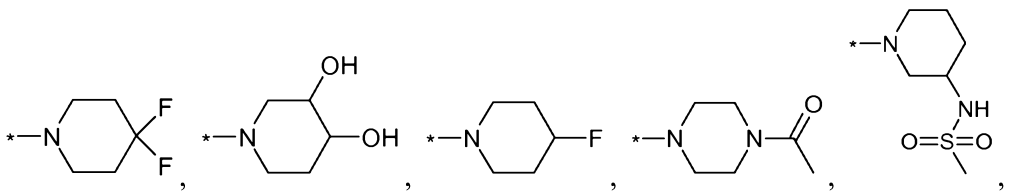
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_3 denotes $-OCH_3$.

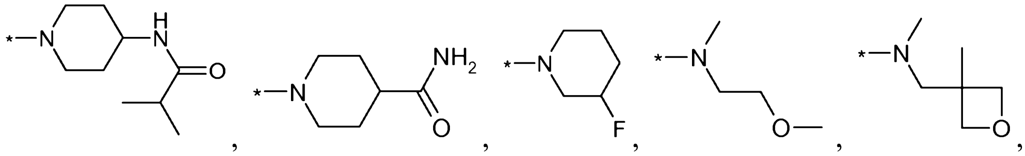
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_3 denotes $-CF_3$.

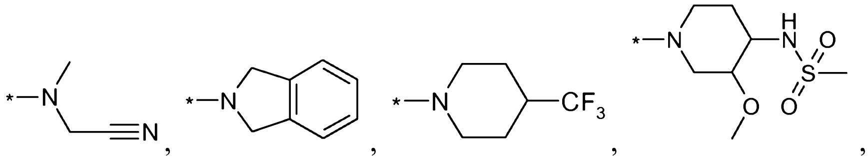
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined,
wherein R_3 is selected from among -H, $-CF_3$, and –methyl, more preferred wherein R_3 is selected from among -H, and –methyl, more preferred wherein R_3 denotes -H.

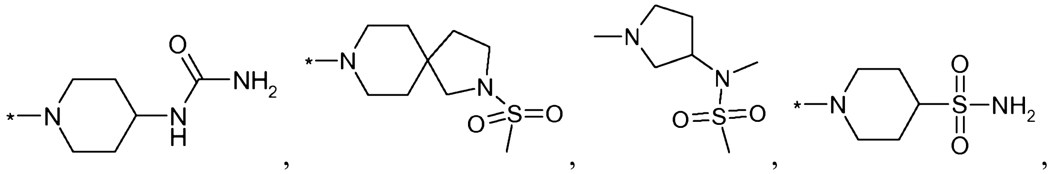
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
R_4 denotes –H, and R_5 is selected from among

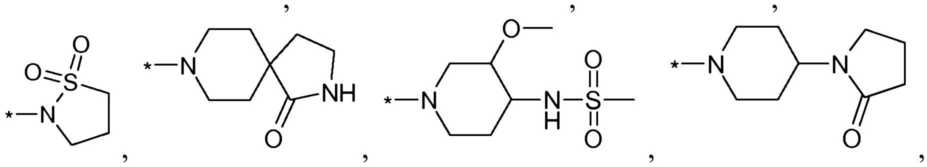


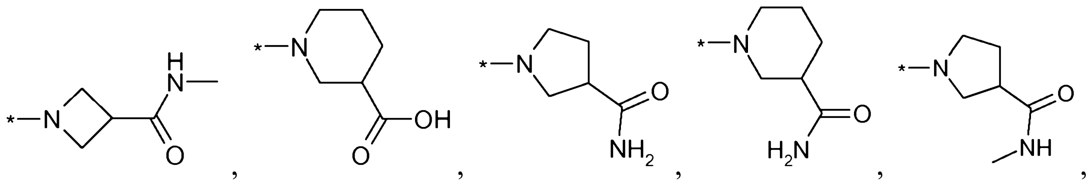


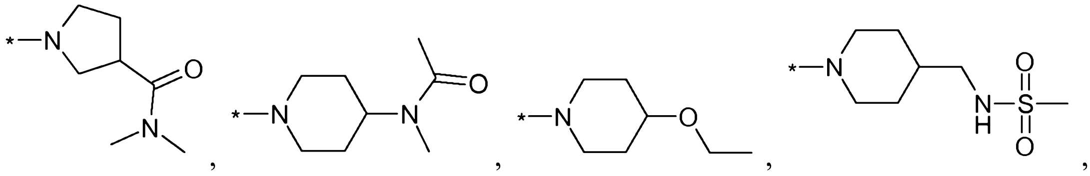


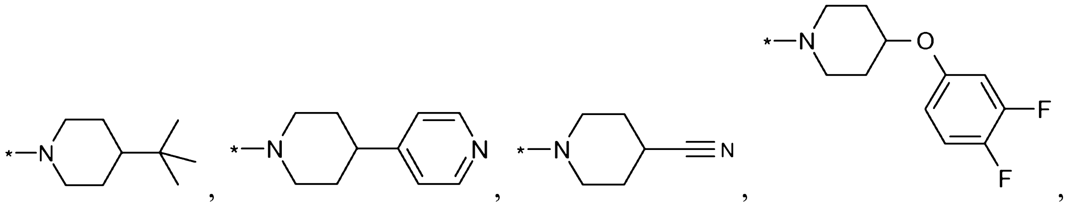


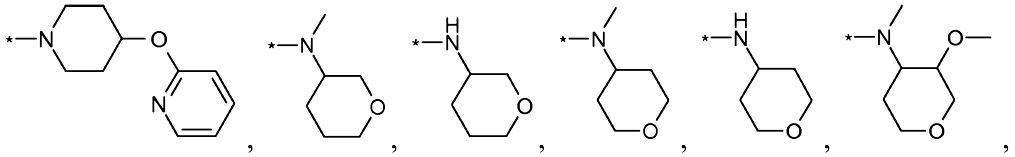


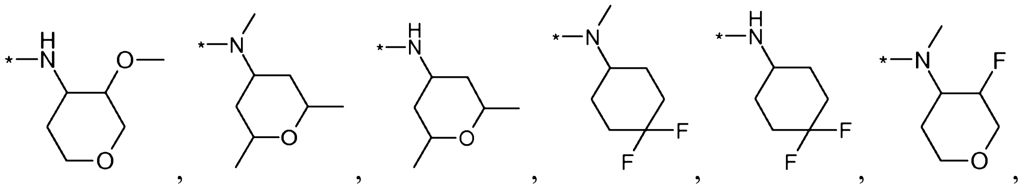


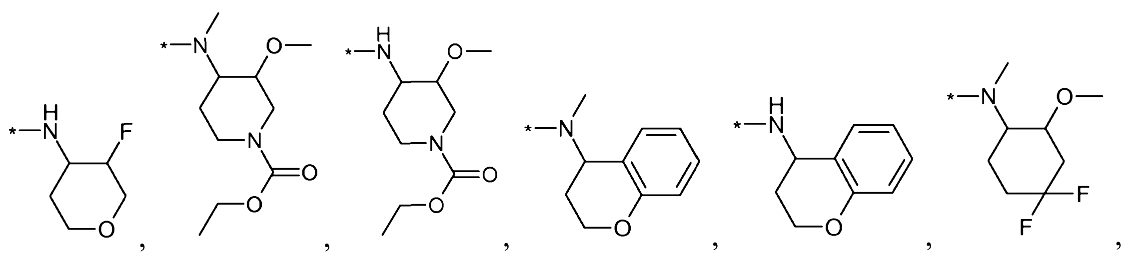


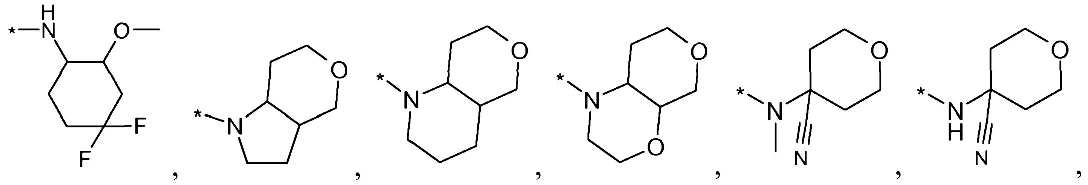


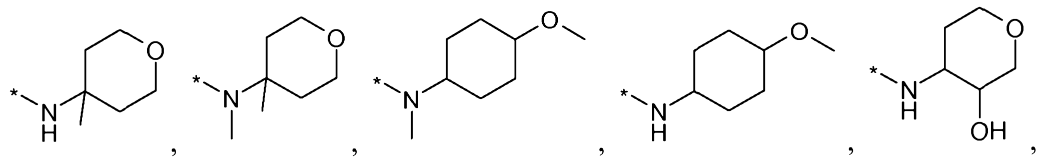


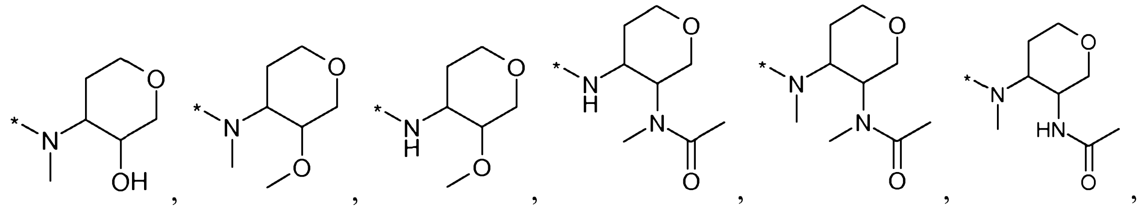


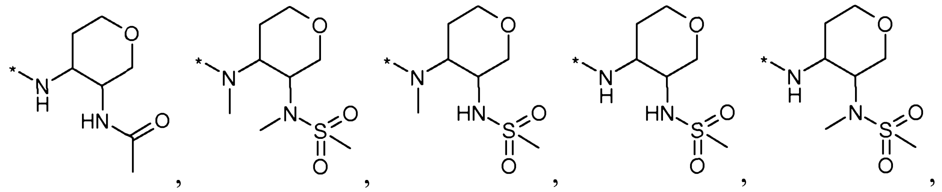


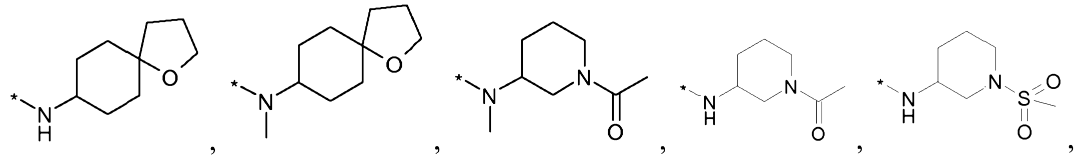


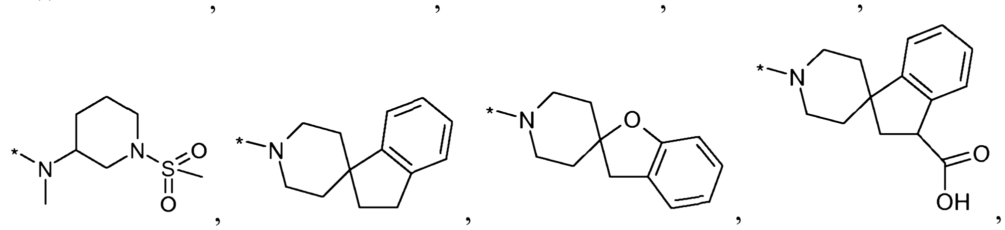


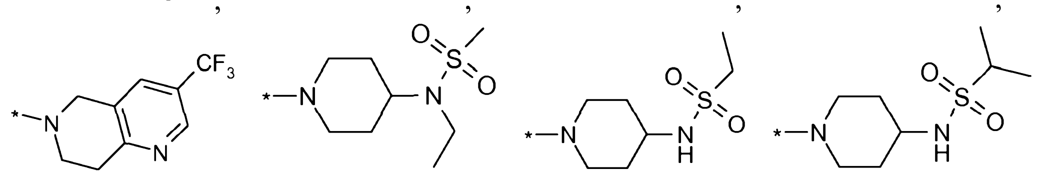


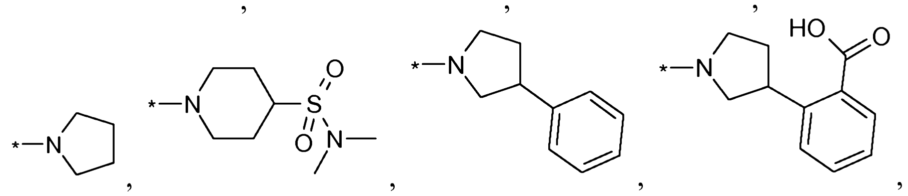


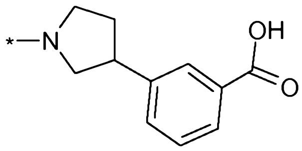
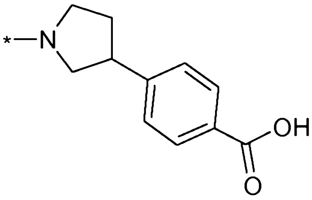
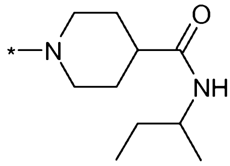


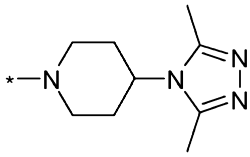
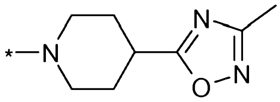
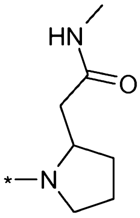
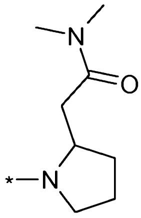
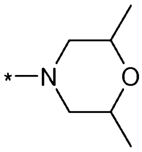


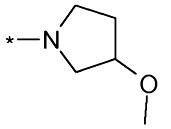
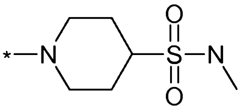
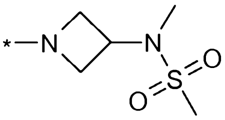
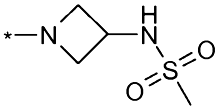


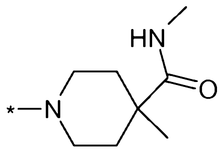
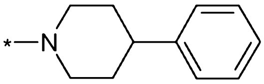
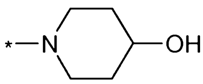
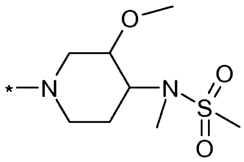


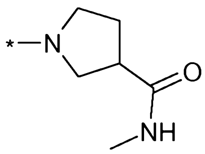
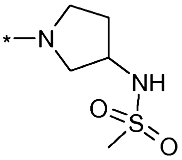
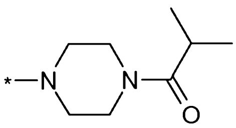
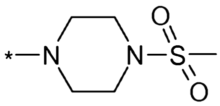
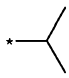


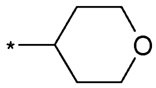
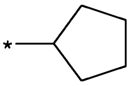
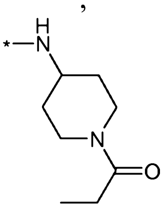
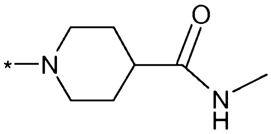
, , ,

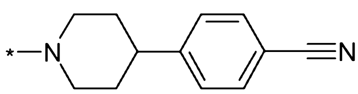
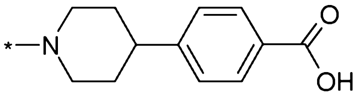
, , , , ,

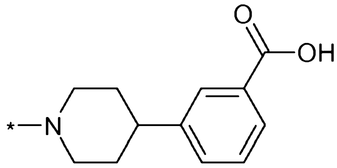
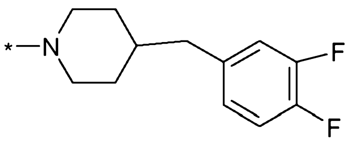
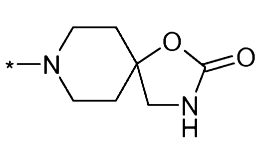
, , , ,

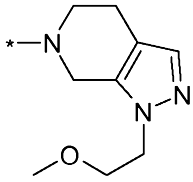
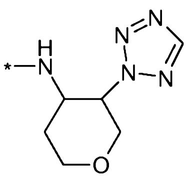
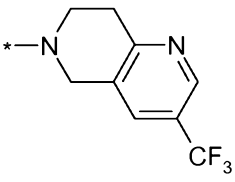
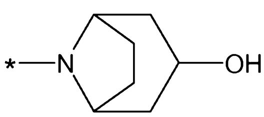
, , , ,

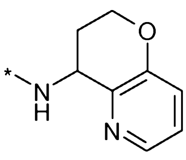
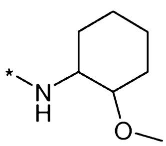
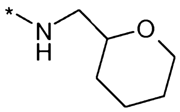
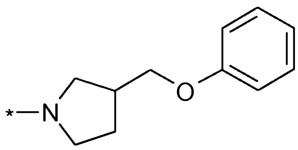
, , , , ,

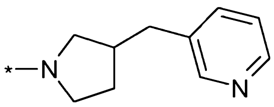
,  , ,

, ,

, , ,

, , , ,

,  , , and

.

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}, R_{18}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes -H, and R_5 denotes -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group such that a ring is formed, more preferred wherein R_{19} and $R_{19'}$ together form a –C_4-C_5-alkylene group such that a ring is formed, most preferred wherein R_{19} and $R_{19'}$ together form a -C_5-alkylene group such that a ring is formed,
wherein such ring is optionally substituted by one or more groups selected from among among -F, -CF_3, -OCF_3, -CN, -OH, -O-CH_3, -CH_3, -NH-C(O)-CH_3, -N(CH_3)-C(O)-CH_3, -C(O)-CH_3, -S(O)$_2$-CH_3, -NH-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_3, -(C_6-aryl)-COOH, -N(CH_3)-S(O)$_2$-CH_2-CH_3, and -C(O)-O-C_2H_5, more preferred wherein such ring is optionally substituted by one or more groups selected from among -O-CH_3, -NH-S(O)$_2$-CH_3, -(C_6-aryl)-COOH, and -N(CH_3)-S(O)$_2$-CH_3, more preferred wherein such ring is optionally substituted by one or more groups selected from among -(C_6-aryl)-COOH, and -N(CH_3)-S(O)$_2$-CH_3, most preferred wherein such ring is optionally substituted by -N(CH_3)-S(O)$_2$-CH_3.

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}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Q, and n as herein before or below defined,
wherein Z is C,
and R_4 denotes –H, and R_5 denotes -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group such that a ring is formed, more preferred wherein R_{19} and $R_{19'}$ together form a -C_5-C_6-alkylene group such that a ring is formed, most preferred wherein R_{19} and $R_{19'}$ together form a -C_5-alkylene group such that a ring is formed,
wherein such ring is optionally substituted by one or more groups selected from among among -F, -CF_3, -OCF_3, -CN, -OH, -O-CH_3, -CH_3, -NH-C(O)-CH_3, -N(CH_3)-C(O)-CH_3, -C(O)-CH_3, -S(O)$_2$-CH_3, -NH-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_2-CH_3, and -C(O)-O-C_2H_5, more preferred wherein such ring is optionally substituted by one or more groups selected from among -O-CH_3, -NH-S(O)$_2$-CH_3, and -N(CH_3)-S(O)$_2$-CH_3, most preferred wherein such ring is optionally substituted by -N(CH_3)-S(O)$_2$-CH_3.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_4 is selected from among -H, and -C(O)-NH2, more preferred wherein R_4 denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_6, R_7, R_8, $R_{8'}$, 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_5 is selected from among -H, and -C(O)-NH2, more preferred wherein R_5 denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_6, R_7, R_8, $R_{8'}$, 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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_5 is selected from among -H, and -C(O)-NH2, more preferred wherein R_5 denotes -H.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, E, G, Z, Q, and n as herein before or below defined, wherein L_1 denotes a bond.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_7, R_8, $R_{8'}$, 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_6 is selected from among -H, $-CH_3$, $-C_2H_5$, $-O-CH_3$, $-O-C_2H_5$, -F, $-CF_3$, and $-OCF_3$, more preferred wherein R_6 is -H or $-O-CH_3$, most preferred wherein R_6 denotes –H.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_7, R_8, $R_{8'}$, 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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_6 is selected from among -H, $-CH_3$, $-C_2H_5$, $-O-CH_3$, $-O-C_2H_5$, -F, $-CF_3$, and $-OCF_3$, more preferred wherein R_6 is -H or $-O-CH_3$, most preferred wherein R_6 denotes –H.

Preferred compounds of formula (I) according to the invention are compounds with 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_1 is –H.

Preferred compounds of formula (I) according to the invention are compounds with 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}, R_{19}, $R_{19'}$, L_1, E, G, Z, Q, and n as herein before or below defined, wherein R_1 is –H.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, and Q, as herein before or below defined, wherein n is 2.
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}, R_{19}, $R_{19'}$, L_1, E, G, Z, and Q, as herein before or below defined, wherein n is 2.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, Z, Q, and n as herein before or below defined, wherein G and E are N.
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}, R_{19}, $R_{19'}$, L_1, Z, Q, and n as herein before or below defined, wherein G and E are N.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, Z, Q, and n as herein before or below defined, wherein G is C-H, and E is N.
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_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}, R_{19}, $R_{19'}$, L_1, Z, Q, and n as herein before or below defined, wherein G is C-H, and E is N.

Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, Z, Q, and n as herein before or below defined, wherein E is C-H, and G is N.
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}, R_{19}, $R_{19'}$, L_1, Z, Q, and n as herein before or below defined, wherein E is C-H, and G is N.

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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Q, and n as herein before or below defined, wherein Z is C.

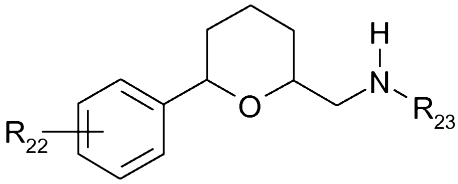
Preferred compounds of formula (I) according to the invention are compounds with R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, $R_{8'}$, R_9, $R_{9'}$, R_{10}, R_{11}, $R_{11'}$ R_{12}, R_{13}, $R_{13'}$, R_{14}, R_{15}, $R_{15'}$, R_{16}, R_{17}, R_{18}, R_{19}, $R_{19'}$, L_1, E, G, Q, and n as herein before or below defined, wherein Z is C.

The present invention also relates to process for preparing a compound of formula (I) as herein before or below defined, wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, Z, E, G, Q, and n have the meanings defined hereinbefore.

The present invention also relates to the following intermediate products for synthesizing the compounds of formula (I) according to the invention:
- compounds according to formula (II) according to preparation method A,
- compounds according to formula (III) according to preparation method A,
- compounds according to formula (V) according to preparation method B,
- compounds according to formula (VI) according to preparation method B,
- compounds according to formula (VIII) according to preparation method C,
- compounds according to formula (X) according to preparation method D,
- compounds according to formula (XI) according to preparation method D,
- compounds according to formula (XIII) according to preparation method E,
- compounds according to formula (XIV) according to preparation method E,

wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, R_{21}, $R_{21'}$, L_1, E, G, Q, Z, CYC, and n have the meanings defined hereinbefore.

The present invention also relates to the following intermediate products according to general formula (XVI) for synthesizing the compounds of formula (I) according to the invention

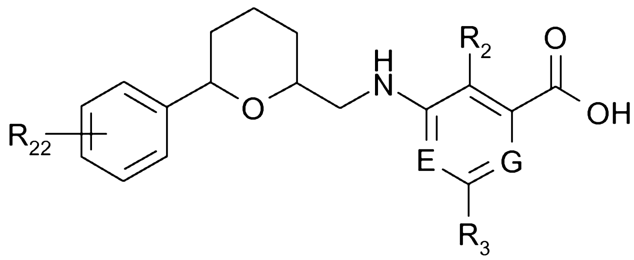


(XVI)

wherein R_{22} is a group selected from among –H, $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, $-C_1-C_6$-alkyl, $-C(CH_3)_2$-CN, and –halogen

or wherein R_{22} is a group selected from among $-C_1-C_6$-alkyl, $-O-C_1-C_6$-alkyl, $-C_5-C_{10}$-aryl, $-C_5-C_{10}$-heteroaryl, $-C_3-C_8$-cycloalkyl, $-C_3-C_8$-heterocyclyl, $-C_2-C_6$-alkenyl, and $-C_2-C_6$-alkynyl, optionally being substituted by one or more groups selected from among -OH, $-NH_2$, $-C_1-C_3$-alkyl, $-O-C_1-C_6$-alkyl, -CN, $-CF_3$, $-OCF_3$, halogen, -methyl, and =O, more preferred wherein R_{22} is a group selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl,$-C(CH_3)_2-CN$, and –halogen, more preferred wherein R_{22} is a group selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl, –F, -Cl, $-C(CH_3)_2-CN$, and –Br, and wherein R_{23} is a group selected from among –H and $-C_1-C_3$-alkyl, more preferred whereinR$_{23}$ denotes –H.

The present invention also relates to the following intermediate products according to general formula (XVII) for synthesizing the compounds of formula (I) according to the invention



(XVII)

wherein R_{22} is a group selected from among –H, $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, $-C_1-C_6$-alkyl, $-C(CH_3)_2-CN$, and –halogen, or wherein R_{22} is a group selected from among $-C_1-C_6$-alkyl, $-O-C_1-C_6$-alkyl, $-C_5-C_{10}$-aryl, $-C_5-C_{10}$-heteroaryl, $-C_3-C_8$-cycloalkyl, $-C_3-C_8$-heterocyclyl, $-C_2-C_6$-alkenyl, and $-C_2-C_6$-alkynyl, optionally being substituted by one or more groups selected from among -OH, $-NH_2$, $-C_1-C_3$-alkyl, $-O-C_1-C_6$-alkyl, -CN, $-CF_3$, $-OCF_3$, halogen, -methyl, and =O, more preferred wherein R_{22} is a group selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl,$-C(CH_3)_2-CN$, and –halogen, more preferred wherein R_{22} is a group selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl, –F, -Cl, $-C(CH_3)_2-CN$, and –Br, and wherein R_2 is a group selected from among -H, -halogen, -CN, $-O-C_2-C_4$-alkyl, $-C_1-C_4$-alkyl, $-CH=CH_2$, $-C\equiv CH$, $-CF_3$, $-OCF_3$, $-OCF_2H$, and $-OCFH_2$, more preferred wherein R_2 is a group selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, $-CH=CH_2$, and $-C\equiv CH$, more preferred wherein R_2 is a group selected from among-H, -Methyl, -Ethyl,and -Br, more preferred wherein R_2 is selected from among -H, and -Methyl, most preferred wherein R_2 denotes –Methyl or wherein R_2 denotes –H; and wherein R_3 is a group selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, $-OCH_3$, $-CF_3$, and –CN, more preferred wherein R_3 is a group selected from among -H, $-CF_3$, $-O-CH_3$, and –methyl, more preferred wherein R_3 is selected from among -H, $-O-CH_3$, and -methyl, more preferred wherein R_3 denotes –H, or wherein R_3 denotes $-O-CH_3$, or wherein R_3 denotes $-CF_3$; and wherein G and E are independently selected from among C-H or N, more preferred wherein G denotes C-H and E denotes N, more preferred wherein G denotes N and E denotes C-H, most preferred wherein G and E are N.

The present invention also relates to process for preparing a compound of formula (II) according to preparation method A wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (III) according to preparation method A wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (V) according to preparation method B wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (VI) according to preparation method B wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (VIII) according to preparation method C wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (X) according to preparation method D wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (XI) according to preparation method D wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, R_{21}, $R_{21'}$, L_1, L_2,E, G, Z, Y_1, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (XIII) according to preparation method E wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, Z, Q, and n have the meanings defined hereinbefore.

The present invention also relates to process for preparing a compound of formula (XIV) according to preparation method E wherein 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, R_{21}, $R_{21'}$, L_1, E, G, Z, Q, CYC, and n have the meanings defined hereinbefore.

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.

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

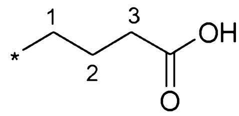
inflammatory and neuropathic pain disease, especially for the treatment of chronic pain. Present invention encloses compounds as herein before or below defined as medicaments for the treatment of immune related diseases, preferably for the treatment of diabetes mellitus. Present invention encloses compounds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

Definitions

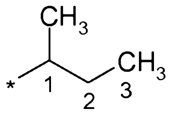
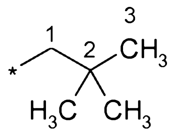
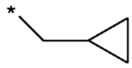
Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, $-C_1-C_6$-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C_1-C_3-alkyl-" means an aryl group which is bound to a C_1-C_3-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

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

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



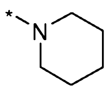
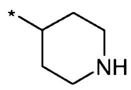
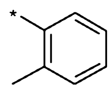
wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:

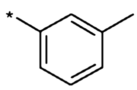
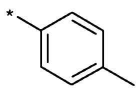
  

The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.
Many of the follwings terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

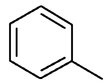
Unless otherwise stated, all the substituents are independent of one another. If for example there might be a plurality of C_1-C_6-alkyl groups as substituents in one group, in the case of three substituents C_1-C_6-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

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:

 Piperidinyl-A,  Piperidinyl-B,  Tolyl-C,

 Tolyl-D, and  Tolyl-E.

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

 Tolyl-F.

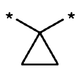
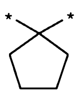
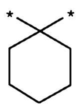
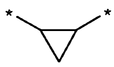
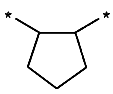
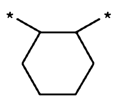
The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

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

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

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 1 to 6 carbon atoms arranged in a row and which can optionally further comprise branches or one or more hetero atoms selected from N, O or S. Said carbon chain can be saturated or unsaturated by comprising double or triple bonds.

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:

 ;  ;  ;  ;  ; and  .

The term "C_1-C_n-alkyl”, wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C_1-C_5-alkyl embraces the radicals H_3C-, H_3C-CH_2-,

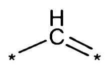
$H_3C-CH_2-CH_2-$, $H_3C-CH(CH_3)-$, $H_3C-CH_2-CH_2-CH_2-$, $H_3C-CH_2-CH(CH_3)-$, $H_3C-CH(CH_3)-CH_2-$, $H_3C-C(CH_3)_2-$, $H_3C-CH_2-CH_2-CH_2-CH_2-$, $H_3C-CH_2-CH_2-CH(CH_3)-$, $H_3C-CH_2-CH(CH_3)-CH_2-$, $H_3C-CH(CH_3)-CH_2-CH_2-$, $H_3C-CH_2-C(CH_3)_2-$, $H_3C-C(CH_3)_2-CH_2-$, $H_3C-CH(CH_3)-CH(CH_3)-$ and $H_3C-CH_2-CH(CH_2CH_3)-$.
By the term "C_1-C_6-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C_1-C_4-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. By the term "C_1-C_3-alkyl" are meant branched and unbranched alkyl groups with 1 to 3 carbon atoms and by the term "C_2-C_4-alkyl" are meant branched and unbranched alkyl groups with 2 to 4 carbon atoms. Examples for alkyl groups with 1-6 carbon atoms include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl or hexyl. Optionally the abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. may also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

The term "C_1-C_n-alkylene" wherein n is an integer 2 to n, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical containing from 1 to n carbon atoms. For example the term C_1-C_4-alkylene includes $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-C(CH_3)_2-$, $-CH(CH_2CH_3)-$, $-CH(CH_3)-CH_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-CH_2-$, $-CH_2-CH(CH_3)-CH_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$, $-CH(CH_3)-CH(CH_3)-$, $-CH_2-CH(CH_2CH_3)-$, $-CH(CH_2CH_3)-CH_2-$, $-CH(CH_2CH_2CH_3)-$, $-CH(CH(CH_3))_2-$ and $-C(CH_3)(CH_2CH_3)-$.
By the term "C_1-C_8-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 "C_2-C_8-alkylene" are meant branched and unbranched alkylene groups with 2 to 8 carbon atoms. By the term "C_2-C_6-alkylene" are meant branched and unbranched alkylene groups with 2 to 6 carbon atoms. By the term "C_1-C_4-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. By the term "C_1-C_2-alkylene" are meant branched and unbranched alkylene groups with 1 to 2 carbon atoms. By the term "C_0-C_4-alkylene" are meant branched and unbranched alkylene groups with 0 to 4 carbon atoms, thus also a single bond is encompassed. By the term "C_1-C_3-alkylene" are meant branched and unbranched alkylene groups with 1 to 3 carbon atoms. Examples for C_1-C_8-alkylene include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, hexylene, heptylene or octylene. Unless stated otherwise, the definitions propylene, butylene, pentylene, hexylene, heptylene and

octylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

The term "C_2-C_n-alkenyl", is used for a group as defined in the definition for "C_1-C_n-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.
By the term "C_2-C_6-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term "C_2-C_4-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms, provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are preferred. Examples for C_2-C_6-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. The asterisks (*) in the structural formula is to be understood as being the linking points to the rest of the molecule, whereas the valency of the rest of the molecule be freed thus a single and a double bond can be formed by replacement of further hydrogens at the binding site if applicable:


(methenylene).

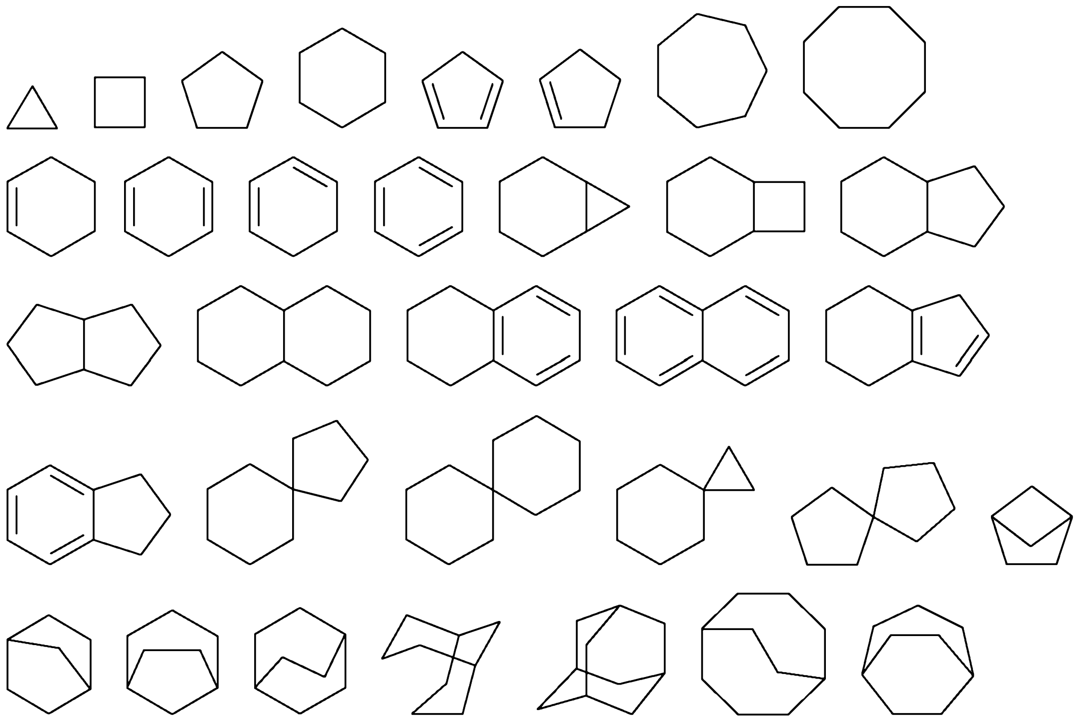
The term "C_2-C_n-alkenylene" is used for a group as defined in the definition for "C_1-C_n-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.
By the term "C_2-C_8-alkenylene" (including those which are part of other groups) are meant branched and unbranched alkenylene groups with 2 to 8 carbon atoms and by the term "C_2-C_6-alkenylene" are meant branched and unbranched alkenylene groups with 2 to 6 carbon atoms. By the term "C_1-C_2-alkenylene" are meant alkenylene groups with 1 to 2 carbon atoms, provided that they have at least one double bond, whereas by the term "C_1-alkenylene" is meant "methenylene". Examples for C_2-C_8-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.

The term "C_2-C_n-alkynyl", is used for a group as defined in the definition for "C_1-C_n-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.
By the term "C_2-C_6-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term "C_2-C_4-alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples for C_2-C_6-alkynyls include: ethynyl, propynyl, butynyl, pentynyl or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1-, 2-, and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

The term "C_2-C_n-alkynylene" is used for a group as defined in the definition for "C_1-C_n-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.
By the term "C_2-C_8-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 8 carbon atoms and by the term "C_2-C_6-alkynylene" are meant branched and unbranched alkynylene groups with 2 to 6 carbon atoms. Examples of C_2-C_8-alkynylenes include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2 -dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene, heptynylene or octynylene. Unless stated otherwise, the definitions propynylene, butynylene, pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1, 1-dimethylethynylene, 1, 2-dimethylethynylene.

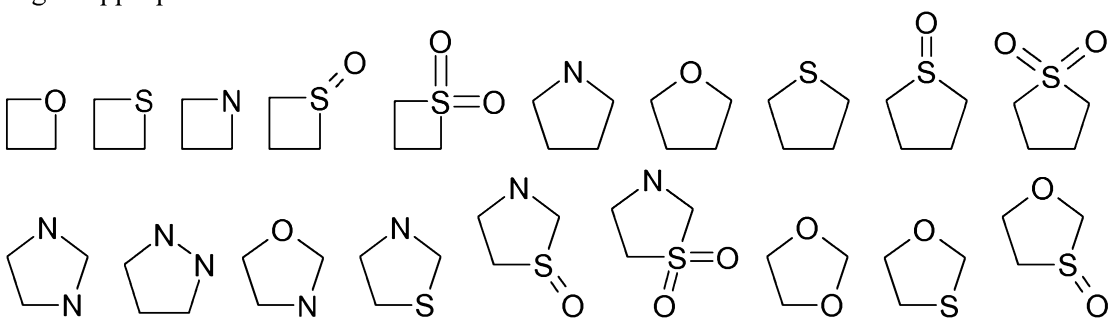
The term "carbocyclyl" as used either alone or in combination with another radical, means a mono- bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The term "carbocycle" refers to fully saturated and aromatic ring systems and partially saturated ring systems. The term "carbocycle" encompasses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

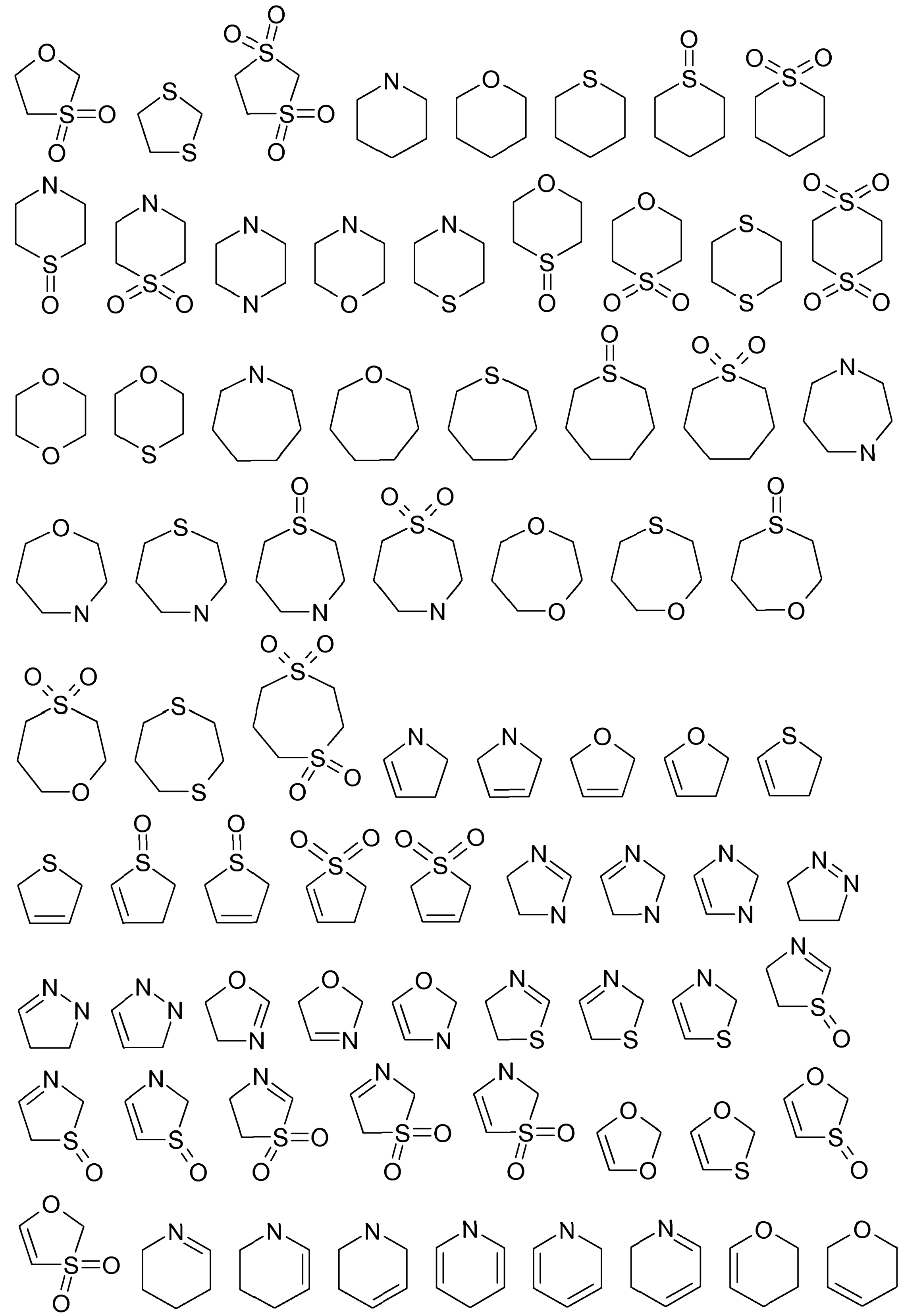


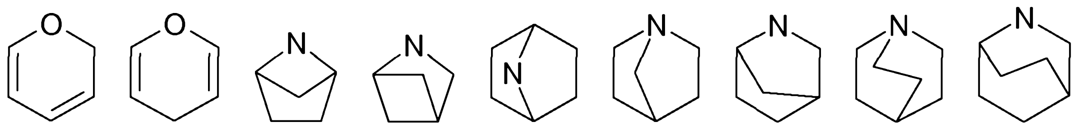
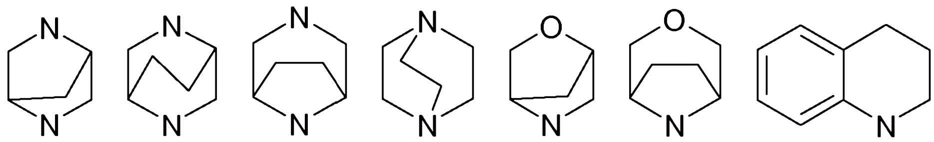
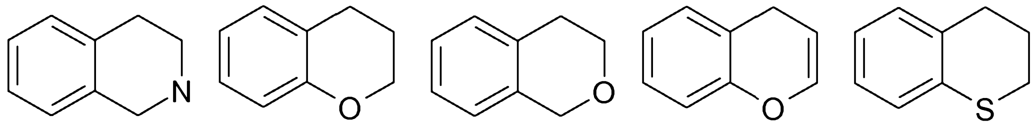
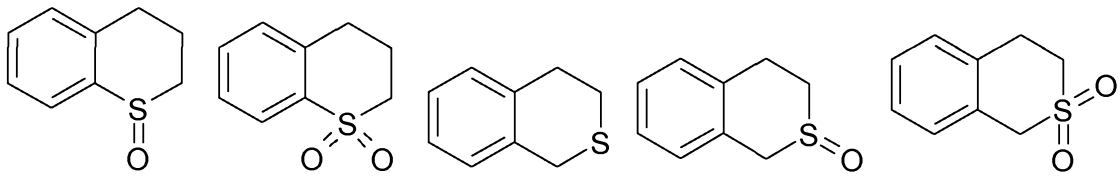
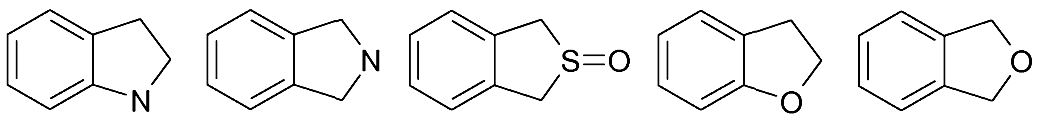
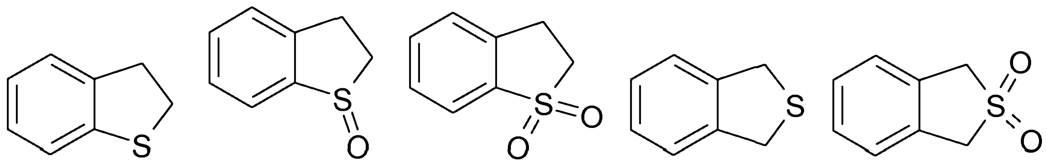
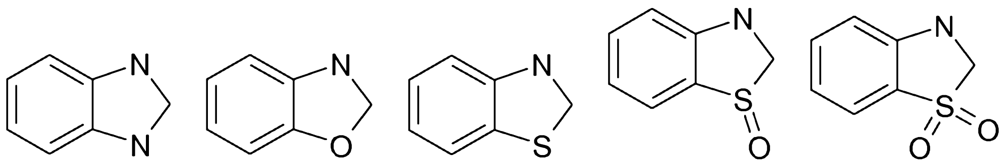
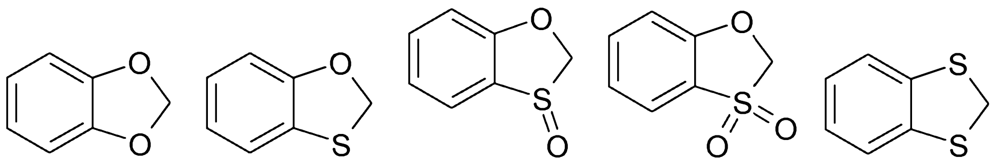
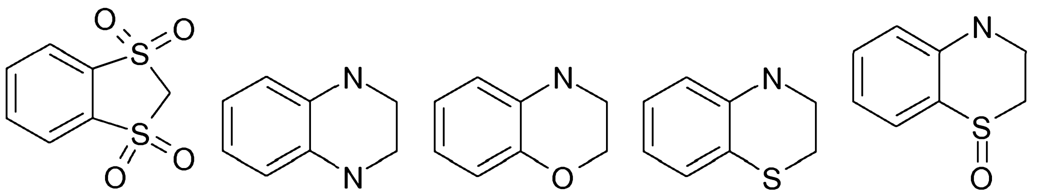
By the term “ring” are meant carbocycles, which can be saturated, unsaturated or aromatic and which optionally can comprise one or more hetero atoms selected from N, O or S.

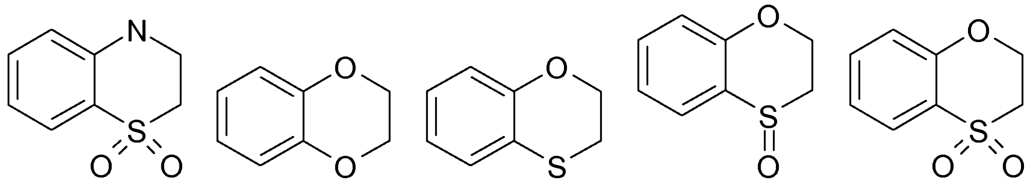
The term "heterocyclyl" means a saturated or unsaturated mono- or polycyclic-ring systems including aromatic ring system containing one or more heteroatoms selected from N, O or $S(O)_r$,wherein r = 0, 1 or 2, consisting of 3 to 14 ring atoms wherein none of the heteroatoms is part of the aromatic ring.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

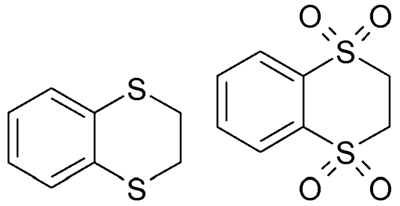
Thus, the term "heterocyclyl” includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:



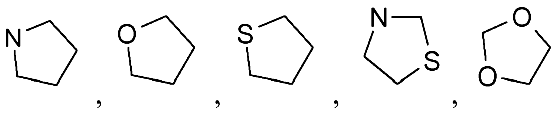


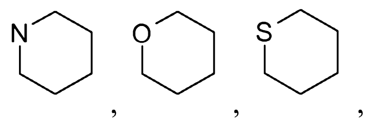


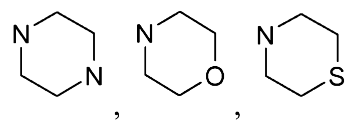
 .

By the term "-C_3-C_8-heterocyclyl" are meant three-, four-, five-, six-, seven, or eight-membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms. The ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. By the term "-C_5-C_8-heterocyclyl" are meant five-, six-, seven or eight-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 for C_5-heterocyclyl include:

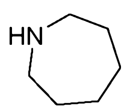
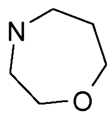
 .

Examples for C_6-heterocyclyl include:

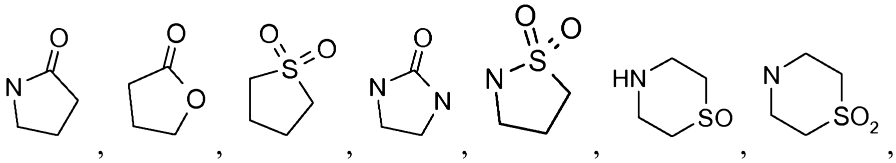
 ,

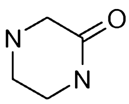
 .

Examples for C_7-heterocyclyl include:

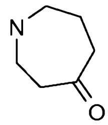
 , and  .

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

 ,



, and



.

The term "C_3-C_n-cycloalkyl", wherein n is an integer from 3 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. For example the term C_3-C_7-cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

By the term "C_3-C_8-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 8 carbon atoms. Likewise, by the term "C_3-C_6-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples of C_3-C_8-cycloalkyls include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Unless otherwise stated, the cyclic alkyl groups may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

The term "C_3-C_n-cycloalkenyl", wherein n is an integer from 3 to n, either alone or in combination with another radical, denotes an cyclic, unsaturated but nonaromatic, unbranched hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a double bond. For example the term $C_{3\text{-}7}$-cycloalkenyl includes cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl cycloheptadienyl and cycloheptatrienyl.

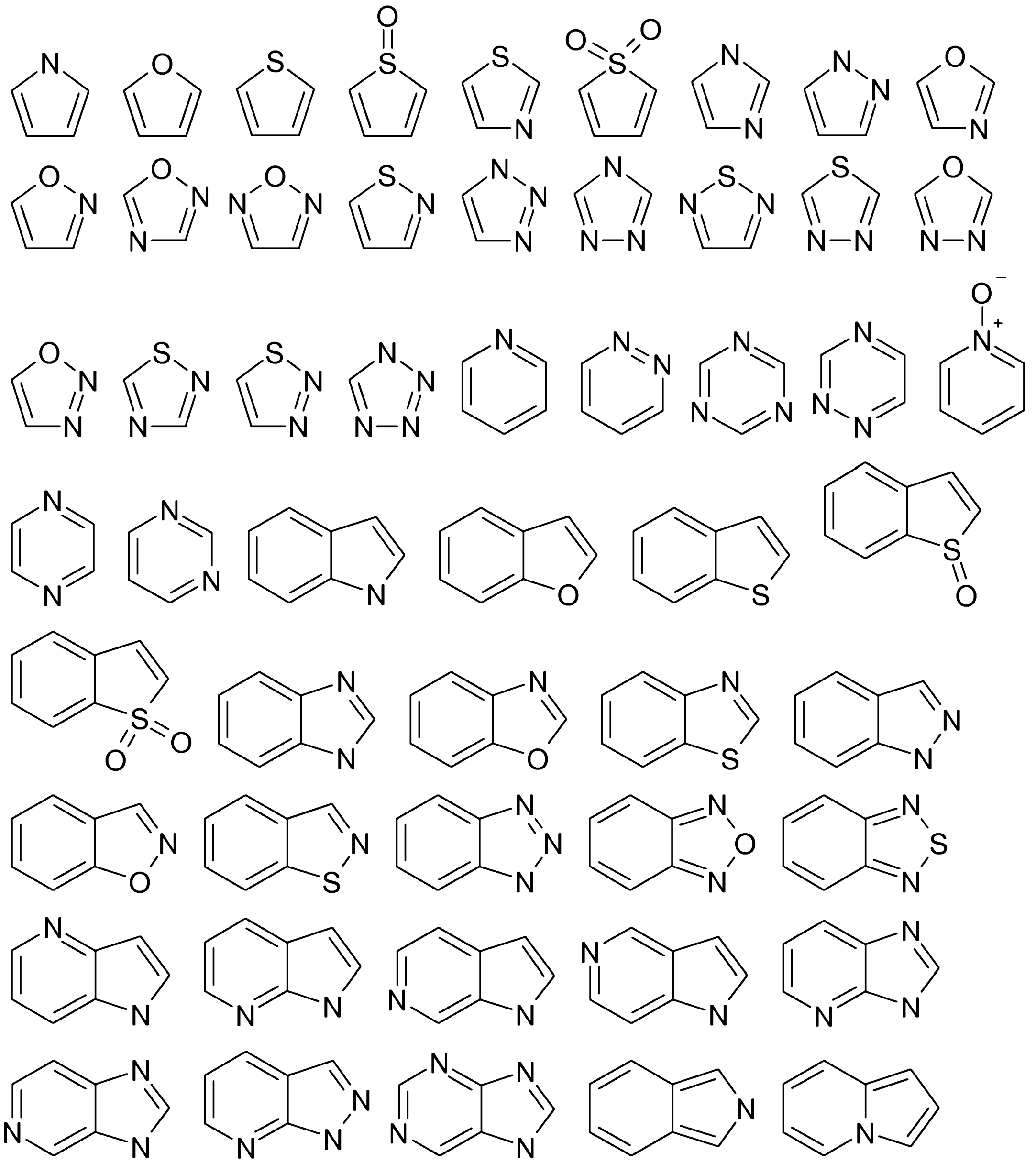
By the term "aryl" (including those which are part of other groups) are meant aromatic ring systems.

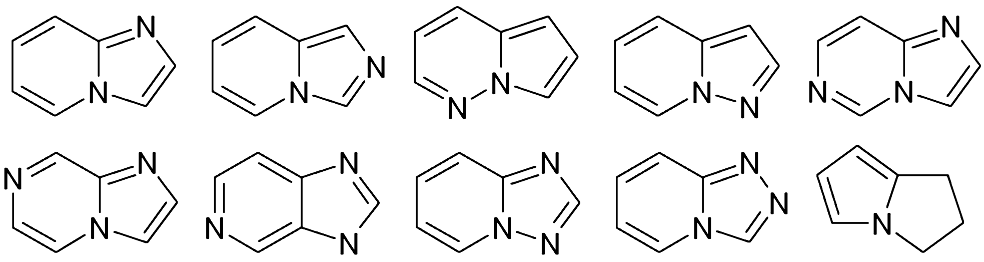
The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

By the term "C_5-C_{10}-aryl" (including those which are part of other groups) are meant aromatic ring systems with 5 to 10 carbon atoms. Preferred are "C_6-C_{10}-aryl" groups whereas aromatic rings are meant with 6 to 10 carbon atoms. Examples include: phenyl or naphthyl. Also preferred are "C_5-C_6-aryl" groups whereas aromatic rings are meant with 5 to 6 carbon atoms. Further preferred are are "C_6-aryl" groups whereas a aromatic ring is meant with 6 carbon atoms. Unless otherwise stated, the aromatic ring systems may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

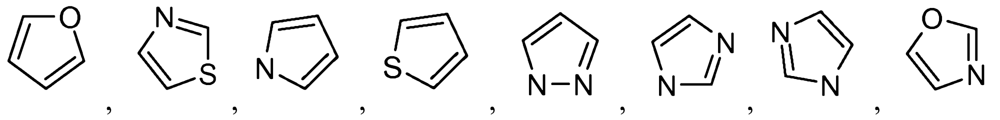
The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or $S(O)_r$, wherein r = 0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of aromatic ring. The term "heteroaryl" is intended to include all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

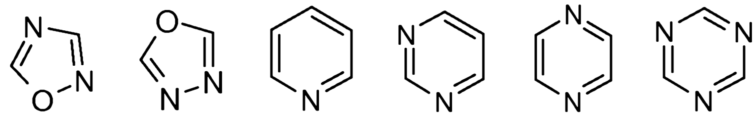
Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

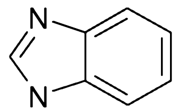




By the term "C_5-C_{10}-heteroaryl" (including those which are part of other groups) are meant five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms, and whereas the rings 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:



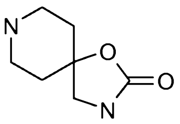
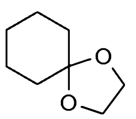
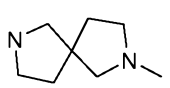


, and  .

Preferred are "C_5-C_6-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-C_1-C_4-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 -C_1-C_4-alkyl chain.

By the term “spiro-C_3-C_8-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-C_3-C_8-heterocyclyl” (spiro) are meant 3-8 membered, spirocyclic rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms. The ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one.
Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl, or ethyl group. Examples include:

 ,  ,  ,  , and  .

"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 alklaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2’-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2’,2"-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2.2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid,

cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).
The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

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.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc…) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.
Hence the invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids – such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

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

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

The compounds according to formula (I) according to the invention have the meanings hereinbefore whereas in particular the preferred embodiments defined by 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}, R_{19}, $R_{19'}$, R_{20}, $R_{20'}$, L_1, E, G, 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 (Gibso 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 resuspendet 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 1x10E9 cells. The membranes were resuspendet 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.

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 hKi) is calculated by iterative fitting of experimental data using the" easy sys" program, which is based on law of mass action (Schittkowski K. (1994), Numerische Mathematik, Vol. 68, 129-142).

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

Example	hKi
1	8 [nM]

Example	hKi
15	24 [nM]

2	151 [nM]
3	203 [nM]
4	26 [nM]
5	237 [nM]
6	190 [nM]
7	36 [nM]
8	185 [nM]
9	13 [nM]
10	142 [nM]
11	53 [nM]
12	27 [nM]
13	486 [nM]
14	479 [nM]

16	11 [nM]
17	11 [nM]
18	10 [nM]
19	162 [nM]
20	11 [nM]
21	11 [nM]
22	11 [nM]
23	494 [nM]
24	4 [nM]
25	418 [nM]
26	6 [nM]
27	12 [nM]
28	658 [nM]

Example	hKi
29	4 [nM]
30	5 [nM]
31	276 [nM]
32	333 [nM]
33	148 [nM]
34	63 [nM]
35	96 [nM]
36	51 [nM]
37	25 [nM]
38	6 [nM]
39	287 [nM]
40	26 [nM]
41	3 [nM]
42	8 [nM]

Example	hKi
43	39 [nM]
44	166 [nM]
45	6 [nM]
46	302 [nM]
47	94 [nM]
48	7 [nM]
49	4 [nM]
50	9 [nM]
51	8 [nM]
52	1 [nM]
53	2 [nM]
54	28 [nM]

Example	hKi
28a	45 [nM]
28b	0.5 [nM]

Example	hKi
53a	7 [nM]
53b	20 [nM]

28c	0.4 [nM]
28d	12 [nM]
28e	20 [nM]
28f	78 [nM]
28g	8 [nM]
28h	4 [nM]
28i	221 [nM]
28j	1 [nM]
28k	3 [nM]

Example	**hKi**
54a	5 [nM]
28l	2 [nM]
28m	1 [nM]
28n	38 [nM]
53n	5 [nM]
53o	1 [nM]
53p	0.8 [nM]
53q	1 [nM]
53r	0.8 [nM]
53s	0.2 [nM]
53t	0.4 [nM]
53u	3 [nM]
53v	7 [nM]
53w	0.6 [nM]
53x	9 [nM]
53y	16 [nM]
53z	3 [nM]

53c	98 [nM]
53d	19 [nM]
53e	16 [nM]
53f	12 [nM]
53g	16 [nM]
53h	2 [nM]
53i	2 [nM]
53j	21 [nM]
53k	9 [nM]
53l	0.5 [nM]
53m	0.3 [nM]

Example	**hKi**
53aa	2 [nM]
53ab	1 [nM]
53ac	0.8 [nM]
53ad	0.3 [nM]
53ae	0.4 [nM]
53af	8 [nM]
53ag	5 [nM]
53ah	0.8 [nM]
53ai	1.1 [nM]
53aj	0.7 [nM]
53ak	0.8 [nM]
53al	0.4 [nM]
53am	0.3 [nM]
55	311 [nM]
56	802 [nM]
57	1802 [nM]
58	1134 [nM]
59	263 [nM]
60	733 [nM]

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

Pulmonary Diseases

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

Malignant Diseases

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chromic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodyplastic 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 spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitisluveitisloptic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitislvasectomy reversal procedures, allergiclatopic 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, meningococcemia, traumalhemo~~hage, 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, hypersensitity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, 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, antireceptor hypersensitivity reactions, Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-meditated cytotoxicity, type IU hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal garnrnopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary billiary cirrhosis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity , contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemachromatosis, 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 hematophagocytic 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 toasthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like.

<u>Cardiovascular Diseases</u>

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 stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic ateriosclerotic 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 inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrythrnias, ventricular fibrillation, His bundle arrythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aordic and peripheral aneuryisms, aortic dissection, inflammation of the aorta, occulsion of the abdominal aorta and its branches, peripheral vascular disorders, occulsive arterial disorders, peripheral atherlosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphederma, 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, 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: Inflammatory pain, chronic pain, Neuropathic pain such as low back pain, hip pain, leg pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury-induced pain, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, toxin and chemotherapy caused nerve injuries, phantom limb pain, multiple sclerosis, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, carpal tunnel syndrome, trigeminal neuralgia, post mastectomy syndrome, postthoracotomy syndrome, stump pain, repetitive motion pain, neuropathic pain associated hyperalgesia and allodynia, alcoholism and other drug-induced pain; neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supra-nucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, and mitochondria1 multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease; and Dementia pugilistica, and the like.

Fibrotic Conditions

In addition to the above described conditions and diseases, the present invention also provides a method for modulating or treating fibrotic conditions of various etiologies such as liver fibrosis (including but not limited to alcohol-induced cirrhosis, viral-induced cirrhosis, autoirnrnune- induced hepatitis); lung fibrosis (including but not limited to scleroderma, idiopathic pulmonary fibrosis); kidney fibrosis (including but not limited to scleroderma, diabetic nephritis, glomerular pehpritis, 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 collegen 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, orchitislepidydimitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitisiaseptic meningitis, and the like.
Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CCR2 antagonist to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

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

Combinations

The compounds of formula (I) may be used on their own or in conjunction with other active substances of formula (I) according to the invention. If desired the compounds of formula (I) may also be used in combination with other pharmacologically active substances. It is preferable to use for this purpose active substances selected for example from among ß2-adrenoceptor-agonists (short and lon-acting betamimetics), anti-cholinergics (short and lon-acting), anti-inflammatory steroids (oral and topical corticosteroids), cromoglycate, methylxanthine, dissociated-glucocorticoidmimetics, PDE3 inhibitors, PDE4- inhibitors, PDE7- inhibitors, LTD4 antagonists, EGFR- inhibitors, Dopamine agonists, statins, PAF antagonists, Lipoxin A4 derivatives, FPRL1 modulators, LTB4-receptor (BLT1, BLT2) antagonists, Histamine H1 receptor antagonists, Histamine H4 receptor antagonists, dual Histamine H1/H3-receptor antagonists, PI3-kinase inhibitors, inhibitors of non-receptor tyrosine kinases as for example LYN, LCK, SYK (spleen tyrosine kinase-inhibitors), ZAP-70, FYN, BTK or ITK, inhibitors of MAP kinases as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, inhibitors of the NF-kappaB signalling pathway as for example IKK2 kinase inhibitors, iNOS inhibitors (inducible nitric oxide synthase-inhibitors), MRP4 inhibitors, leukotriene antagonists, leukotriene biosynthese inhibitors as for example 5-Lipoxygenase (5-LO) inhibitors, cPLA2 inhibitors, Leukotriene A4 Hydrolase inhibitors or FLAP inhibitors, non-steroidal antiinfiammatory drugs (NSAIDs) including COX-2 inhibitors, CRTH2 antagonists, DP1-receptor modulators, Thromboxane receptor antagonists, CCR1 antagonists, CCR4 antagonists, CCR5 antagonists, CCR6 antagonists, CCR7 antagonists, CCR8 antagonists, CCR9 antagonists, CCR10 antagonists, CCR11 antagonists, CXCR1 antagonists, CXCR2 antagonists, CXCR3 antagonists, CXCR4 antagonists, CXCR5 antagonists, CXCR6 antagonists, CX3CR1 antagonists, Neurokinin (NK1, NK2) antagonists, Sphingosine 1-Phosphate receptor modulators, Sphingosine 1 phosphate lyase inhibitors, Adenosine receptor modulators as for example A2a-agonists, modulators of purinergic rezeptors as for example P2X7 inhibitors, Histone Deacetylase (HDAC) activators, Bradykinin (BK1, BK2) antagonists, TACE inhibitors, PPAR gamma modulators, Rho-kinase inhibitors, interleukin 1-beta converting enzyme (ICE) inhibitors, Toll-Like receptor (TLR) modulators, HMG-CoA reductase inhibitors, VLA-4 antagonists, ICAM-1 inhibitors, SHIP agonists, GABAa receptor antagonist, ENaC-inhibitors, Melanocortin receptor (MC1R, MC2R, MC3R, MC4R, MC5R) modulators, CGRP antagonists, Endothelin antagonists, TNFalpha antagonists, anti-TNF antibodies, anti-GM-CSF antibodies, anti-CD46 antibodies, anti-IL-1 antibodies, anti-IL-2 antibodies, anti-IL-4 antibodies, anti-IL-5 antibodies, anti-IL-13 antibodies, anti-IL-4/IL-13 antibodies, anti-TSLP antibodies, anti-OX40 antibodies, mucoregulators, immunotherapeutic agents, compounds agianst swelling of the airways, compounds against cough, antiviral drugs, opiate receptor agonists, cannabionoid agonists, sodium channel blockers, N-type calcium channel blockers, serotonergic and noradrenergic modulators, proton pump inhibitors, local anesthetics, VR1 agonists and antagonists, Nicotinic acetylcholine receptor agonists, P2X3 receptor antagonists, NGF agonists and antagonists, NMDA antagonist, potassium channel modulators, GABA modulators, serotonergic and noradrenergic modulators, anti-migraine drugs. The invention also encompasses combinations of three active substances, each selected from one of the above-mentioned categories of compounds. Said list is not considered to have a limiting character.

The betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenol, sulphonterol, tiaramide, terbutaline, tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-

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

Preferably the beta mimetics are selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one , 4-hydroxy-7-[2-{[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)-1.1dimethyl-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)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Of these betamimetics those which are particularly preferred according to the invention are formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-

ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

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

The anticholinergics used are preferably compounds selected from among the tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, -scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate -methobromide, tropenol 9-fluoro-fluorene-9-carboxylate -methobromide, scopine 9-hydroxy-fluoren-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine

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

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

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

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.

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.

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.

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

The PDE4-inhibitor used are preferably compounds selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, Cl-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], 9-

cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

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

LTD4-antagonists which may be used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2- hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2.3-dichlorothieno[3,2-b]pyridin-5-yI)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane-acetic acid and [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.
Preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.
Particularly preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001 and MEN-91507 (LM-1507), optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.
By acid addition salts with pharmacologically acceptable acids which the LTD4-antagonists may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and

hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. By salts or derivatives which the LTD4-antagonists may be capable of forming are meant, for example: alkali metal salts, such as, for example, sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

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

quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidin, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)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.-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-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2.6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-

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

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

methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-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.-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-

isopropyloxycarbonyl-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.

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

fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

EGFR-inhibitors are preferably selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

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

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

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

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

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

enantiomers from the racemates can be carried out using methods known from the art (e.g. chromatography on chiral phases, etc.) .

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

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

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^{ω}-nitro-L-arginine), L-NAME (N^{ω}-nitro-L-arginine methylester), L-NMMA (N^{G}-monomethyl-L-arginine), L-NIO (N^{ω}-iminoethyl-L-ornithine), L-NIL (N^{ω}-iminoethyl-lysine), (S)-6-acetimidoylamino-2-amino-hexanoic acid (1*H*-tetrazol-5-yl)-amide (SC-51) (*J. Med. Chem.* 2002, *45*, 1686-1689), 1400W, (S)-4-(2-acetimidoylamino-ethylsulphanyl)-2-amino-butyric acid (GW274150) (*Bioorg. Med. Chem. Lett.* 2000, *10*, 597-600), 2-[2-(4-methoxy-pyridin-2-yl)-ethyl]-3*H*-imidazo[4,5-*b*]pyridine (BYK191023) (*Mol. Pharmacol.* 2006, *69*, 328-337), 2-((R)-3-amino-1-phenyl-propoxy)-4-chloro-5-fluorobenzonitrile (WO 01/62704), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-6-trifluoromethyl-nicotinonitrile (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-4-chloro-benzonitrile (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-benzonitrile (WO 2004/041794), (2S,4R)-2-amino-4-(2-chloro-5-trifluoromethyl-phenylsulphanyl)-4-thiazol-5-yl-butan-1-ol (WO 2004/041794), 2-((1R.3S)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-nicotinonitrile (WO 2004/041794), 4-((S)-3-amino-4-hydroxy-1-phenyl-butylsulphanyl)-6-methoxy-nicotinonitrile (WO 02/090332), substituted 3-phenyl-3,4-dihydro-1-isoquinolinamines such as e.g. AR-C102222 (*J. Med. Chem.* 2003, *46*, 913-916), (1S.5S.6R)-7-chloro-5-methyl-2-aza-bicyclo[4.1.0]hept-2-en-3-ylamine (ONO-1714) (*Biochem. Biophys. Res. Commun.* 2000, *270*, 663-667), (4R.5R)-5-ethyl-4-methyl-thiazolidin-2-ylideneamine (*Bioorg. Med. Chem.* 2004, *12*, 4101), (4R.5R)-5-ethyl-4-methylselenazolidin-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-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.

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

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

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

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

Examples of preferred non-steroidal anti-inflammatory agents (NSAIDs) which may be mentioned include COX-2 inhibitors :propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenhufen, fenoprofen, flubiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (meclofenamic acid, mefenamic acid, and tolfenamic acid), biphenyl- carboxylic acid derivatives, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoxib, rofecoxib and etoricoxib) optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

Examples of preferred CCR1 antagonists which may be mentioned include AZD-4818, CCX-354, MLN-3701, MLN-3897, optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred CCR5 antagonists which may be mentioned include maraviroc, INCB-15050. CCR5mAb004, GSK-706769, PRO-140, SCH-532706, vicriviroc and nifeviroc optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred CXCR1 or CXCR2 antagonists which may be mentioned include SCH-527123 and SB-656933 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred Neurokinin (NK1 or NK2) antagonists which may be mentioned include Saredutant, Nepadutant, PRX-96026 und Figopitant optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred purinergic receptor modulators, including P2X7 inhibitors, which may be mentioned include AZD-9056 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred PPAR gamma modulators which may be mentioned include Rosiglitazone, Ciglitazone, Pioglitazone and SMP-028 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred Interleukin 1-beta converting enzyme (ICE) inhibitors which may be mentioned include Pralnacasan, VRT-18858, RU-36384, VX-765 and VRT-43198 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred Toll-like receptor (TLR) modulators which may be mentioned include Resiquimod, PF-3512676, AVE-0675, Heplisav, IMO-2055, CpG-28, TAK-242, SAR-21609, RC-52743198 and 852A optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.

Examples of preferred VLA4 antagonists which may be mentioned include Natalizumab, Valategrast, TBC-4746, CDP-323 andTL-1102 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred ICAM-1 inhibitors which may be mentioned include BIRT-2584 optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred anti-TNF antibodies which may be mentioned include Infliximab, Adalimumab, Golimumab. CytoFab and Etanercept.
Examples of preferred mucoregulators which may be mentioned include MSI-2216, Erdosteine, Fluorovent, Talniflumate, INO-4995, BIO-11006, VR-496 and fudosteine optionally in racemic form, as enantiomers, diastereomeres or as pharmacologically acceptable salts, solvates or hydrates.
Examples of preferred Antiviral drugs which may be mentioned include acyclovir, tenovir, pleconaril, peramivir, pocosanol.
Examples of preferred Antibiotic drugs like gentamicin, streptomycin, geldanamycin, doripenem, cephalexin, cefaclor, ceftazichine, cefepime, erythromycin, vancomycin, aztreonam, amoxicillin, bacitracin, enoxacin, mafenide, doxycycline, chloramphenicol.
Examples of preferred opiate receptor agonists are selected from among morphine, propoxyphene (Darvon), tramadol , buprenorphin.
Examples of preferred anti-TNF antibodies or TNF-receptor antagonists such as but not limited to Etanercept, Infliximab, Adalimumab (D2E7), CDP 571, and Ro 45-2081 (Lenercept), or biologic agents directed against targets such as but not limited to CD-4, CTLA-4, LFA-1, IL-6, ICAM-1, C5 and Natalizumab.
Examples of preferred IL-1 receptor antagonists such as but not limited to Kineret;
Sodium channel blockers: carbamazepine, mexiletine, lamotrigine, tectin, lacosamide
Examples of preferred N-type calcium channel blockers are selected from among Ziconotide.
Examples of preferred Serotonergic and noradrenergic modulators such as but not limited to paroxetine, duloxetine, clonidine, amitriptyline, citalopram;
Examples of preferred Histamine H1 receptor antagonists such as but not limited to bromophtniramint, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdiJazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, deslo- ratadine, fexofenadine and levocetirizine.
Examples of preferred Histamine H2 receptor antagonists such as but not limited to cimetidine, famotidine and ranitidine.
Examples of preferred proton pump inhibitors such as but not limited to omeprazole, pantoprazole and esomeprazole.
Examples of preferred Leukotriene antagonists and 5-lipoxygenase inhibitors such as but not limited to zafirlukast, mon- telukast, pranlukast and zileuton.

Examples of preferred local anesthetics such as but not limited to ambroxol, lidocaine.
Examples of preferred potassium channel modulators such as but not limited to retigabine.
Examples of preferred GABA modulators such as but not limited to lacosamide, pregabalin, gabapentin.
Examples of preferred anti-migraine drugs such as but not limited to sumatriptan, zolmitriptan, naratriptan, eletriptan, telcegepant.
Examples of preferred NGF antibodies such as but not limited to RI-724.

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

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 range specified hereinafter.

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

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

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

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

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

Capsules containing one or more active substances or combinations of active substances 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.

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

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 tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

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

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

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

Propellant-free inhalable solutions
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 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 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.

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

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

Experimental procedures and synthetic examples

LIST of ABBREVIATIONS

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

ANALYTICAL METHODS

HPLC methods

Methods:

- **1E**

  Column: Symmetry C8, 5 µm, 3 x 150 mm

Mobile phase:	A = (10 nM aqueous solution of NH_4COOH) + 10% ACN; B = ACN + 10% (10 nM aqueous solution of NH_4COOH).
Flow rate:	1200 µL/min
Gradient:	A (100%) for 1.5 min then to B (100%) in 10 min for 3 min

- **1E (Hydro)**

Column:	Synergy Hydro RP80A, 4 µm, 4.6 x 100 mm
Mobile phase:	A = (10 nM aqueous solution of NH_4COOH) + 10% ACN; B = ACN + 10% (10 nM aqueous solution of NH_4COOH).
Flow rate:	1200 µL/min
Gradient:	A (100 %) for 1.5 min then to B (100 %) in 10 min for 3 min

Equipment:

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

Methods:

- **2F**

Column:	Symmetry Shield RP8, 5µm, 4.6 x 150 mm
Mobile phase:	A = (H_2O + HCOOH 0.1%) + 10% ACN B = ACN + 10% (H_2O + 0.1% HCOOH)
Flow rate:	1000 µL/min
Gradient:	A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min

- **2M**

Column:	Symmetry Shield RP8, 5µm, 4.6 x 150 mm
Mobile phase:	A = (H_2O + HCOOH 0.1%) + 10% ACN B = ACN + 10% (H_2O + 0.1% HCOOH)
Flow rate:	1200 µL/min
Gradient:	A/B (90/10 %) for 1.5 min then to A/B (5/95 %) in 10 min for 2 min

Equipment:

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

Detection: Finnigan LCQDuo Ion Trap
Ion source: ESI

Method:

- **2FF**

Column: Symmetry Shield RP8, 5µm, 4.6 x 150 mm
Mobile phase: A = (H_2O + HCOOH 0.1%) + 10% ACN
B = ACN + 10% (H_2O + 0.1% HCOOH)
Flow rate: 1000 µL/min
Gradient: A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min

Equipment:

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

Methods:

- **2Ia (isocratic)**

Column: DAICEL Chiralpack AS-H 5 µm, 4.6x250 mm
Mobile phase: A = Hexane; B = EtOH
A/B = 98/2%
Flow rate: 1 ml/min

- **2Ib (isocratic)**

Column: DAICEL Chiralpack AS-H 5 µm, 4.6x250 mm
Mobile phase: A = Hexane; B = EtOH
A/B = 95/5%
Flow rate: 1 ml/min

- **2Ic (isocratic)**

Column: DAICEL Chiralpack AS-H 5 µm, 4.6x250 mm
Mobile phase: A = Hexane; B = EtOH
A/B = 70/30%

- **2J (isocratic)**

Column: DAICEL Chiralpack AD-H 5 µm, 4.6x250 mm
Mobile phase: A = Hexane; B = Isopropanol

A/B = 98/2%

Flow rate: 1 ml/min

- **2Ja (isocratic)**

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

  Mobile phase: A = Hexane; B = Isopropanol

  A/B = 80/20%

  Flow rate: 1 ml/min

- **2K (isocratic)**

  Column: DAICEL Chiralcel OJ-H 5 µm, 4.6x250 mm

  Mobile phase: A = Hexane; B = EtOH

  A/B = 85/15%

  Flow rate: 1 ml/min

- **2Ka (isocratic)**

  Column: DAICEL Chiralcel OJ-H 5 µm, 4.6x250 mm

  Mobile phase: A = Hexane; B = EtOH

  A/B = 98/2%

  Flow rate: 1 ml/min

Equipment

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

Detection: UV 220 - 300nm

Method:

- **2Ha**

  Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm

  Mobile phase: A = Water + 0.1% HCOOH; B = ACN + 0.1% HCOOH

  Flow rate: 1.6 µL/min

  Gradient:

% B	Minutes
10	0.00
90	2.70
90	3.00
10	3.30

Equipment:

Instrument: Agilent Technology; HP 1100 Series , DAD

Detection: UV 190 - 400 nm

Detection:	Agilent Technology; HP 1100 MSD
Ion source:	ESI +

Methods:

- **2Ga**

Column:	ACQUITY UPLC BEH C18, 1.7um, 2.1 x 50 mm
Mobile phase:	A = (NH4COOH 5mM) + 10% ACN B = ACN + 10% water
Flow rate:	700 µL/min
Gradient:	from A/B (100/0 %) to A/B (0/100 %) in 2.4 min, then A/B (0/100 %) for 0.3 min

- **2Gb**

Column:	ACQUITY UPLC HSS C18, 1.7um, 2.1 x 50 mm
Mobile phase:	A = Water + 0.0.5% TFA; B = ACN + 0.1% water
Flow rate:	700 µL/min
Gradient:	from A/B (100/0 %) to A/B (0/100 %) in 2.4 min, then A/B (0/100 %) for 0.3 min

Equipment:

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

GC-MS methods:

Methods:

- **3A**

Column:	Agilent DB-5MS, 25m x 0.25mm x 0.25 µm
Carrier gas:	Helium, 1 ml/min costant 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

- **3B**

Column:	Agilent DB-5MS, 25m x 0.25mm x 0.25 µm
Carrier gas:	Helium, 1 ml/min costant flow
Oven Program:	80°C to 110°C in 10°C / min (hold 40 min), to 280°C in 30°C / min

Equipment

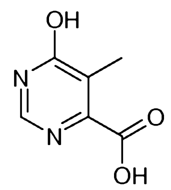
Instrument: GC/MS Finnigan TRACE GC, TRACE MS quadrupole
Detection: TRACE MS quadrupole
Ion source: EI

MICROWAVE HEATING:

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

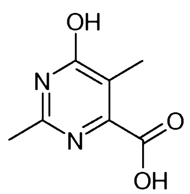
SYNTHESIS OF INTERMEDIATES

Intermediate 1a



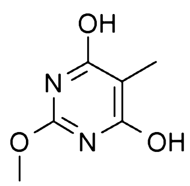
Potassium hydroxide (37.9 g, 0.67 mol) was suspended in 200 ml of dry ethanol, formamidine acetate (28.1 g, 0.27 mol) and commercially available diethyl oxalpropionate (50 ml, 0.27 mol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to room temperature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



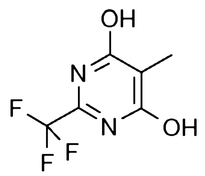
was synthesized in analogy to Intermediate 1a, starting from acetamidine hydrochloride.

Intermediate 1c



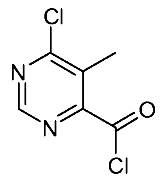
Diethylmethyl malonate (17 ml, 107 mmol) was added to sodium methoxide (30% in methanol, 101 ml, 547 mmol) and stirred for 15 min at 0°C. A solution of commercially available *O*-methylisourea hydrochloride (14.5 g, 131 mmol) in 20 ml MeOH was added dropwise to the reaction mixture. The reaction mixture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

Intermediate 1d



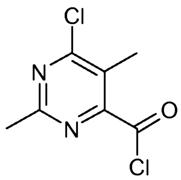
was synthesized in analogy to intermediate 1c starting from commercially available 2,2,2,-trifluoro-acetamidine.

Intermediate 2a



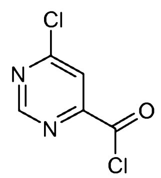
Intermediate 1a (7.0 g, 45.4 mmol) was suspended in 35 ml of thionyl chloride (0.45 mol), 0.10 ml of DMF was added and the reaction mixture was refluxed for 1h. The reaction mixture was concentrated in vacuum. 8.6 g (45 mmol) of the desired product were obtained and used in the next steps without further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

Intermediate 2b



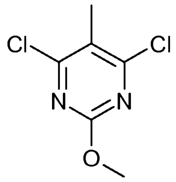
was synthesized in analogy to Intermediate 2a, starting from Intermediate 1b.

Intermediate 2c



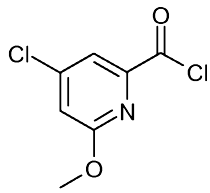
was synthesized in analogy to Intermediate 2a starting from commercially available 6-hydroxypyrimidine-4-carboxylic acid.

Intermediate 2d



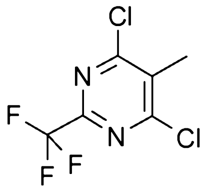
Intermediate 1c (1.9 g, 12.2 mmol) was added to phosphoryl chloride (17 ml) and the reaction mixture was stirred overnight at 60°C. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane. The combined organic layers were concentrated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

Intermediate 2e



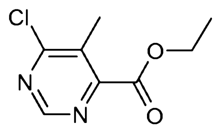
Commercially available 1-chloro-*N*,*N*,2-trimethylpropenylamine (70.5 µl, 533 µmol) was slowly added to a solution of commercially available 4-chloro-6-methoxy-pyridine-2-carboxylic acid (50 mg, 267 µmol) in 3 ml dichoromethane at 0°C, and the reaction mixture was stirred for 3 h at room temperature. The solvent was removed in vacuum to give the desired product (55 mg) which was used in the next step without purification.

Intermediate 2f



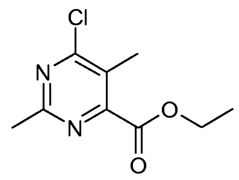
Thionylchloride (11.2 ml, 155 mmol) and DMF (250 µl) were added to a solution of intermediate 1d (3.0 g, 15.5 mmol) in 9 ml dichloromethane and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane.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

Intermediate 3a



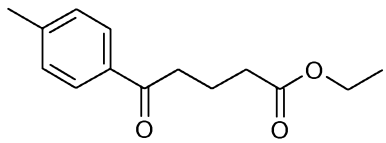
Potassium carbonate (43.34 g, 0.31 mol) was suspended in 350 ml of dry ethanol. A solution of Intermediate 2a (20 g, 0.10 mol) in 10 ml of dichloromethane was added slowly at 0°C. The reaction mixture was allowed to reach room temperature and stirred for 1h. Potassium carbonate was filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromathography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/ethyl acetate=95/5%). 5.3 g (26 mmol) of the desired compound were obtained.

Intermediate 3b



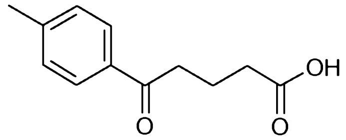
was synthesized in analogy to Intermediate 3a, starting from Intermediate 2b.

Intermediate 4a



To a solution of lithium bromide (24 g, 277.06 mmol) in 500 ml of dry tetrahydrofurane, stirred under nitrogen atmosphere, copper(I) bromide (19,87 g, 138,52 mmol) was added. The reaction mixture was stirred at room temperature until a solution was obtained. Then, the reaction mixture was cooled to 0°C and a 0.5M solution of commercially available 4-tolyl magnesium bromide in THF (277.05 ml, 138,52 mmol) was added. Then, commercially available 4-chlorocarbonyl-butyric acid ethyl ester (19 g, 115,44 mmol) was added and the reaction mixture was stirred at 0°C for 18h.
500 ml of a saturated aqueous ammonium chloride solution was added and the reaction mixture was extracted twice with dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulphate and concentrated under vacuum. The crude product (20 g) was used in the next step without any purification.

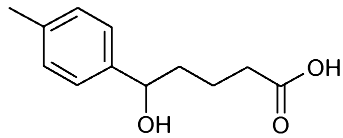
Intermediate 5a



To a solution of intermediate 4a (20 g, 90,80 mmol) in 50 ml of tetrahydrofurane 50 ml of water and lithium hydroxide monohydrate (11,43 g, 274,40 mmol) were added and the reaction mixture was stirred at 50°C for 1h.

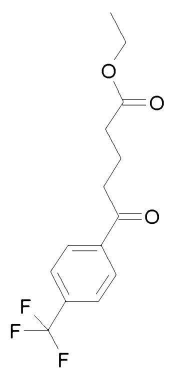
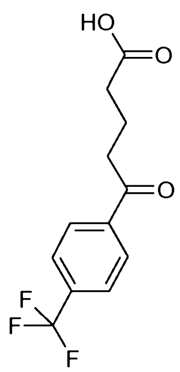
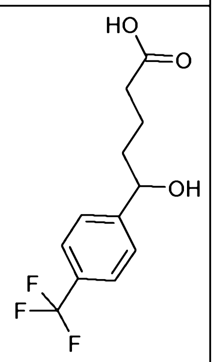
The reaction mixture was extracted with ethyl acetate and the layers were separated. The water phase was acidified with aqueousHCl (37%) until pH 1 and then extracted with dichloromethane. The organic layer was dried ver sodium sulfate and concentrated under vacuum. The crude product was triturated with diisopropyl ether. The solvent was removed by filtration yielding the desired product (13g, 63.10 mmol).

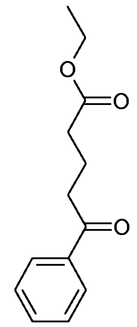
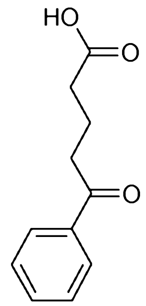
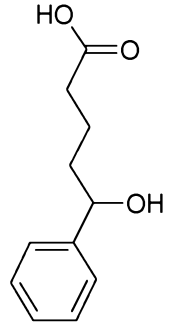
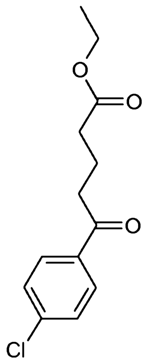
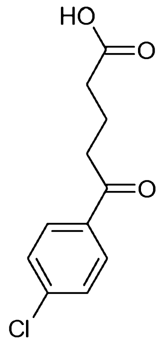
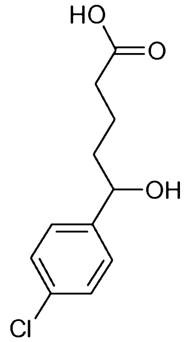
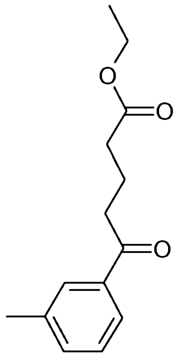
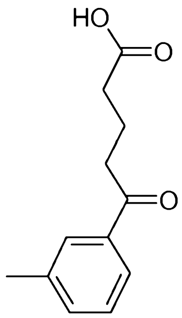
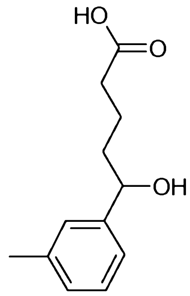
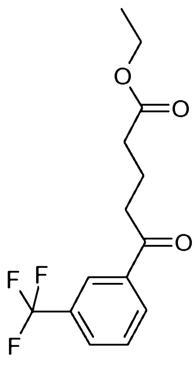
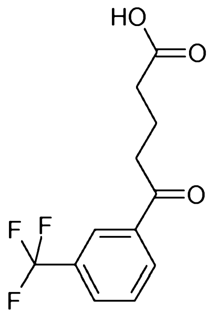
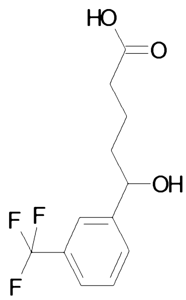
Intermediate 6a

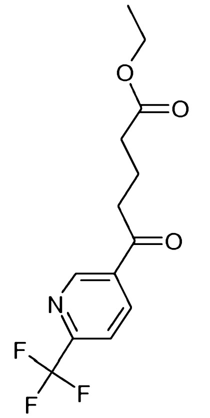
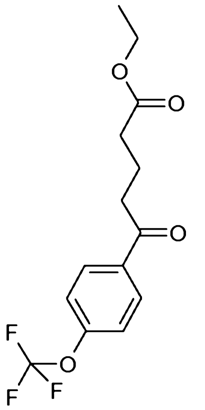
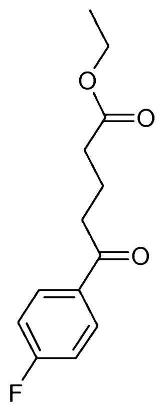
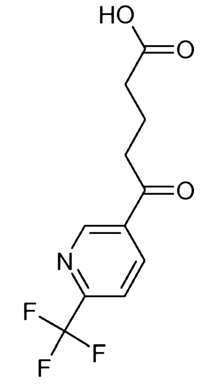
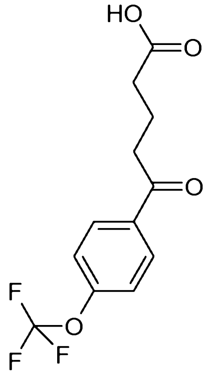
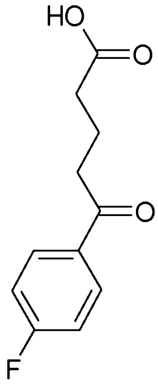
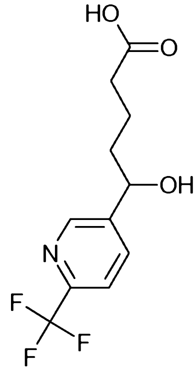
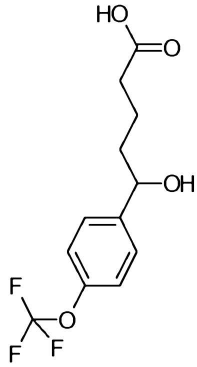
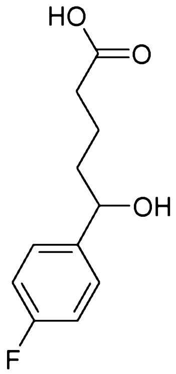


A suspension of Intermediate 5a (11.5 g, 55.76 mmol) in 250 ml of water was cooled to 10°. Then, potassium hydroxide (7.82 g, 139.4 mmol) and sodium borohydride (1.83 g, 48.51 mmol) were added and the reaction mixture was allowed to reach room temperature and stirred for 2h. 13 ml of a 12M aqueous hydrochloric acid was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum to give the crude product (11 g, 52.82 mmol).

The following intermediates were synthesized in analogy to Intermediates 4a, 5a and 6a.

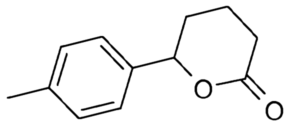
synthesis in analogy to intermediate 4a				*synthesis in analogy to intermediate 5a*		*synthesis in analogy to intermediate 6a*	
Starting Grignard	**Source/Reference**	**Keto-ester Intermediate**	**STRUCTURE**	**Keto-acid Intermediate**	**STRUCTURE**	**Hydroxy-acid Intermediate**	**STRUCTURE**
4-((Trifluoro-methyl)-phenyl)-magnesium bromide	WO2009/73203	4b		5b		6b	

Phenyl magnesium bromide	Commercially available	4c		5c		6c	
4-Chloro-phenyl magnesium bromide	Commercially available	4d		5d		6d	
3-Tolyl-magnesium bromide	Commercially available	4e		5e		6e	
3-((Trifluoro-methyl)-phenyl)-magnesium bromide	WO2009/73203	4f		5f		6f	

Grignard reagent	(6-(Trifluoro-methyl)pyridin-3-yl)magnesium bromide	4-((Trifluoro-methoxy)-phenyl)-magnesium bromide	4-Fluoro-phenyl-magnesium bromide
Source	*)	Commercially available	Commercially available
	4g	4h	4i
			
	5g	5h	5i
			
	6g	6h	6i
			

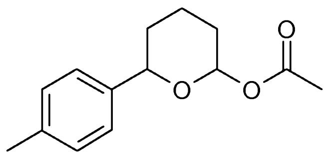
***)** 6-(Trifluoro-methyl)pyridin-3-yl)magnesium bromide was prepared by adding 5 ml of dry tetrahydrofurane and 0.061 ml (0.061 mmol) of a 1M solution of diisobutyl aluminium hydride in hexane to magnesium turnings (3.9 g, 160 mmol) and of lithium chloride (6.27 g, 148 mmol. The reaction mixture was stirred at 0°C for 5 min, then a solution of of (6-(trifluoro-methyl)pyridin-3-yl)-bromide (7.5g, 32.2 mmol) in 30 ml of dry tetrahydrofurane was added dropwise. The reaction mixture was allowed to reach room temperature, stirred for 30 min and used directly.

Intermediate 7a



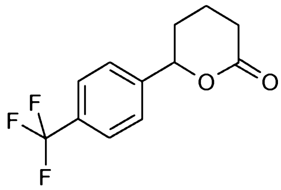
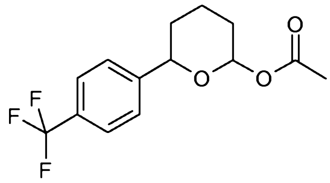
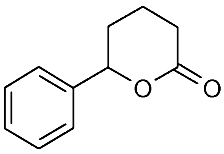
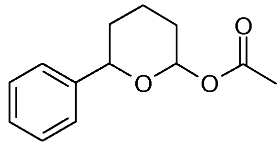
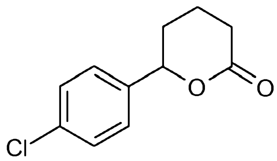
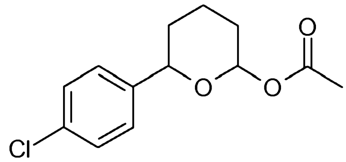
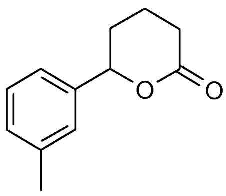
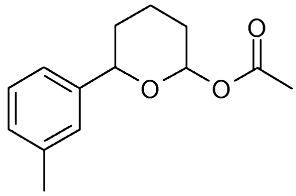
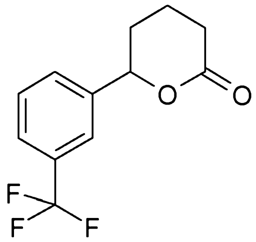
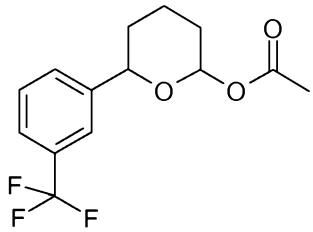
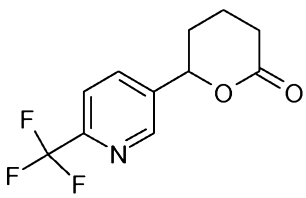
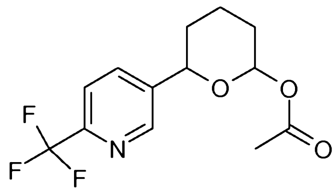
Intermediate 6a (6 g, 28.81 mmol) was dissolved in 100 ml of dichloromethane. 1.5 ml of trifluoroacetic acid was added and the reaction mixture was stirred at room temperature for 18h. The reaction mixture was diluted with 50 ml of dichloromethane and washed with 50 ml of a saturated aqueous sodium bicarbonate solution and water. The organic layer was dried over sodium sulfate and removed under vacuum to give the desired product (4.38 g (23.0 mmol).

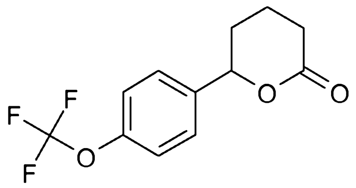
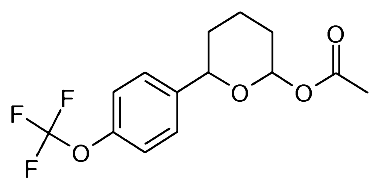
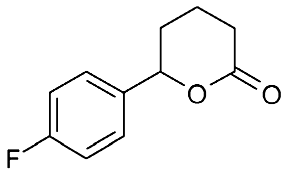
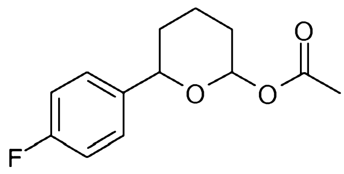
Intermediate 8a



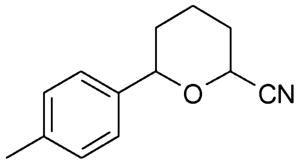
A solution of intermediate 7a (4.38 mg, 3,94 mmol) in 110 ml of dichloromethane was cooled to -78°C. Then, a 1M solution of of diisobutylaluminiumhydride (46.15 ml, 46.15 mmol) in dichloromethane was added dropwise. The reaction mixture was stirred at -78°C for 120 min. The conversion into the lactol intermediate was confirmed by GC-MS analysis of a sample of the reaction mixture treated with water and extracted with dichloromethane. 100 ml of methanol was added at -78°C and the reaction mixture was allowed to reach room temperature. The reaction mixture was concentrated under vacuum and the crude product obtained was triturated with ethyl ether. The precipitate was filtered off and washed with ethyl ether. The organic layer was removed under vacuum to give the crude lactol (4.4g, 22.9 mmol). The lactol was dissolved in 80 ml of dry dichloromethane and cooled to 0°C. Then triethylamine (4.96 ml, 34.33 mmol), acetic anhydride (2.54 ml, 27.46 mmol) and 4-dimethylaminopyridine (279.59 mg, 2.29 mmol) were added. The reaction mixture was allowed to reach room temperature and stirred for 1h. A saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane. The organic phase was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (Biotage SP1 cartridge 50g, eluent: cyclohexane/ethyl acetate=95/5) to give desired product (4 g, 17.1 mmol).

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

synthesis in analogy to intermediate 7a			*synthesis in analogy to intermediate 8a*	
Starting Hydroxy-acid Intermediate	**Lactone Intermediate**	**STRUCTURE**	**Lactol-acetate Intermediate**	**STRUCTURE**
6b	7b		8b	
6c	7c		8c	
6d	7d		8d	
6e	7e		8e	
6f	7f		8f	
6g	7g		8g	

6h	7h		8h	
6i	7i		8i	

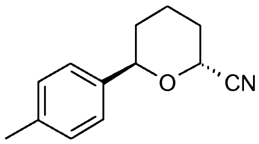
<u>Intermediate 9a</u>



Trimethylsilylcyanide (0.52 ml, 4.16 mmol) and borontrifluoride etherate (0,27 ml, 2,22 mmol) were added to a solution of Intermediate 8a (650 mg, 2,77 mmol) in 50 ml of acetonitrile under nitrogen atmosphere at room temperature.The reaction mixture was stirred for 18h. The reaction mixture was concentrated under vacuum to give the desired product (mixture of diastereoisomers).

GC/MS (method 3A) R_t = 10.47 min and 10.68 min (diastereoisomeric mixture, ratio trans/cis = 8/2)

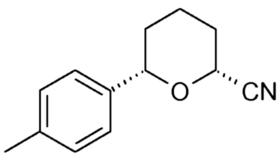
<u>Intermediate 10a</u>



Intermediate 9a was purified by flash chromatography (Biotage SP1 cartridge 25g, eluent: cyclohexane/ethyl acetate=99/1). 400 mg of diastereomerically pure trans stereoisomer was obtained (racemate, relative configuration assigned by NMR).

GC/MS (method 3A) R_t = 10.47 min

<u>Intermediate 11a</u>

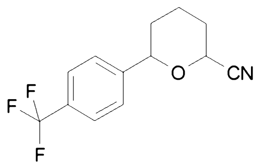
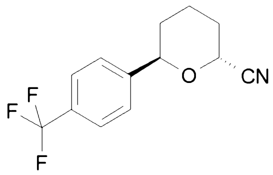
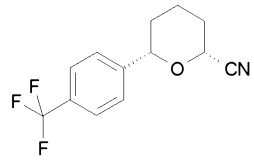
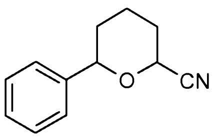
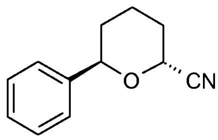
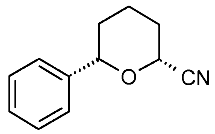
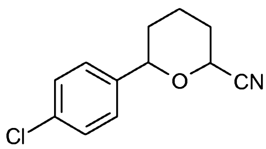
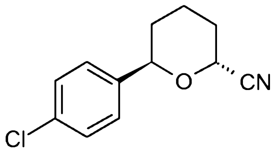
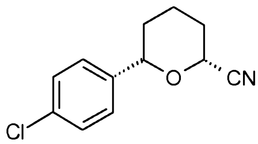
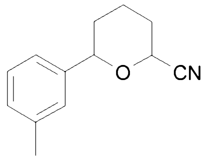
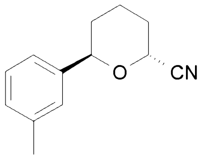
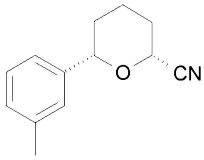


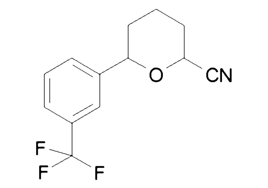
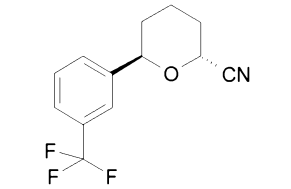
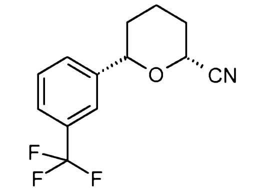
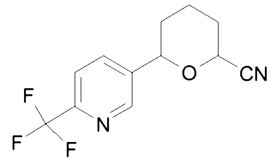
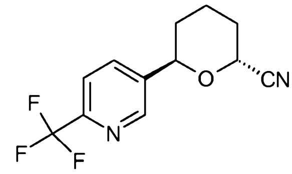
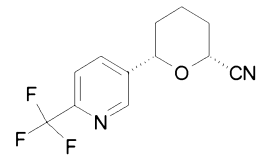
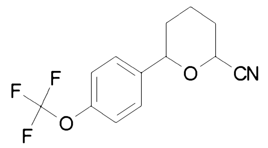
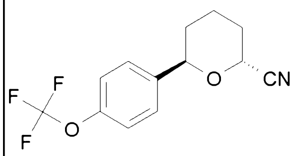
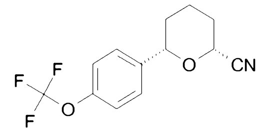
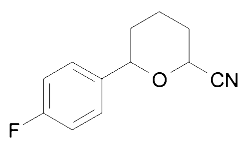
Further elution of the column gave 100 mg of the diastereomerically pure cis stereoisomer (racemate, relative configuration assigned by NMR).

GC/MS (method 3A) R_t = 10.68 min

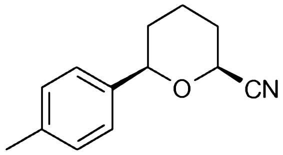
Intermediate 11a was also obtained by epimerization of Intermediate 10a: Intermediate 10a (3.2 g, 15 mmol) was dissolved in 40 ml of tetrahydrofurane. Potassium tert-butoxide (178 mg, 1 mmol) was added and the reaction mixture was stirred at room temperature for 0.5h. The solid was removed by filtration and the reaction mixture was concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1 cartridge 50g, eluent: cyclohexane/ethyl acetate=99/1). 1.45 g of the desired cis diastereoisomer was obtained.

The following intermediates were synthesized in analogy to Intermediates 9a, 10a and 11a.

synthesis in analogy to intermediate 9a			*synthesis in analogy to intermediate 10a*		*synthesis in analogy to intermediate 11a*	
Starting Lactol-acetate Intermediate	**Intermediate**	**STRUCTURE**	**Intermediate**	**STRUCTURE**	**Intermediate**	**STRUCTURE**
8b	9b		10b		11b	
8c	9c		10c		11c	
8d	9d		10d		11d	
8e	9e		10e		11e	

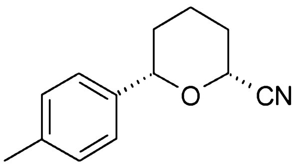
8f	9f		10f		11f	
8g	9g		10g		11g	
8h	9h		10h		11h	
8i	9i					

Intermediate 12a



Racemic Intermediate 11a (1.17 g, 2.06 mmol) was separated by chiral HPLC (semi-preparative column). 400 mg (1.99 mmol) were obtained as single stereoisomer.
Chiral HPLC (method 2Ia isocratic): R_t = 8.74 min

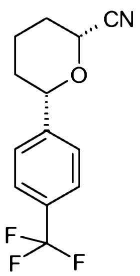
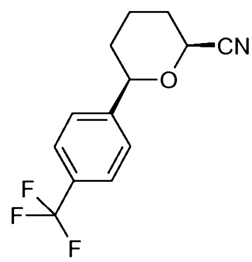
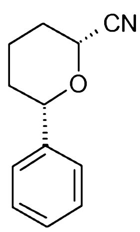
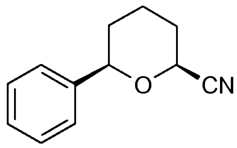
Intermediate 13a

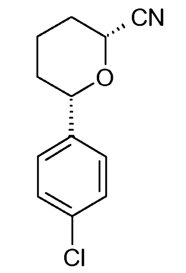
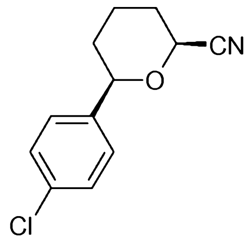
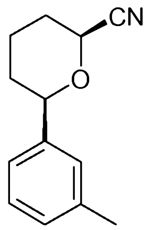
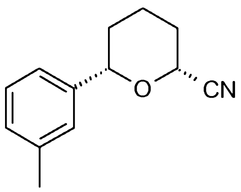
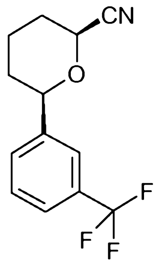
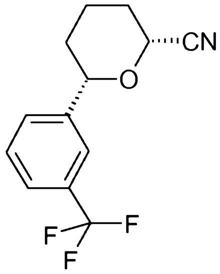
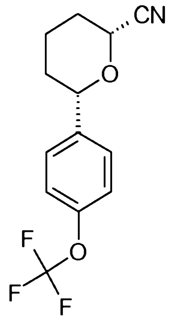
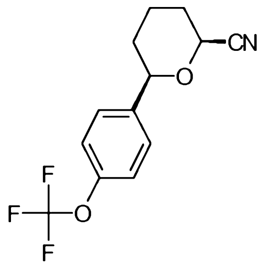


Further elution of the column gave 390 mg (1.94) of the corresponding single enantiomer.
Chiral HPLC (method 2Ia isocratic): R_t = 9.06 min
Absolute stereochemistry was determined by X-ray crystallography :
Absolute stereochemistry was derived from the refinement of anomalous dispersion data. While an unambiguous assignment is not possible due to the lack of heavy atoms, the Flack parameter gave a clear tendency toward the indicated chiral configuration.

Crystal Data: C_{13} H_{15} N_1 O_1 M_r = 201.26, orthorhombic, $P2_12_12_1$, a=8.0519(16)Å, b=11.185(2)Å, c=12.637(3)Å, V = 1138.2(4)Å^3, Z = 4, D_x = 1.175g/cm^3, l = 1.542 Å , m = 0.58mm^{-1}, F(000) = 423, T = 100(1) K. Data Collection: 12235 measured reflections, 1888/1130 unique, Rint= 0.079. Refinement: 138 parameters; hydrogen atoms were included as riding atoms, S =1.02, R1 = 0.052 for 1393 reflections with Fo > 4sig(Fo), wR = 0.128 (Weight w=1/[s^2(Fo^2)+(0.0864P)^2+0.0P] where P=(Fo^2+2Fc^2)/3, largest difference peak: 0.31 e/Å^3; largest difference hole -0.22 e/Å^3, Flack= 0.2(5).

The following intermediates were separated in analogy to Intermediates 12a and 13a.

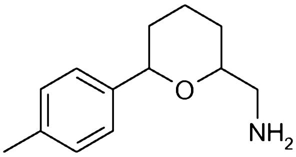
Starting syn-racemate	Chiral HPLCMethod	First Single syn-stereoisomer	R_t (min)	STRUCTURE	Second Single syn-stereoisomer	R_t (min)	STRUCTURE	Stereochemistry
11b	2Ia	12b	13.25		13b	14.33		Absolute stereochemistry as shown*
11c	2J	12c	9.94		13c	10.84		relative stereochemistry cis

11d	2K	12d	9.09		13d	9.76		relative stereochemistry cis
11e	2Ib	12e	7.23		13e	8.24		relative stereochemistry cis
11f	2K	12f	6.03		13f	6.67		relative stereochemistry cis
11h	2Ka	12h	13.65		13h	14.53		relative stereochemistry cis

*Absolute stereochemistry for intermediate 12b was derived from the refinement of anomalous dispersion data for Intemediate 12b. While an unambiguous assignment is not possible due to the lack of heavy atoms, the Flack parameter gave a clear tendency toward the indicated chiral configuration.

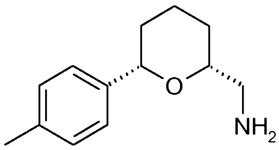
Crystal Data: C_{13} H_{12} N_1 O_1 F_3, M_r =255.24, orthorhombic, $P2_12_12_1$, a=7.5726(15)Å, b=11.053(2)Å, c=14.173(3)Å, V = 1186.3(4)Å^3, Z = 4, D_x = 1.429g/cm^3, l = 1.542 Å, m = 1.061mm^{-1}, F(000) = 528, T = 100(1) K. Data Collection: 8980 measured reflections, 1900/1131 unique, Rint= 0.045. Refinement: 164 parameters; hydrogen atoms were included as riding atoms, S =1.10, R1 = 0.065 for 1710 reflections with Fo > 4sig(Fo), wR = 0.167 (Weight w=1/[$s^2(Fo^2)+(0.1147P)^2+1.0917P$] where P=($Fo^2+2Fc^2$)/3, largest difference peak: 0.43 e/Å^3; largest difference hole -0.39 e/Å^3, Flack= 0.2(3).

<u>Intermediate 14a</u>



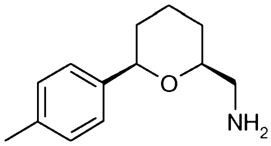
Intermediate 9a was dissolved in 20 ml of tetrahydrofurane, a 1M solution of borane-tetrahydrofurane complex (3.28 ml, 3.28 mmol) was added and the reaction mixture was stirred at room temperature for 18h. 20 ml of a saturated aqueous sodium bicarbonate solution and 50 ml of dicholometane were added. The organic layer was dried over magnesium sulfate and concentrated under vacuum. 90 mg (0.44 mmol) of the desired product were obtained.

<u>Intermediate 15a</u>



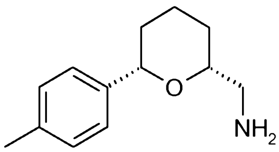
was synthesized in analogy to Intermediates 14a starting from intermediate 11a

<u>Intermediate 16a</u>



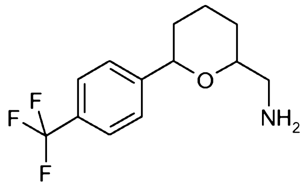
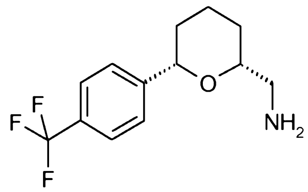
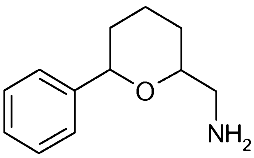
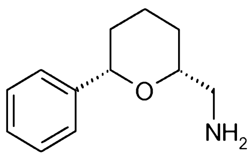
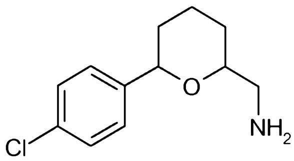
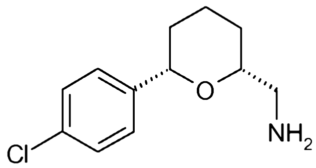
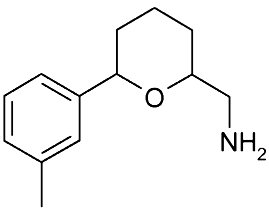
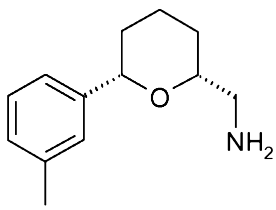
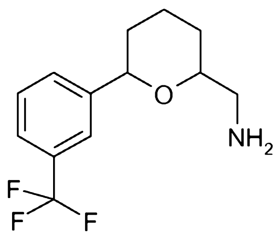
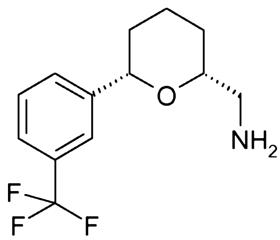
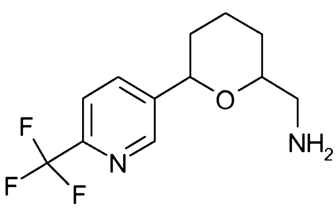
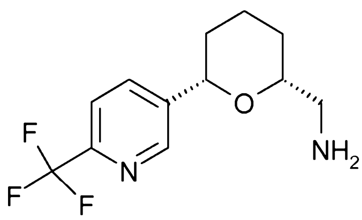
was synthesized in analogy to Intermediates 14a starting from intermediate 12a. Absolute stereochemistry known.

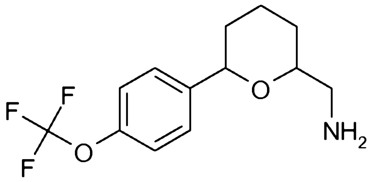
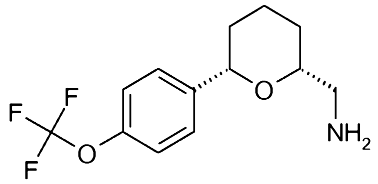
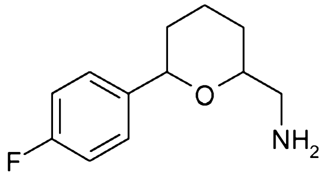
<u>Intermediate 17a</u>



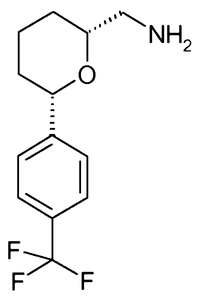
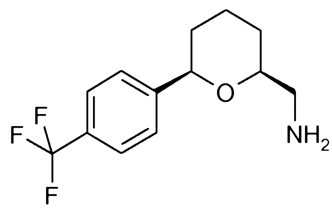
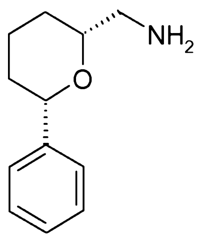
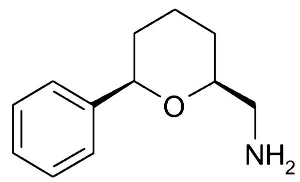
was synthesized in analogy to intermediate 14a starting from intermediate 13a. Absolute stereochemistry known.

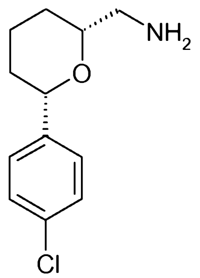
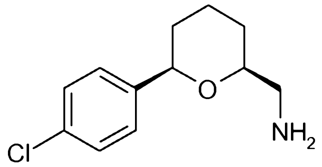
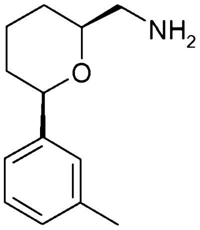
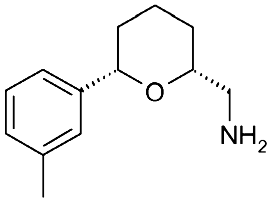
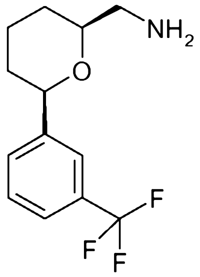
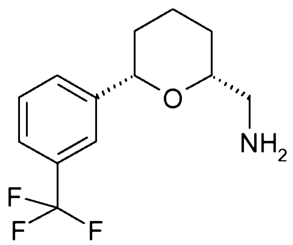
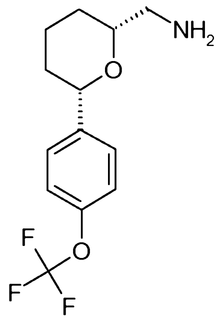
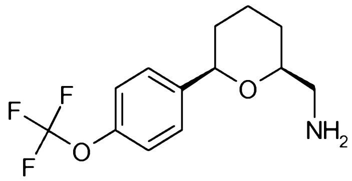
The following intermediates were synthesized in analogy to Intermediates 14a and 15a.

synthesis in analogy to intermediate 14a			*synthesis in analogy to intermediate 15a*		
Starting Intermediate	**Intermediate**	**STRUCTURE**	**Starting intermediate**	**Intermediate**	**STRUCTURE**
9b	14b		11b	15b	
9c	14c		11c	15c	
9d	14d		11d	15d	
9e	14e		11e	15e	
9f	14f		11f	15f	
9g	14g		11g	15g	

9h	14h		11h	15h	
9i	14i				

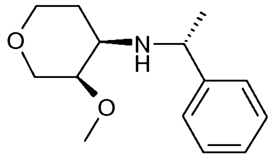
The following intermediates were synthesized in analogy to Intermediates 16a and 17a.

synthesis in analogy to intermediate 16a			*synthesis in analogy to intermediate 17a*			
Starting Intermediate	**Intermediate**	**STRUCTURE**	**Starting intermediate**	**Intermediate**	**STRUCTURE**	**Stereochemistry**
12b	16b		13b	17b		absolute stereochemistry as shown
12c	16c		13c	17c		relative stereochemistry cis *

12d	16d		13d	17d		relative stereochemistry cis
12e	16e		13e	17e		relative stereochemistry cis
12f	16f		13f	17f		relative stereochemistry cis
12h	16h		13h	17h		relative stereochemistry cis

* Shown stereochemistry corresponds to stereoselective synthesis of intermediate 39d using (S,S)-teth-TsDpen ruthenium chloride (Johnson Matthey Catalysts).

Intermediate 18a

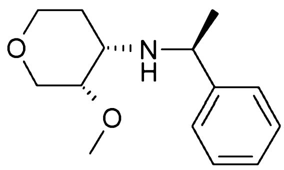


3-Methoxy-tetrahydro-pyran-4-one* (1 g, 7.68 mmol), commercially available (R)-(+)-1-phenylethylamine (0.99 ml, 7.68 mmol) and Raney-Nickel (200 mg) in 10 ml of dry ethanol were stirred under a hydrogen atmosphere (5 bar) for 15 days. The reaction mixture was diluted with 20 ml of methanol and 20 ml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

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

* Tetrahedron Letters, **2005** , 447 - 450

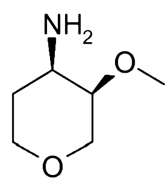
Intermediate 18b



was synthesised in analogy to Intermediate 18a, starting from 3-Methoxy-tetrahydro-pyran-4-one and commercially available (S)-(-)-1-phenylethylamine (diastereoisomeric purity confirmed and relative cis configuration assigned by NMR).

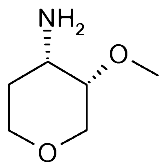
GC/MS (method 3B) R_t = 35.04 min

Intermediate 19a



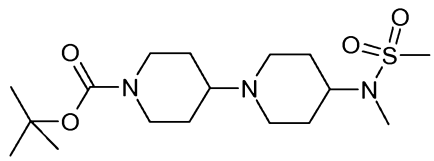
Intermediate 18a (1.18 g, 5.01 mmol), Pd/C 10% (200 mg) and acetic acid (0.3 ml, 5.01 mmol) in 20 ml of methanol were stirred under a hydrogen atmosphere (5 bar) for 18h. The reaction mixture was diluted with 20 ml of methanol, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum.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

Intermediate 19b



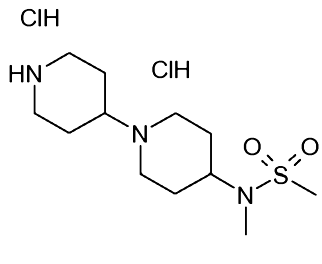
was synthesised in analogy to Intermediate 19a, starting from Intermediate 18b.

Intermediate 20a



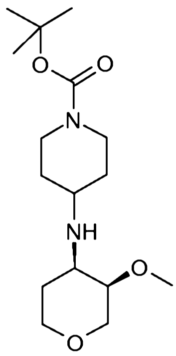
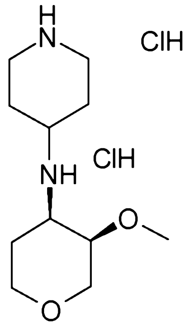
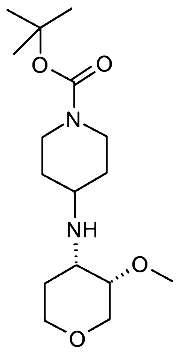
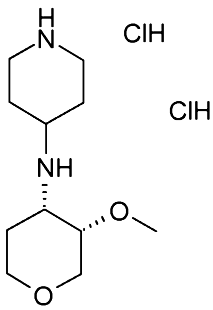
N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (11 g, 47.91 mmol; WO2009/47161) was suspended in 200 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (17,12 ml, 96.17 mmol) and commercially available 1-(tert-butoxycarbonyl)-piperidin-4-one (9.58 g, 48.08 mmol) were added and the reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (12.23 g, 57.50 mmol) was added and the reaction mixture was stirred at room temperature for 72h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution.
The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1; silica gel cartridge: 65i; eluent: ethyl acetate/methanol=50/50%) to obtain 7.2 g (19.2 mmol) of the desired compound.

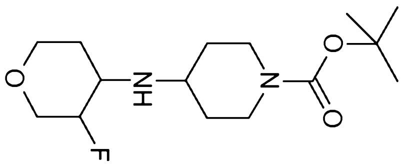
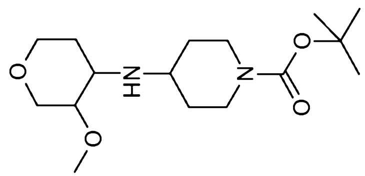
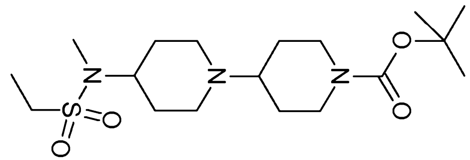
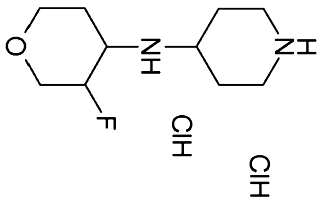
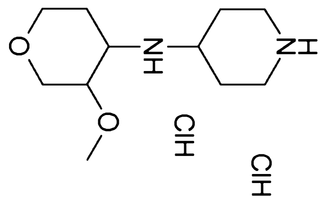
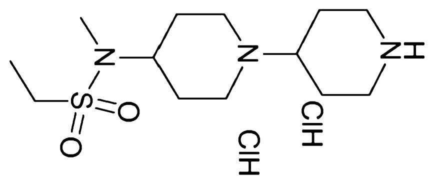
Intermediate 21a

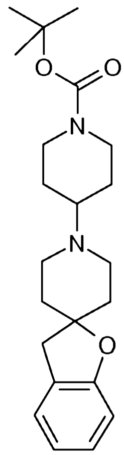
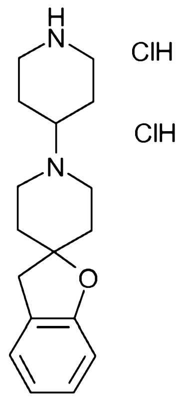


Intermediate 20a (7.2 g, 19.2 mmol) was suspended in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (48 ml, 192 mmol) in 1,4-dioxane was added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 6.3 g (18 mmol) of the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

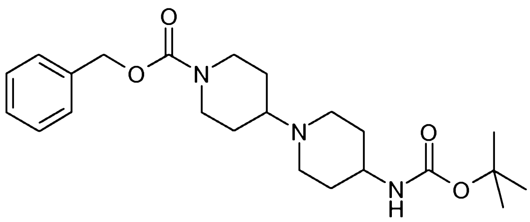
The following intermediates were synthesized in analogy to Intermediates 20a and 21a.

synthesis in analogy to intermediate 20a						*synthesis in analogy to intermediate 21a*	
Starting intermediate	**Source/Reference**	**Starting intermediate**	**Source/Reference**	**Carbamate Intermediate**	**STRUCTURE**	**Diamino Intermediate**	**STRUCTURE**
1-(tert-butoxycarbonyl)-4-oxopiperidine	commercially available	19a	-	20b		21b	
1-(tert-butoxycarbonyl)-4-oxopiperidine	commercially available	19b	-	20c		21c	

3-Fluoro-tetrahydro-pyran-4-one	3-Methoxy-tetrahydro-pyran-4-one	1-(tert-butoxycarbonyl)-4-oxopiperidine
WO2003/93231	Tetrahedron Letters, **2005**, 447 - 450	Commercially available
4-amino-piperidine-1-carboxylic acid tert-butyl-ester	4-amino-piperidine-1-carboxylic acid tert-butyl-ester	N-methyl-N-piperidin-4-yl-ethanesulfonamide
Commericlly available	Commericlly available	Prepared in analogy to N-methyl-N-piperidin-4-yl-methanesulfonamide starting from ethansulfonyl chloride (see intermediate 20a)
20f	20e	20d
		
21f	21e	21d
		

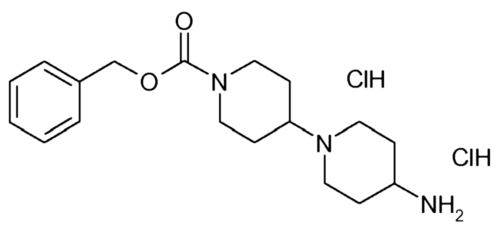
3H-spiro[1-benzofuran-2,4'-piperidine]	Commericlly available	1-(tert-butoxycarbonyl)-piperidin-4-one	Commericlly available	20g		21g	

<u>**Intermediate 22**</u>



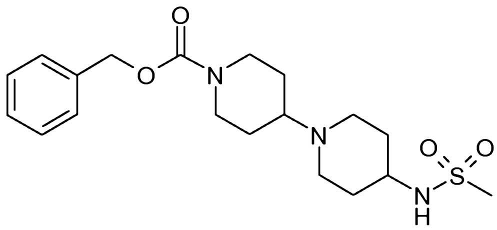
Commercially available piperidin-4-yl-carbamic acid tert-butyl ester (6 g, 30 mmol) and commercially available 1-(benzyloxycarbonyl)-4-oxopiperidine (9.6 g, 48 mmol) were dissolved in 50 ml of dichloromethane and the reaction mixture was stirred at room temperature for 30 min; sodium triacetoxyborohydride (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.

<u>**Intermediate 23**</u>



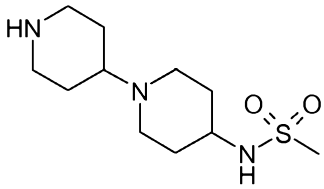
A solution of intermediate 22 (8.4 g, 20 mmol) in 150 ml of 1,4-dioxane was cooled to 0°C. Then, 12.6 ml (50 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise; the reaction mixture was allowed to warm to room temperature and stirred overnight. The precipitate was filtered off and dried at 50°C under vacuum to give the desired product (6g, 15 mmol).

Intermediate 24



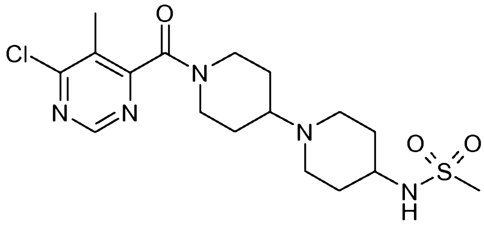
Intermediate 23 (6.0 g, 15 mmol) was suspended in 55 ml of dichloromethane; triethylamine (6.43 ml, 46 mmol) was added and the reaction mixture was cooled to 0°C and stirred for 30 min. Methanesulfonyl chloride (1.43 ml, 18 mmol) in 5 ml of dichloromethane was added dropwise. The reaction mixture was 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 25



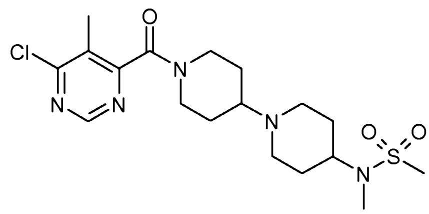
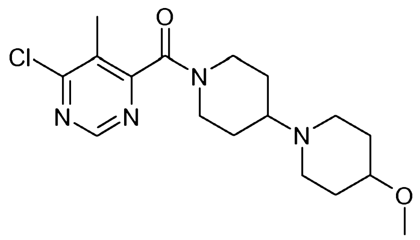
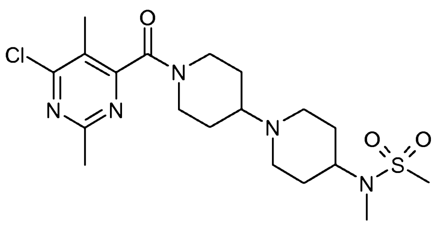
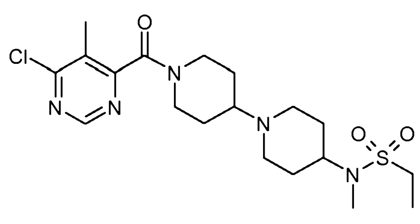
Intermediate 24 (5 g, 13 mmol) was dissolved in 50 ml of methanol; acetic acid (1.5 ml, 25.3 mmol) and Pd/C 10% (500 mg) were added in sequence and the reaction mixture was stirred under a hydrogen atmoshere (3 bar) at room temperature for 5 days. The reaction mixture was filtered on a celite pad and 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 desired product were obtained.

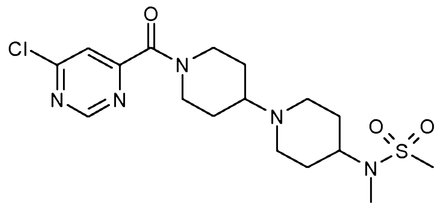
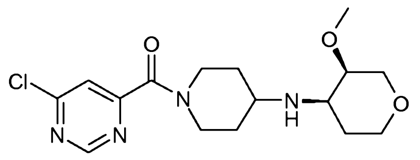
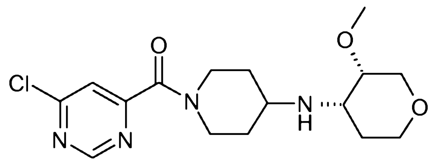
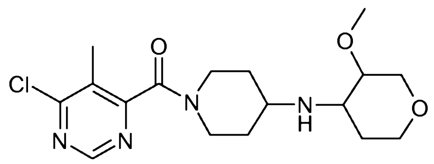
Intermediate 26a



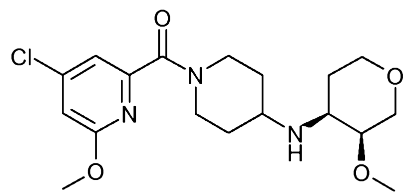
Intermediate 25 (1.1 g, 4.21 mmol) was suspended in 20 ml of dry dichloromethane, N,N-diisopropylethylamine (1.47 ml, 8.42 mmol) and DMF (137 µl, 1.67 mmol) were added and the reaction mixture was stirred under nitrogen atmosphere and cooled to 0°C. Intermediate 2a (812 mg, 4.21 mmol) in 5 ml of dichloromethane was added dropwise and the reaction mixture was allowed to warm 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.

The following intermediates were synthesized in analogy to Intermediate 26a.

Core Intermediate	**Piperidine Intermediate**	**Chloro-pyrimidine Intermediate**	**STRUCTURE**
2a	21a	26b	
2a	4-Methoxy-[1,4']bi piperidinyl (commercially available)	26c	
2b	21a	26d	
2a	21d	26e	

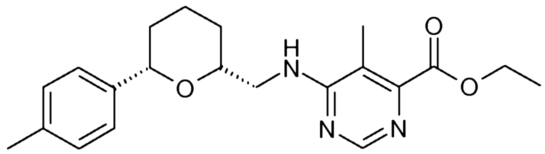
2c	21a	26f	
2c	21b	26g	
2c	21c	26h	
2a	21e	26i	

Intermediate 26j



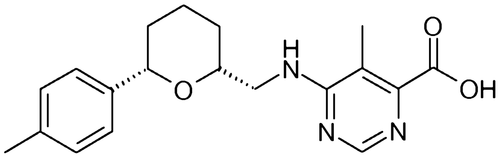
Intermediate 2e (55 mg, 267 µmol) was added to a solution of triethylamine (111 µl, 800 µmol) and Intermediate 21c (73 mg, 291 µmol) in 2.5 ml dichloromethane, and the reaction mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product (133 mg).

Intermediate 27a



Intermediate 3a (976 mg, 4.6 mmol) and N,N-diisopropylethylamine (0.9 ml, 5.24 mmol) were dissolved in 15 ml of dry 1,4-dioxane; intermediate 17a (430 mg, 2.09 mmol) was added and the reaction mixture was refluxed for 6h. The reaction mixture was cooled 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 and concentrated under vacuum. 770 mg (2.08 mmol) of the desired compound were obtained as crude product. Absolute stereochemistry known.

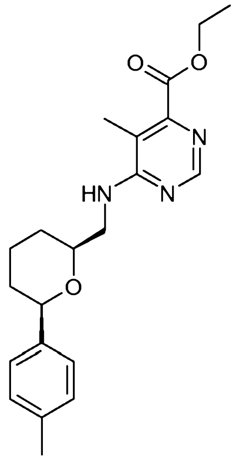
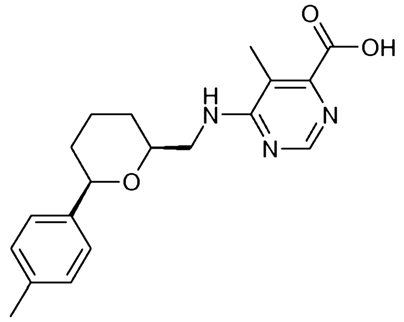
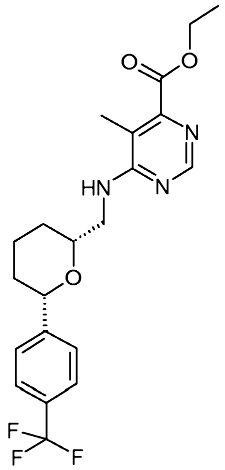
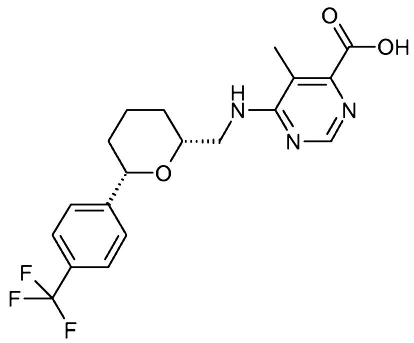
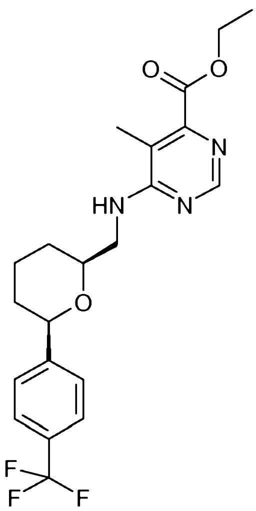
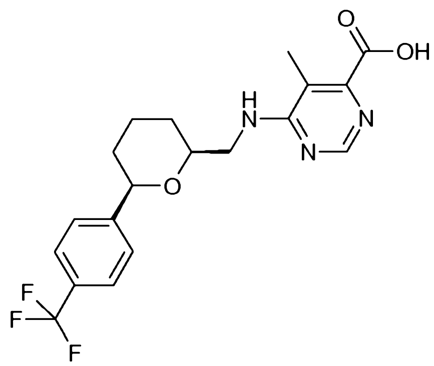
Intermediate 28a

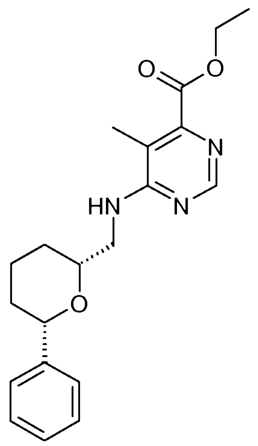
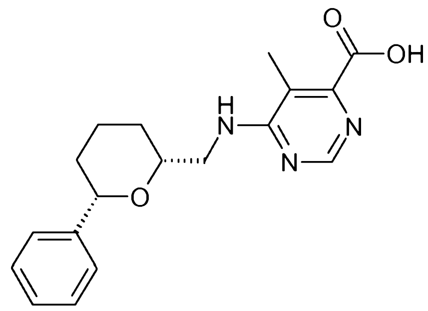
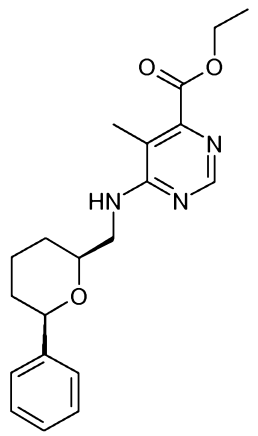
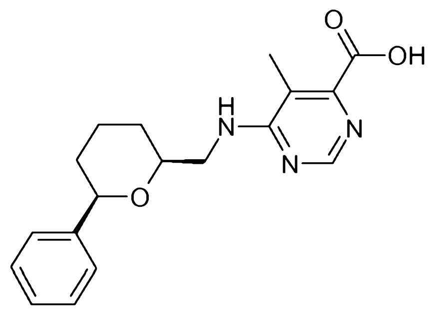
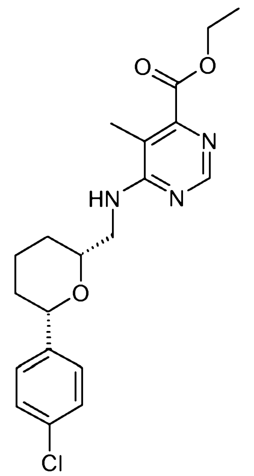
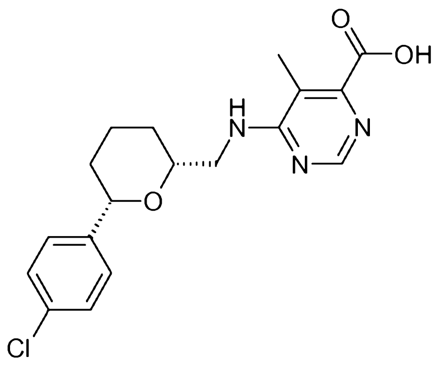


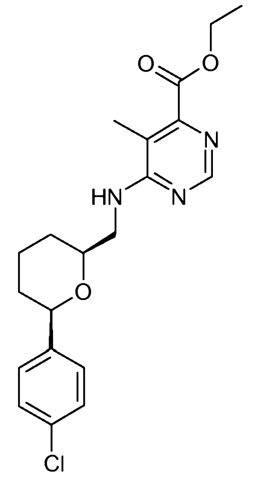
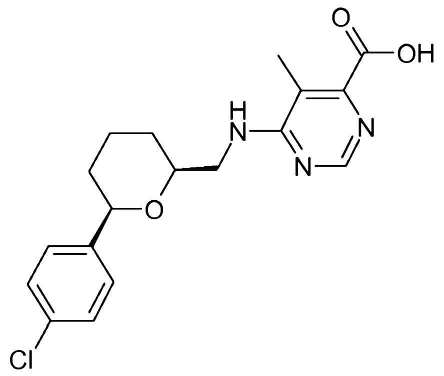
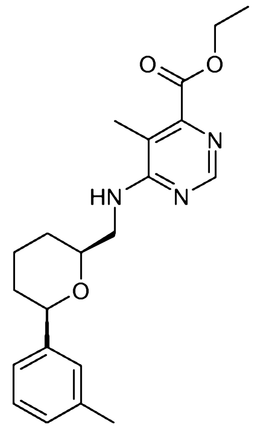
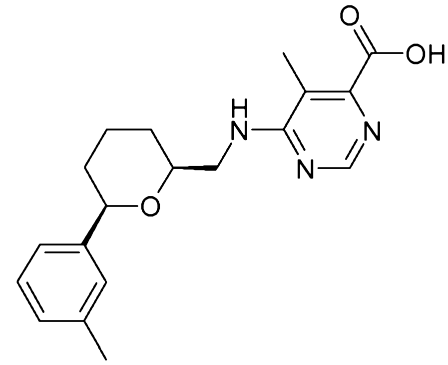
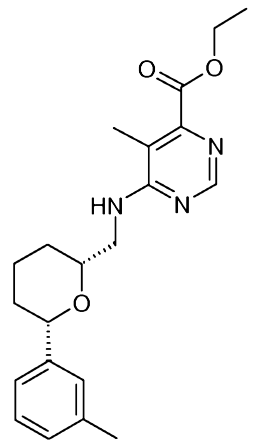
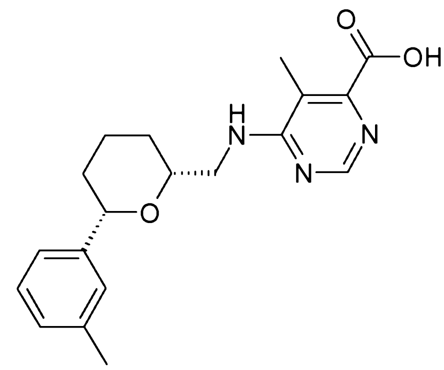
Intermediate 27a (770 mg, 2.08 mmol) was dissolved in 8 ml of tetrahydrofurane and a solution of LiOH (262 mg, 6.24 mmol) in 8 ml of water was added. The reaction mixture was stirred at 70°C for 1 hour and then concentrated under vacuum. 20 ml of water was added and the reaction mixture was acidified with 5 ml of a 4M solution of hydrochloric acid in water. The aqueous phase was extracted with dichloromethane (2x20ml). The organic phase was dried over sodium sulfate and removed under vacuum. 670 mg (1.96 mmol) of the desired product were obtained. Absolute stereochemistry known.

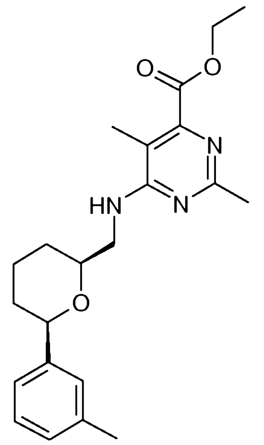
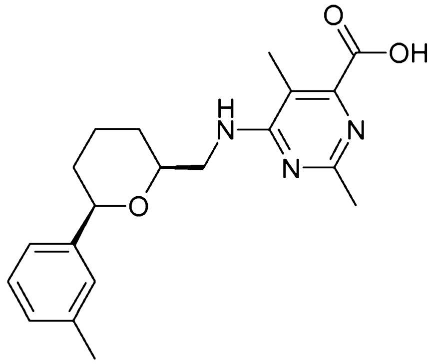
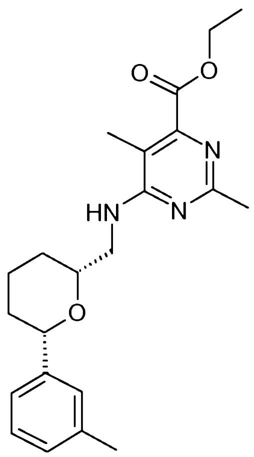
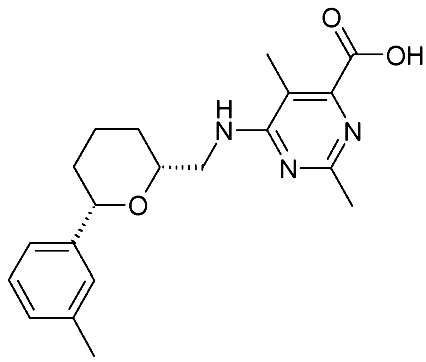
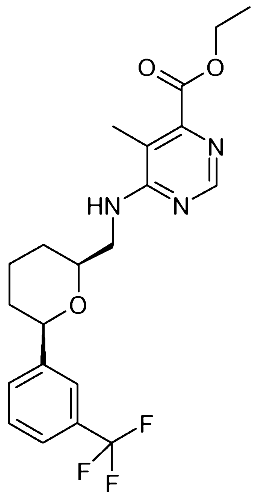
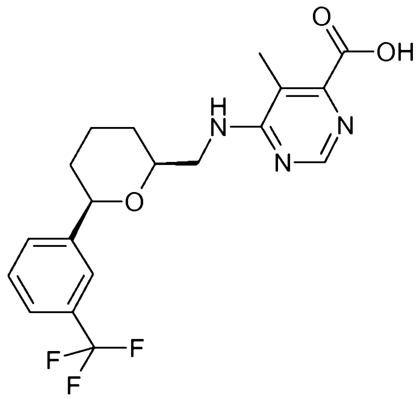
The following intermediates were synthesized in analogy to Intermediates 27a and 28a .

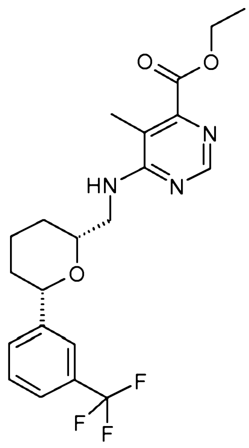
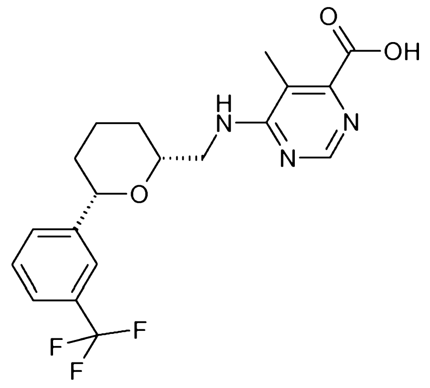
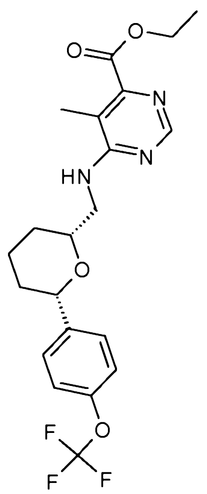
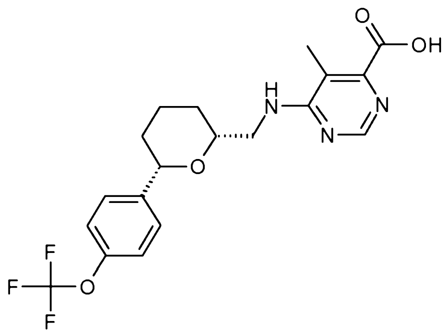
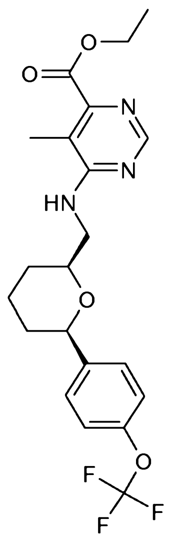
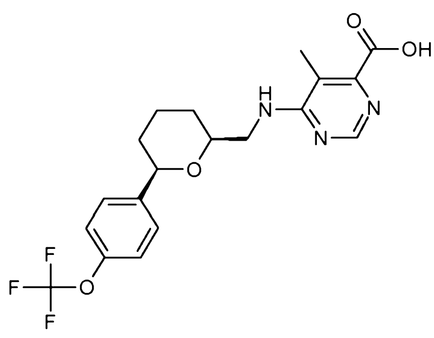
Synthesis in analogy to intermediate 27a				*Synthesis in analogy to intermediate 28a*		
Core Intermediate	**Amine**	**Ester Intermediate**	**STRUCTURE**	**Acid Intermediate**	**STRUCTURE**	**Stereochemistry**

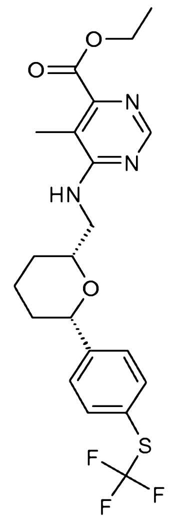
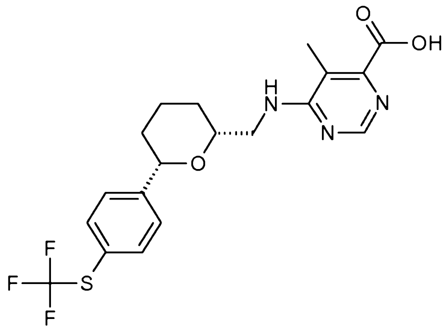
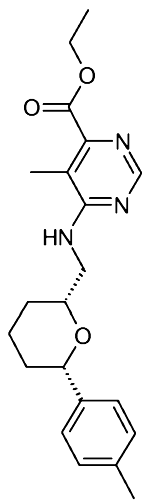
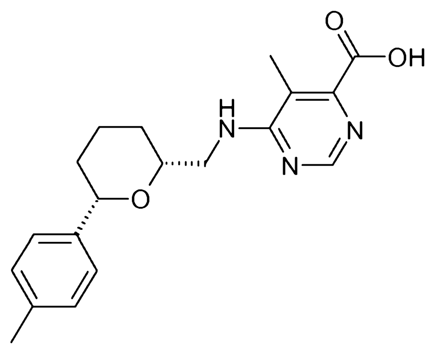
3a	16a	27b		28b		absolute streochemistry as shown
3a	16b	27c		28c		absolute stereochemistry as shown
3a	17b	27d		28d		absolute stereochemistry as shown

3a	16c	27e		28e		relative stereochemistry cis
3a	17c	27f		28f		relative stereochemistry cis
3a	16d	27g		28g		relative stereochemistry cis

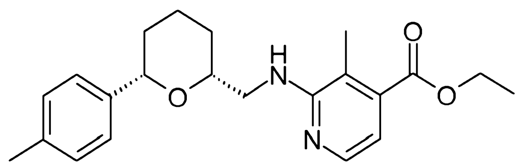
3a	17d	27h		28h		relative stereochemistry cis
3a	16e	27i		28i		relative stereochemistry cis
3a	17e	27j		28j		relative stereochemistry cis

3b	16e	27k		28k		relative stereochemistry cis
3b	17e	27l		28l		relative stereochemistry cis
3a	16f	27m		28m		relative stereochemistry cis

3a	17f	27n		28n		relative stereochemistry cis
3a	16h	27o		28o		relative stereochemistry cis
3a	17h	27p		28p		relative stereochemistry cis

3a	42	27pa		28pa		relative stereochemistry cis
3a	15a	27pb		28pb		relative stereochemistry cis

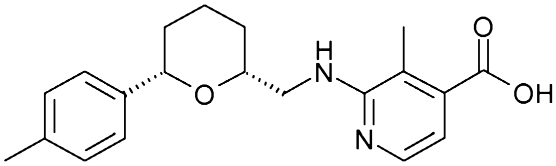
Intermediate 27q



Commercially available 2-chloro-3-methylpyridine-4-carboxylic acid ethyl ester (243 mg, 1.22 mmol), Intermediate 17a (250 mg, 1.22 mmol), palladium (II) acetate (27 mg, 0.12 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (379 mg, 0.61 mmol) and sodium tert-butoxide (163 mg, 1.07 mmol) were suspended in 20 ml of 1,2-dimethoxyethane and refluxed for 12h. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge:

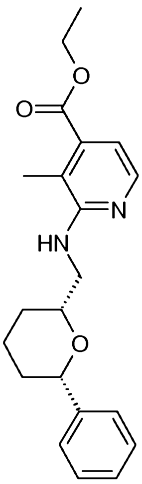
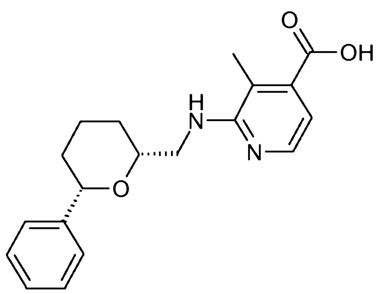
10g; eluent: cyclohexane/ethyl acetate=90/10%). 70 mg (0.19 mmol) of the desired product were obtained. Absolute stereochemistry known.

Intermediate 28q

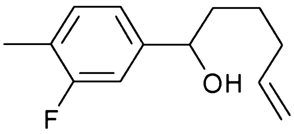


was synthesized in analogy to Intermediates 28a starting from intermediate 27q

The following intermediates were synthesized in analogy to Intermediates 27q and 28q.

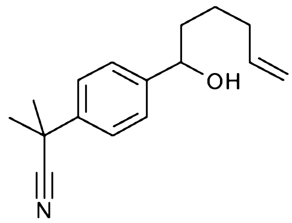
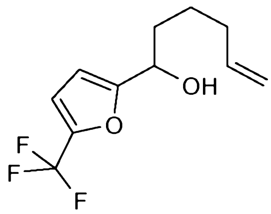
Synthesis in analogy to intermediate 27q				*Synthesis in analogy to intermediate 28q*		
Core Intermediate	**Amine**	**Ester Intermediate**	**STRUCTURE**	**Acid Intermediate**	**STRUCTURE**	**Stereochemistry**
3a	16c	27r		28r		relative stereochemistry cis

Intermediate 29a

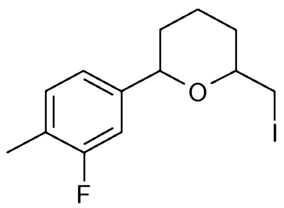


Commercially available 3-fluoro-4-methylbenzaldehyde (2.6g, 18.82 mmol) was dissolved in 30ml of tetrahydrofurane and the reaction mixture was cooled to -78°C under nitrogen atmosphere. 60 ml of a cooled 0.5 M solution of (pent-4-enyl)magnesium bromide (Liebigs Annalen der Chemie **1982,** 1478) was added and the reaction was stirred at -78°C for 1h. The reaction mixture was quenched with an saturated aqueous ammonium chloride solution and extracted with dichloromethane. The organic phase was separated, dried on sodium sulfate and concentrated under vacuum. 3.9 g of a crude oil were obtained.

The following intermediates were synthesized in analogy to intermediate 29a.

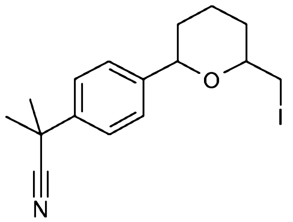
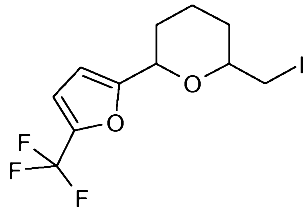
Aldehyde	**Source/Reference**	**Intermediate**	**STRUCTURE**
2-(4-formyl-phenyl)-2-proprionitrile	Commercially available	29b	
5-trifluoromethyl-furan-2-carbaldehyde	Commercially available	29c	

Intermediate 30a

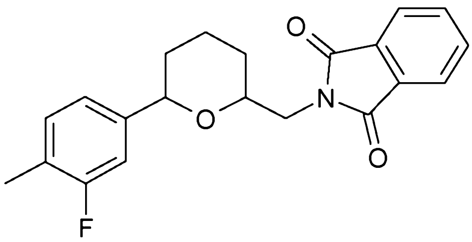


Sodium bicarbonate (4.72g, 56.18 mmol) was suspended in 100 ml of acetonitrile and, under nitrogen atmosphere, intermediate 29a (3.9g, 18.73 mmol) and iodine (14.26g, 56.18 mmol) were added. The reaction mixture was stirred at room temperature for 30 minutes, then a 10% water solution of sodium thiosulfate was added. The reaction mixture was extracted with diethyl ether and the organic phase was separated, dried on sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (SP1 SNAP cartridge 50g; eluent: cyclohexane/dichloromethane=95/5%). 2.5g (7.48 mmol) of the desired product were obtained.

The following intermediates were synthesized in analogy to intermediate 30a.

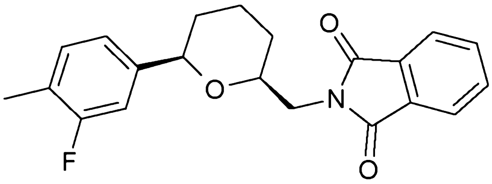
Starting intermediate	Intermediate	STRUCTURE
29b	30b	
29c	30c	

Intermediate 31a



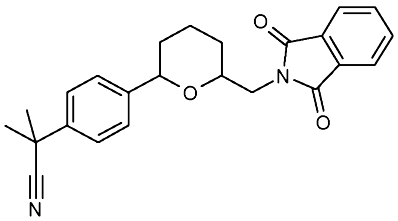
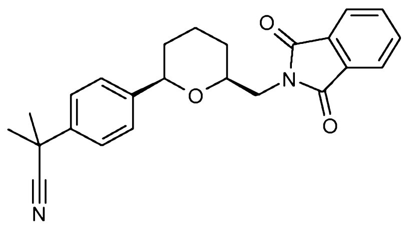
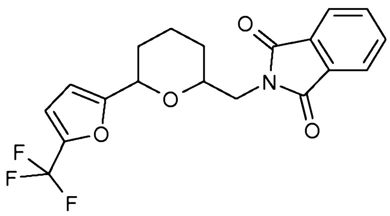
Intermediate 30a (2.5g, 7.48 mmol) was dissolved in 40 ml of DMF and, under nitrogen atmosphere, potassium phtalimide (1.66g, 8.98 mmol) was added. The reaction mixture was warmed to 90°C for 4h, then cooled to room temperature and diluted with 100 ml of a saturated aqueous sodium bicarbonate solution. The reaction mixture was extracted with diethyl ether and the organic phase was separated, dried on sodium sulfate and concentrated under vacuum. 2.2 g of the crude product were obtained,

Intermediate 32a

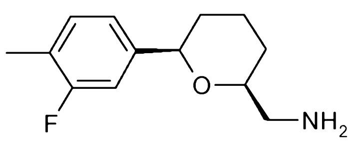


The crude product (2.2 g) was precipitated with 100 ml of a cyclohexane/ethyl acetate=50/50% solution and 1.8 g (5.06 mmol) of the desired cis racemate were obtained (stereochemistry assigned by 1H-NMR).

The following intermediates were synthesized in analogy to intermediate 31a and 32a.

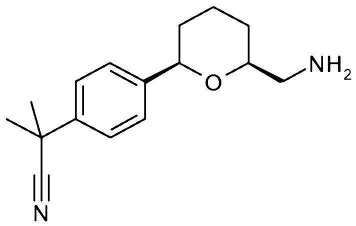
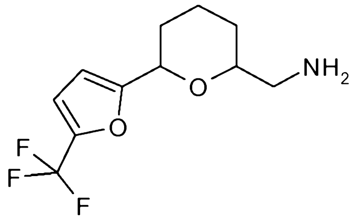
Synthesis in analogy to intermediate 31a			*Synthesis in analogy to intermediate 32a*	
Starting intermediate	**Intermediate**	**STRUCTURE**	**Intermediate**	**STRUCTURE**
30b	31b		32b	
30c	31c			

Intermediate 33a

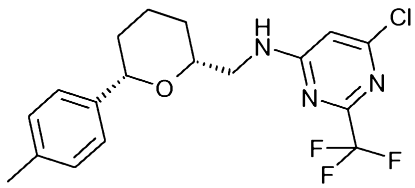


Intermediate 32a (200 mg, 0.57 mmol) was suspended in 5 ml of methanol and hydrazine hydrate (0.21 ml, 4.41 mmol) was added. The reaction mixture was stirred at room temperature for 2h, then it was concentrated under vacuum. The residue was treated with dichloromethane, the solid residue was filtered off and the filtrate was concentrated under vacuum to yield 120 mg of the crude amine.

The following intermediates were synthesized in analogy to intermediate 33a.

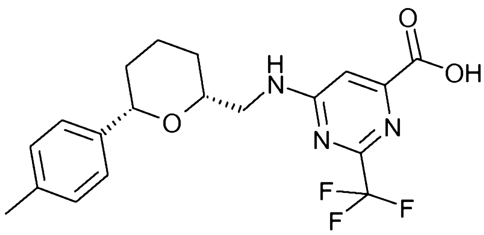
Starting intermediate	Intermediate	STRUCTURE
32b	33b	
31c	33c	

Intermediate 34



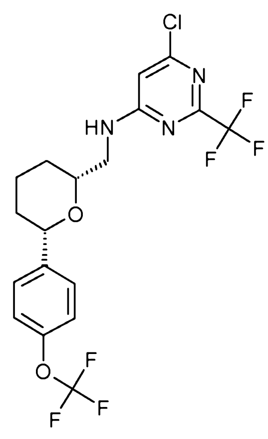
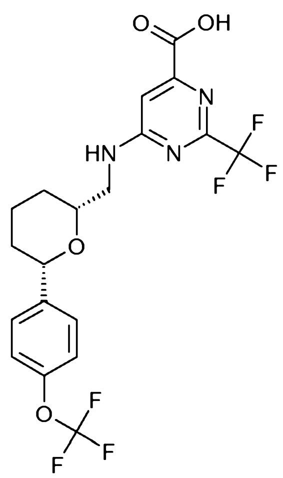
N,N-diisopropylethylamine (213 µl, 1.15 mmol) was added to a mixture of intermediate 15a (94 mg, 461 µmol) and commercially available 4,6-dichloro-2-trifluoromethyl-pyrimidine (100 mg, 461 µmol) in 2 ml NMP. The reaction mixture was heated in the microwave for 1 h at 120°C. The mixture was purified by reversed phase HPLC to give the desired product (95 mg).

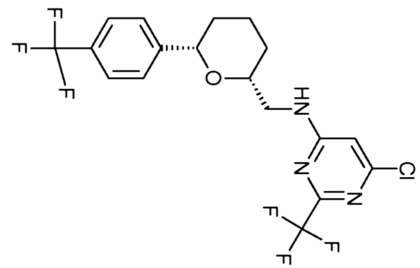
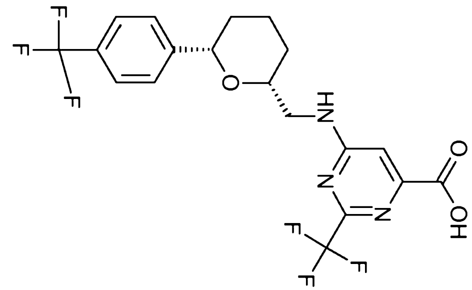
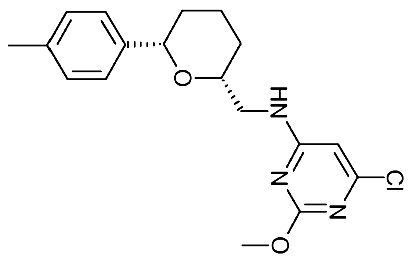
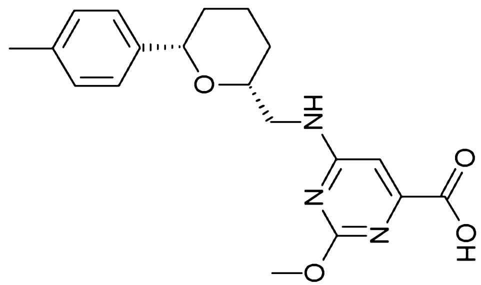
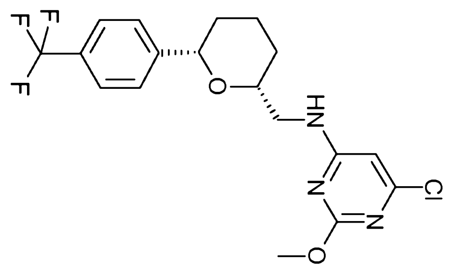
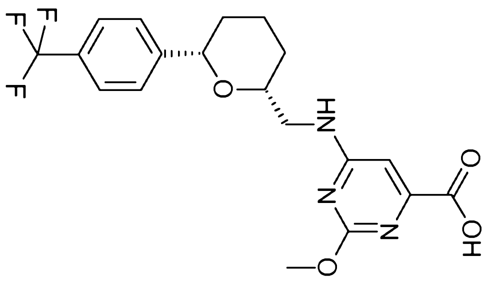
Intermediate 35

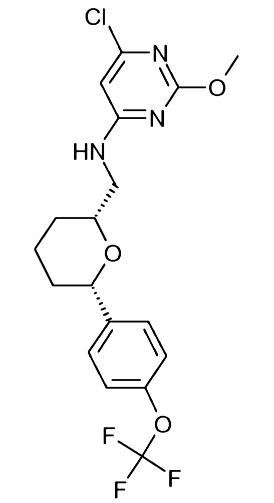
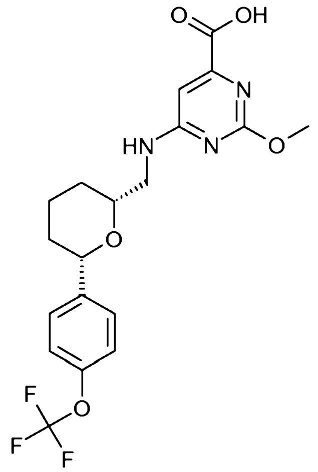
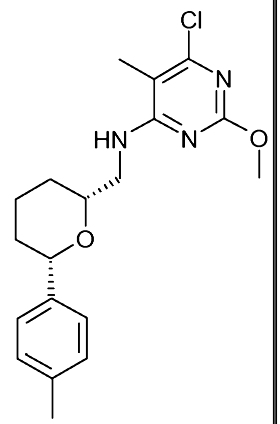
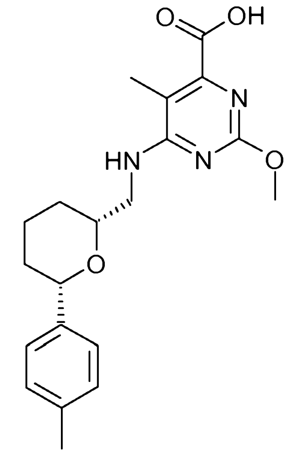
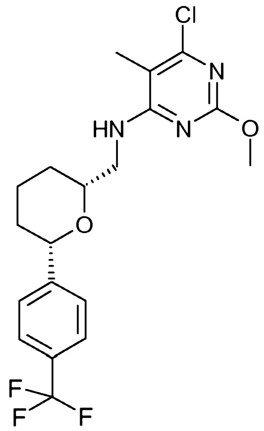
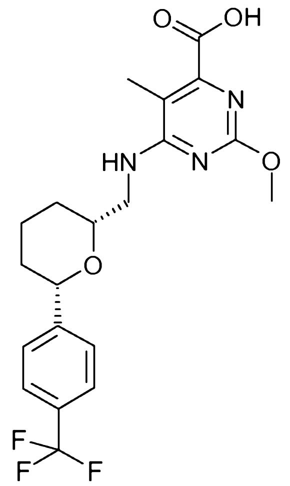


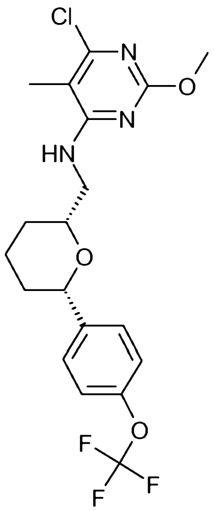
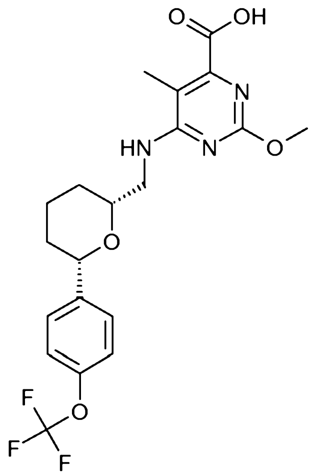
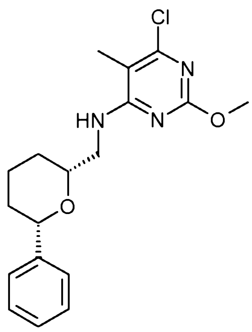
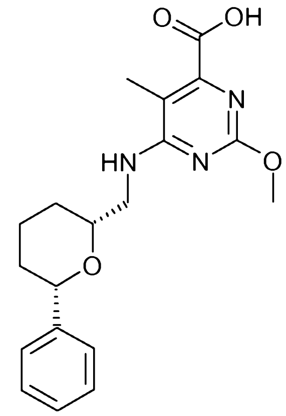
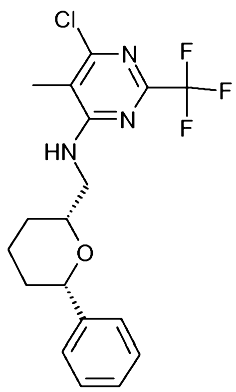
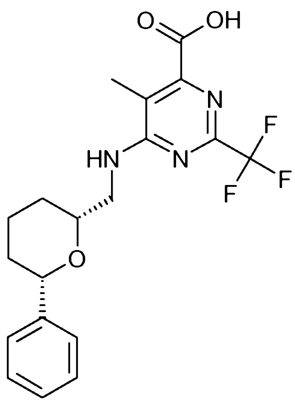
A mixture of intermediate 34 (95 mg, 246 µmol), palladium acetate (5.5 mg, 25 µmol), 1,1'-bis(diphenylphosphino)-ferrocene (13 mg, 25 µmol), sodium acetate (60 mg, 739 µmol) in 5 ml methanol and 5 ml DMF was stirred under a carbon monoxide atmosphere (5 bar) over night at 70°C. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase HPLC to give the corresponding ester (88 mg, 168 µmol).
Lithium hydroxide (28 mg, 672 µmol) was added to a solution of the ester (88 mg, 168 µmol) in 3 ml THF and 3 ml water. The reaction mixture was heated for 15 min at 100°C. Then, the solvent was removed in vacuum and the residue was purified by reversed phase HPLC to give the desired product (61 mg).

The following intermediates were synthesised in analogy to Intermediate 34 and 35.

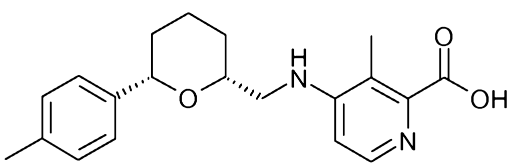
Synthesis in analogy to intermediate 34					*Synthesis in analogy to intermediate 35*		
Core Intermediate	**Source/Reference**	**Amine**	**Chloro Intermediate**	**STRUCTURE**	**Acid Intermediate**	**STRUCTURE**	**Stereochemistry**
4,6-dichloro-2-trifluoromethyl-pyrimidine	Commercially available	16h	34a		35a		relative stereochemistry cis

4,6-dichloro-2-trifluoromethyl-pyrimidine	Commercially available	16b	34b		35b		absolute streochemistry as shown
4,6-dichloro-2-methoxypyrimidine	Commercially available	17a	34c		35c		absolute streochemistry as shown
4,6-dichloro-2-methoxypyrimidine	Commercially available	16b	34d		35d		absolute streochemistry as shown

4,6-dichloro-2-methoxypyrimidine	Commercially available	16h	34e		35e		relative stereochemistry cis
2d	-	17a	34f		35f		absolute stereochemistry as shown
2d	-	16b	34g		35g		absolute streochemistry as shown

2d	-	16h	34h		35h		relative stereochemistry cis
2d	-	16c	34i		35i		relative stereochemistry cis
2f	-	16c	34j		35j		relative stereochemistry cis

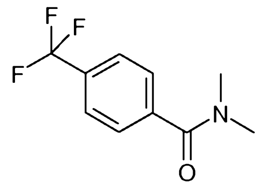
Intermediate 36



Commercially available 4-chloro-3-methyl-picolinate (100mg, 0.5 mmol), Intermediate 17a (205 mg, 1 mmol) and N,N-diisopropyl-ethyl-amine (0.18 ml, 1 mmol) were dissolved in 3 ml of N,N-dimethylacetamide and refluxed overnight. The reaction mixture was purified by preparative LC/MS (reverse phase). 120 mg (0.35 mmol) of the desired product were obtained. Absolute stereochemistry known.

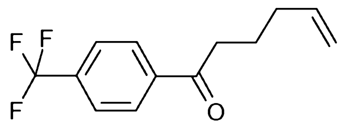
The following synthesis sequence allows the preparation of Intermediates 16b, 16c, 16h, 17a, and preparation of Intermediate 42:

Intermediate 37a



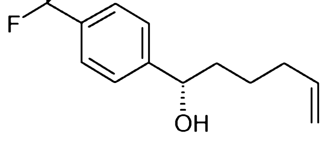
To a solution of commercially available 4-(trifluoromethyl)-benzoyl chloride (25 g, 112 mmol) in 250 ml dry tetrahydrofurane under nitrogen atmosphere, dimethylamine dihydrochloride (14.7 g, 180 mmol) and potassium carbonate (49.62 g, 360 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum, the crude product was dissolved in ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was used in the next step without any purification.

Intermediate 38a



Intermediate 37a (25g) was dissolved in 125 ml of dry tetrahydrofurane and the reaction mixture was cooled to 0°C. 350 ml of a cooled 0.5 M solution of (pent-4-enyl)magnesium bromide (Liebigs Annalen der Chemie **1982,** 1478) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography to give 25g of the desired product.

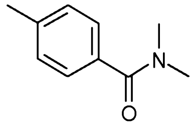
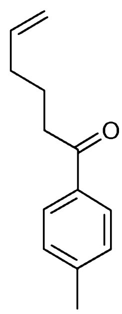
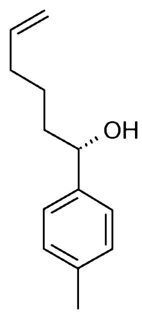
Intermediate 39a

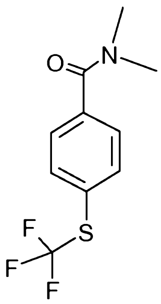
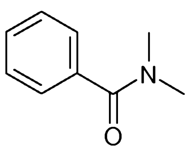
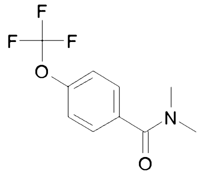
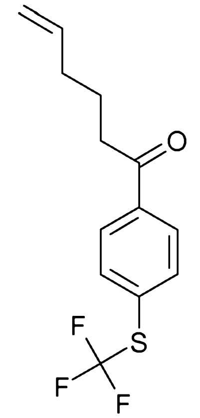
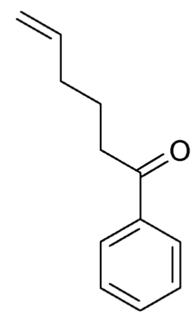
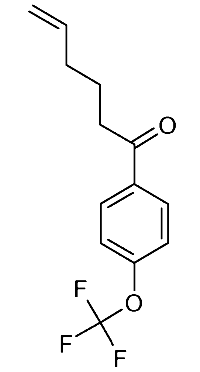
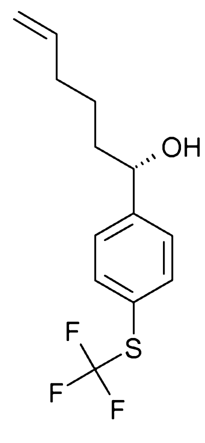
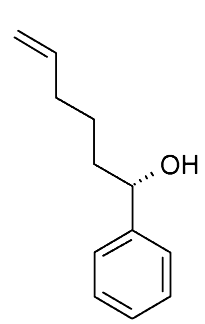
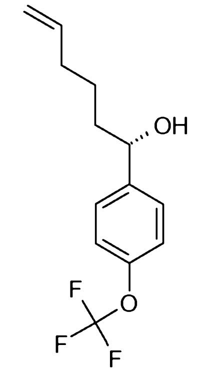


Intermediate 38a was added dropwise to a suspension of (S,S)-teth-TsDpen ruthenium chloride (20 mg, 0.032 mmol; Johnson Matthey Catalysts) in 200 ml formic acid/triethylamine complex under argon atmosphere. The reaction mixture was warmed to 70°C for 18 h. Then, water was added and the reaction mixture was extracted with diethyl ether. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product (40 g) was used in the next step without any purification.

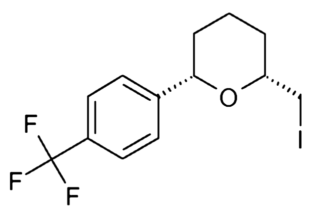
Stereochemistry in analogy to Organic Letters **2000**, 1749-51.

The following intermediates were synthesized in analogy to Intermediates 37a, 38a and 39a.

synthesis in analogy to intermediate 37a				*synthesis in analogy to intermediate 38a*		*synthesis in analogy to intermediate 39a*		
Starting Benzoyl chloride	**Source**	**Amide Intermediate**	**STRUCTURE**	**Keton Intermediate**	**STRUCTURE**	**Alcohol Intermediate**	**STRUCTURE**	**Stereochemistry**
4-methyl-benzoyl chloride	Commercially available	37b		38b		39b		in analogy to Organic Letters **2000**, 1749-51

4-(trifluoromethylthio)benzoyl chloride	Benzoyl chloride	4-(trifluoromethoxyl)benzoyl chloride
Chlorination of commercially available 4-(trifluoromethylthio) benzoic acid using thionylchloride	Commercially available	Commercially available
37e	37d	37c
		
38e	38d	38c
		
39e	39d	39c
		
in analogy to Organic Letters **2000**, 1749-51	in analogy to Organic Letters **2000**, 1749-51	in analogy to Organic Letters **2000**, 1749-51

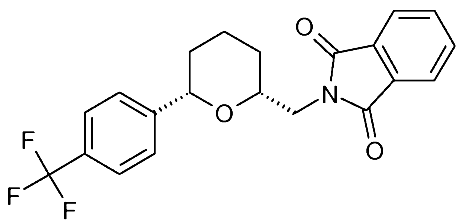
Intermediate 40a



To a suspension of sodium bicarbonate (40.6 g, 482 mmol) in 600 ml of acetonitrile, a solution of Intermediate 39a (40 g) in 100 ml of acetonitrile was added, followed by the

addition of iodine (122 g, 482 mmol). The reaction mixture was stirred at room temperature for 1 h, then 1000 ml of a saturated aqueous $Na_2S_2O_3$ solution were added. The mixture was extracted with diethyl ether. Then, the organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography to yield 29 g of the desired cis stereoisomer.
Relative stereochemistry was assigned by 1H-NMR.

Intermediate 41a



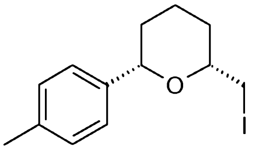
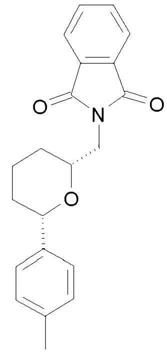
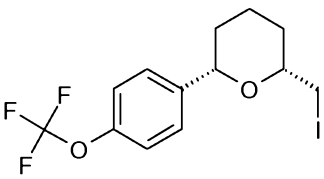
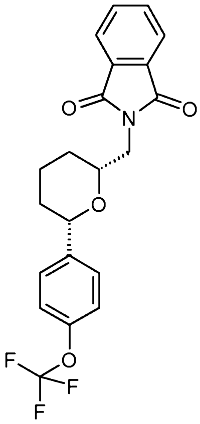
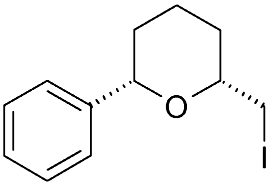
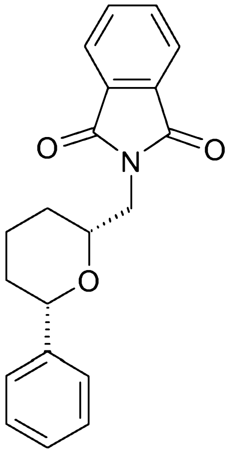
Commercially available phthalimide potassium salt (17.4 g, 94.0 mmol) was added to a solution of Intermediate 40a (29 g, 78.4 mmol) in 250 ml DMF. The reaction mixture was stirred at 90°C for 18 h. The reaction mixture was concentrated under vacuum, diethyl ether was added and the organic phase was washed with an aqueous 1 M sodium hydroxide solution. The organic layer was separated, dried over sodium sulfate and concentrated under vacuum. The crude product (28.7g) was re-crystallised using 350 ml of methylcyclohexane. 9.5 g of enantiomerically enriched product were obtained.

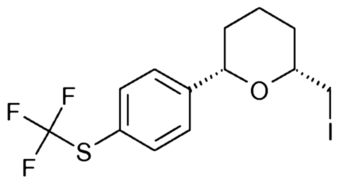
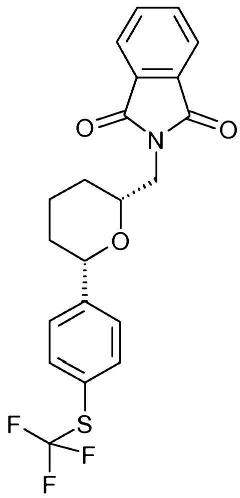
Enantiomerical purity was determined by chiral HPLC (Method 2Ja):
R_t (preferred stereoisomer) = 6.69 min
R_t (second stereoisomer) = 6.00 min

Repeated re-crystallisations with methylcyclohexane allowed to increase the yield of the enantiopure preferred stereoisomer.

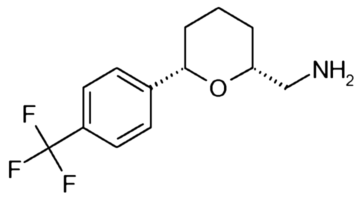
The following intermediates were synthesized in analogy to Intermediates 40a and 41a.

synthesis in analogy to intermediate 40a			*synthesis in analogy to intermediate 41a*			
Starting Intermediate	**Iodo Intermediate**	**STRUCTURE**	**Ftalimide Intermediate**	**STRUCTURE**	**Chiral HPLC method**	**R_t (min)**

39b	40b		41b		Method 2Ja	R_t (preferred s stereoisomer)=6.27 R_t (second stereoisomer)=5.62
39c	40c		41c		Method 2Ja	R_t (preferred stereoisomer)=6.14 R_t (second stereoisomer)=5.64
39d	40d		41d		Method 2Ja	R_t (preferred stereoisomer)= 6.58 R_t (second stereoisomer= 5.95

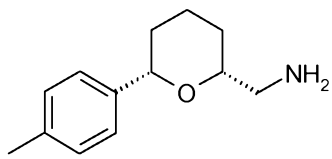
39e	40e		41e		Method 2Ja	R_t (preferred stereoisomer)= 6.73 R_t (second stereoisomer)= 5.86

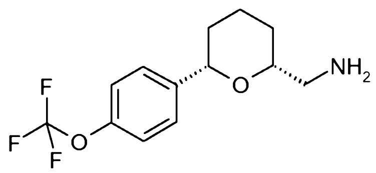
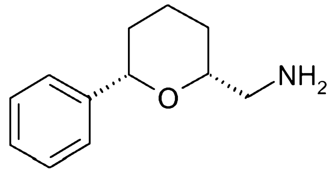
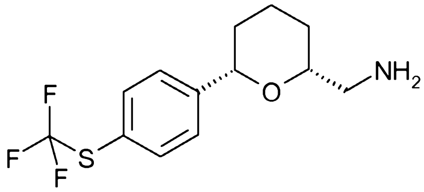
Intermediate 16b



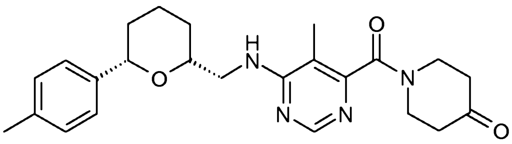
Ethanolamine (8.84 ml, 146.4 mmol) was added to a solution of Intermediate 41a (9.5 g, 24.4 mmol) in 100 ml of toluene. The reaction mixture was stirred at 70°C for 3 h. Then, the mixture was cooled to room temperature and diluted with water and ethyl acetate. The organic phase was separated and washed with an aqueous 1M solution of sodium hydroxide, dried over sodium sulfate and concentrated under vacuum to give the desired product (6.1 g). The crude product was used in the next step without any purification.

The following intermediates were synthesized in analogy to Intermediate 16b.

Starting Intermediate	**Amine Intermediate**	**STRUCTURE**
41b	17a	

41c	16h	
41d	16c	
41e	42	

Intermediate 43

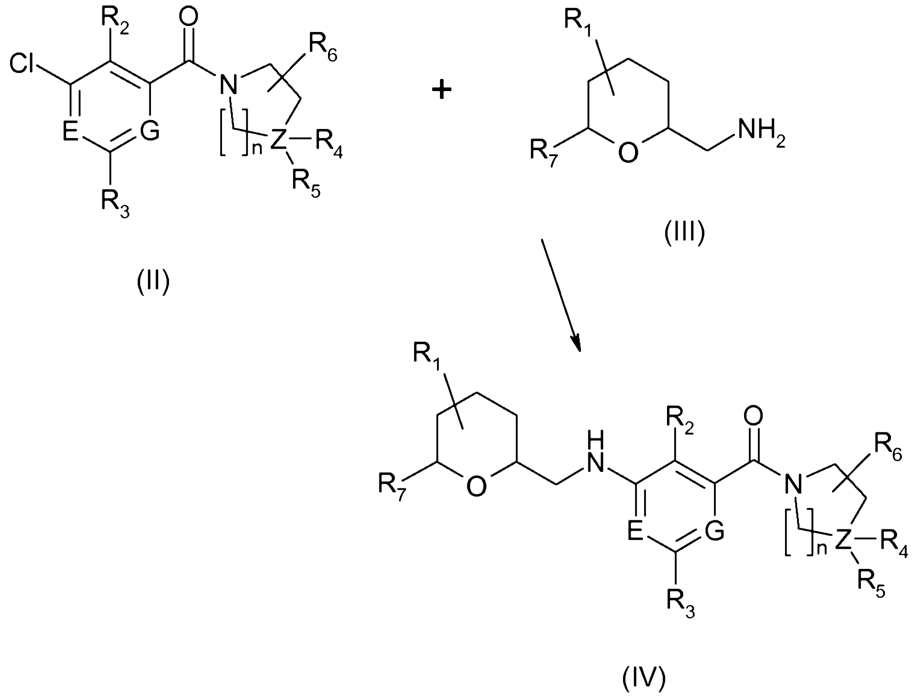


Intermediate 28pb (870 mg, 2.55 mmol), HATU (1.07 g, 2.8 mmol) and N,N-diisopropyl-ethylamine (1.1 ml, 6.4 mmol) in 6 ml DMF were stirred at room temperature for 15 min. 4-Piperidone (345 mg, 2.6 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was treated with 80 ml of a 5% aqueous solution of sodium hydroxide and extracted 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 to give 843 mg (2.0 mmol) of the desired product.

SYNTHESIS OF EXAMPLES

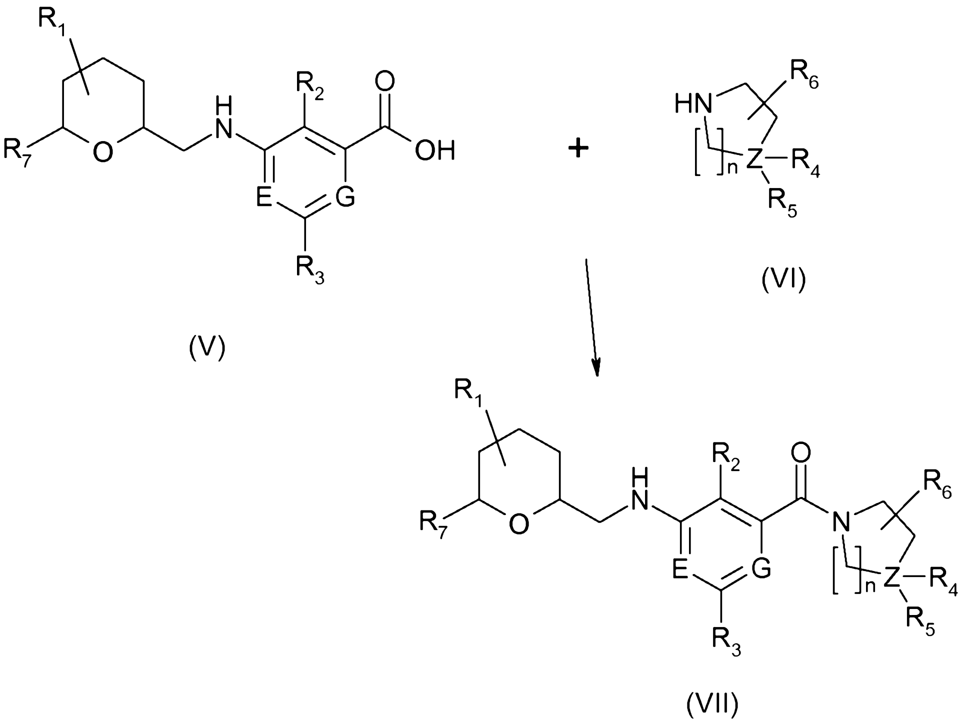
The examples of this invention are synthesized according to the following general synthetic procedures:

Synthetic Procedure A:



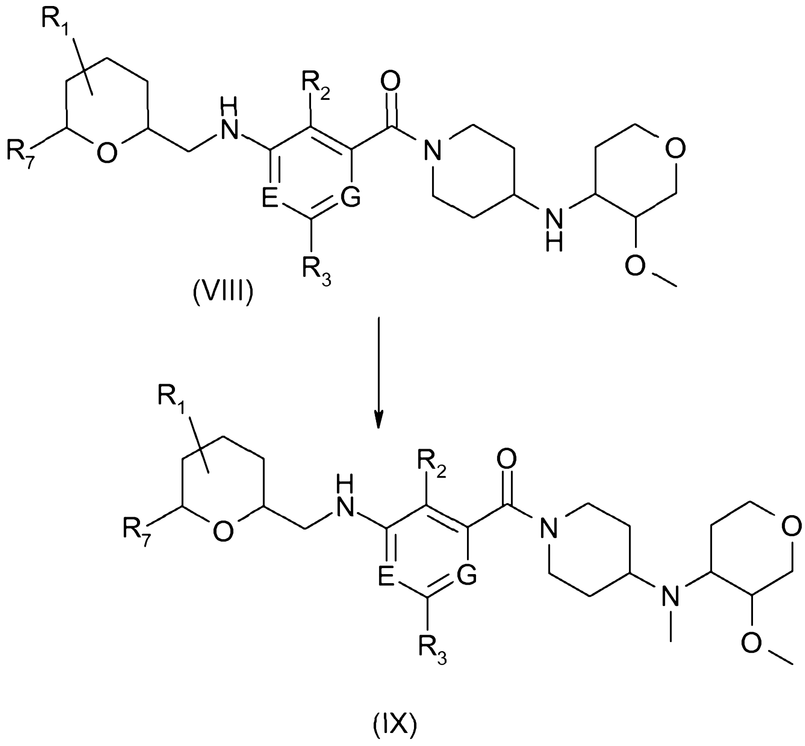
Examples: 1-28; 28a - 28n

Synthetic Procedure B:



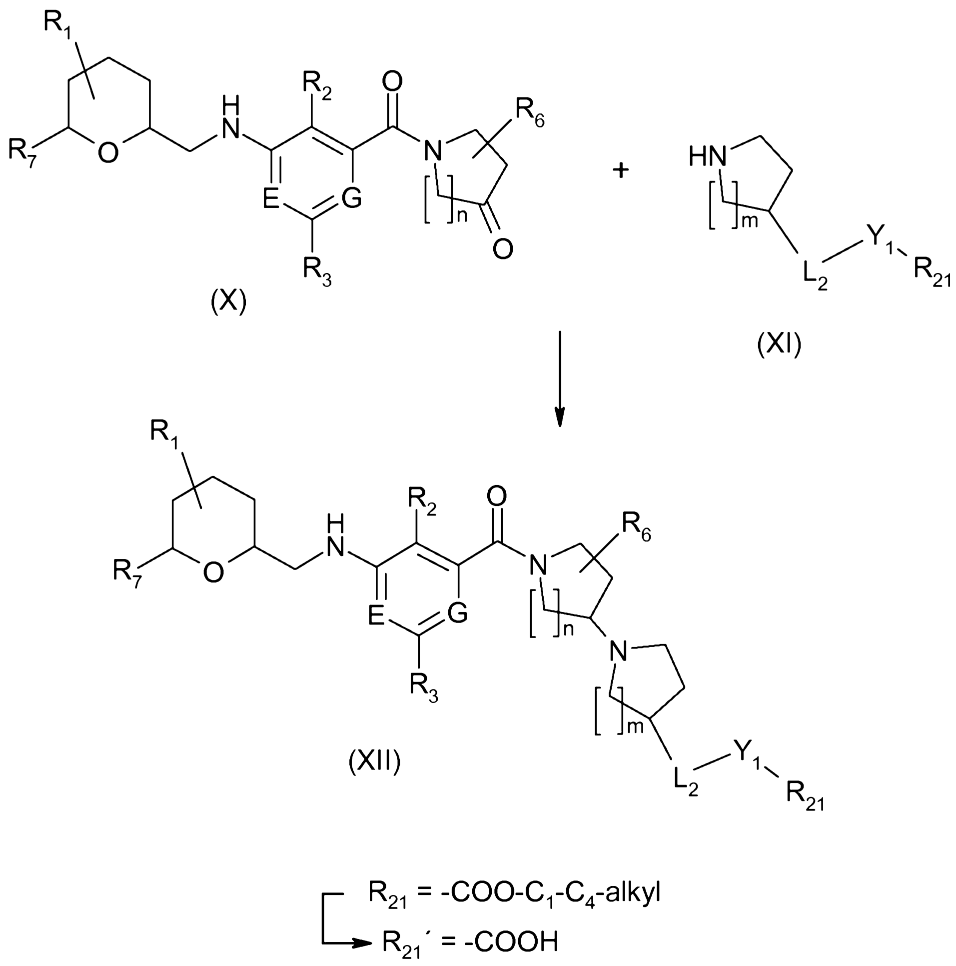
Examples: 29-53; 53a – 53z ; 53aa – 53am

Synthetic Procedure C:



Examples: 54, 54a

Synthetic Procedure D:



Examples: 55 – 59

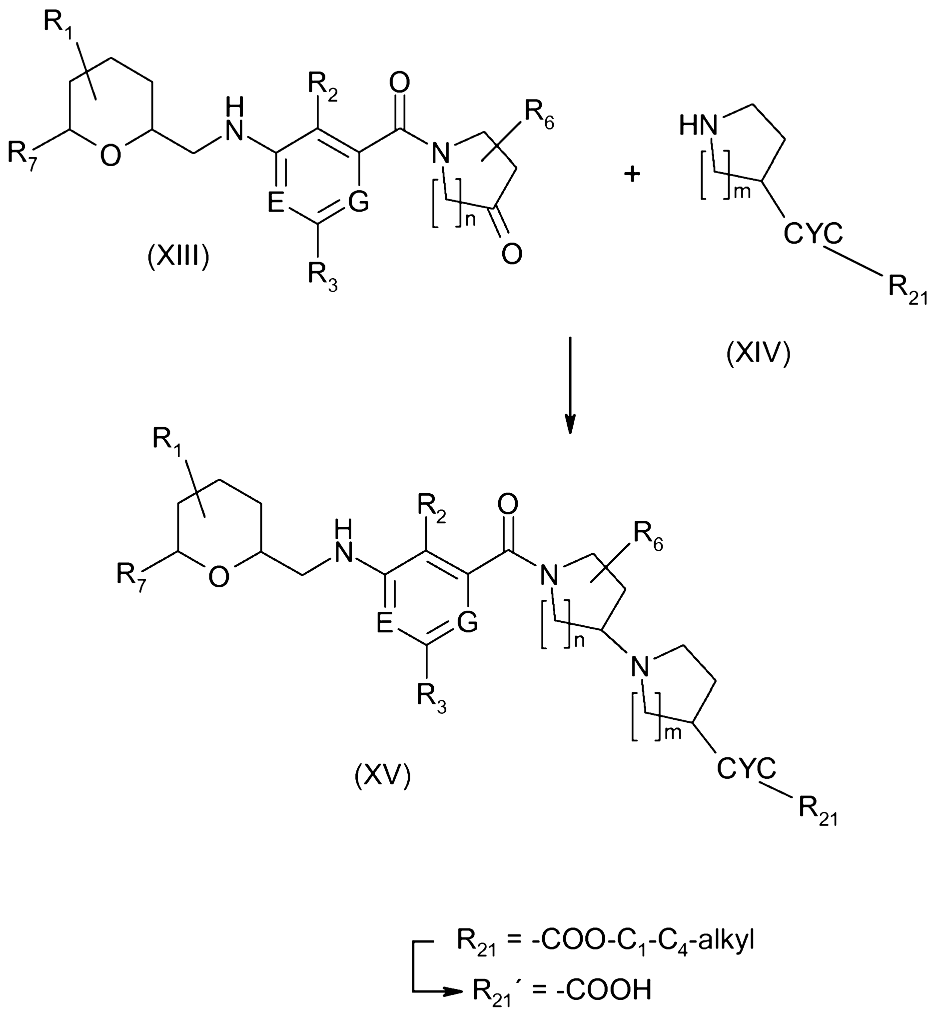
For synthetic procedure D the L_2 group represents a linker wherein L_2 is a group selected from among -C_0-C_4-alkylene, preferred wherein L_2 is a group selected from among a bond, -CH_2-, -CH_2-CH_2-, and –$(CH_2)_3$-, most preferred wherein L_2 denotes a bond (which reflects examples 55 to 59);

wherein m is 1 or 2;

wherein Y_1 is a group selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring, more preferred wherein Y_1 is a group selected from -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, most preferred wherein Y_1 denotes -C_6-aryl (which reflects examples 55 to 59);

and wherein the group Y_1 is optionally substituted with the group R_{21}, wherein R_{21} is selected from among -OH, -OCH_3, -CF_3, -COO- C_1-C_4-alkyl, -OCF_3, -CN, -halogen, -C_1-C_4-alkyl, =O, and -SO_2-C_1-C_4-alkyl, more preferred wherein R_{21} denotes -COO- C_1-C_4-alkyl. In the case that R_{21} denotes -COO- C_1-C_4-alkyl the compound (XII) is modified by an additional step wich results in a transformation of R_{21} to $R_{21'}$, wherein $R_{21'}$ denotes –COOH (which reflects examples 55 to 59).

Synthetic Procedure E:

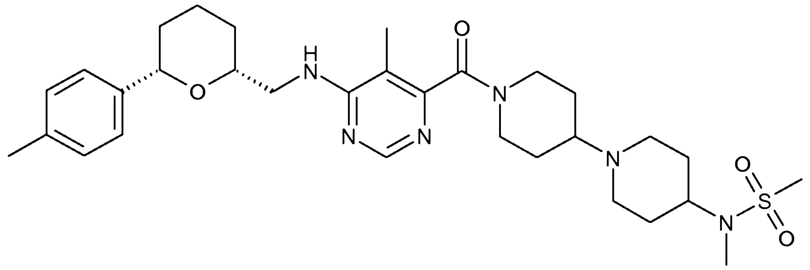


Example: 60

For synthetic procedure E the CYC group represents a group selected from among -C_0-C_4-alkylene(R_{20},$R_{20'}$), more preferred wherein CYC is selected from among -C_0-alkylene(R_{20},$R_{20'}$) whereas R_{20} and $R_{20'}$ together form a spiro-C_3-C_8-carbocycle or spiro-C_3-C_8-heterocycle comprising one or more groups selected from O in the ring and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among -C_1-C_6-alkylene, -C_2-C_6-alkenylene, and -C_4-C_6-alkynylene as well as wherein said spirocycle is optionally further substituted by R_{21}, most preferred wherein the CYC group denotes -C_0-alkylene(R_{20},$R_{20'}$) whereas R_{20} and $R_{20'}$ together form a spiro-C_5-carbocycle wherein said spirocycle is further bi-valently substituted by an annellated

ring forming group selected from $-C_4$-alkenylene and wherein said spirocycle is further substituted by R_{21} (which reflects examples 60);
wherein m is 1 or 2, more preferred wherein m is 1;
and wherein R_{21} is selected from among –H, -OH, $-OCH_3$, $-CF_3$, -COO- C_1-C_4-alkyl, $-OCF_3$, -CN, -halogen, -C_1-C_4-alkyl, =O, and $-SO_2$-C_1-C_4-alkyl, more preferred wherein R_{21} denotes -COO- C_1-C_4-alkyl. In the case that R_{21} denotes -COO- C_1-C_4-alkyl the compound (XV) is modified by an additional step wich results in a transformation of R_{21} to $R_{21'}$, wherein $R_{21'}$ denotes –COOH (which reflects example 60).

Example 1

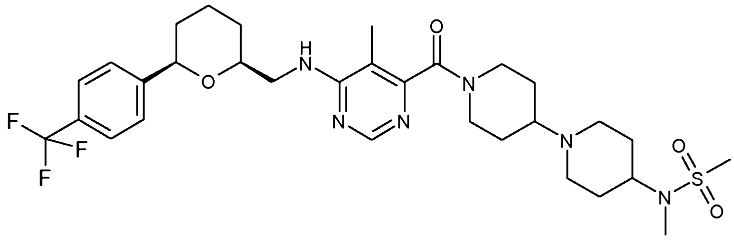
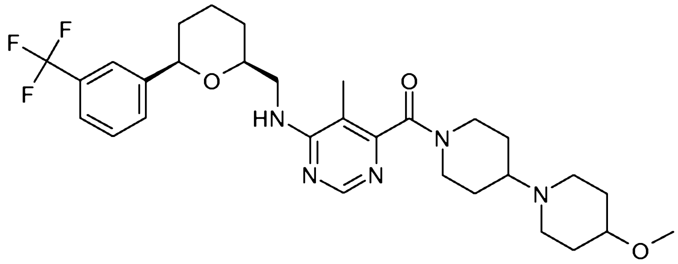
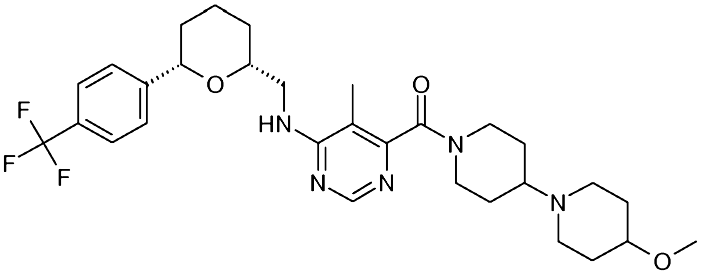
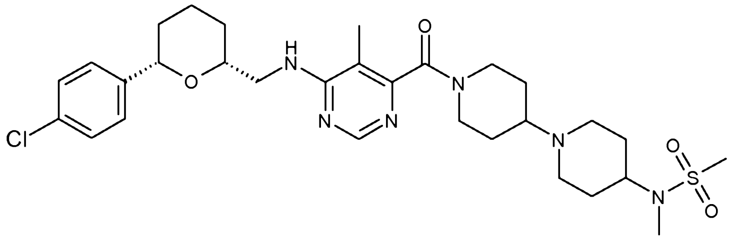
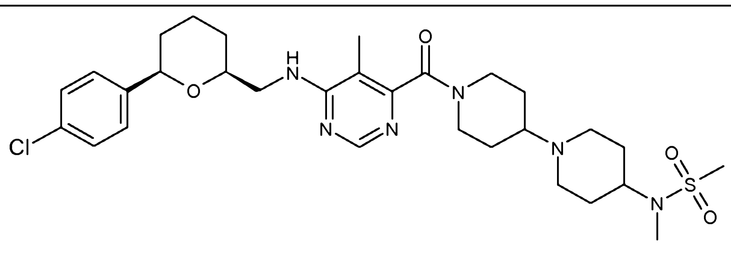


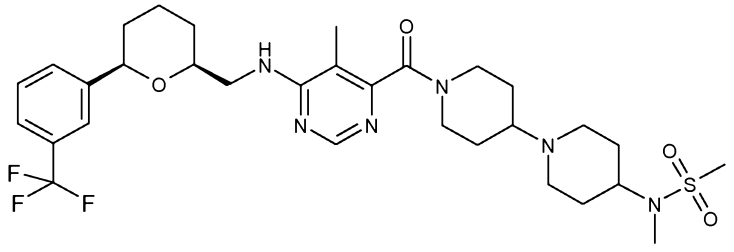
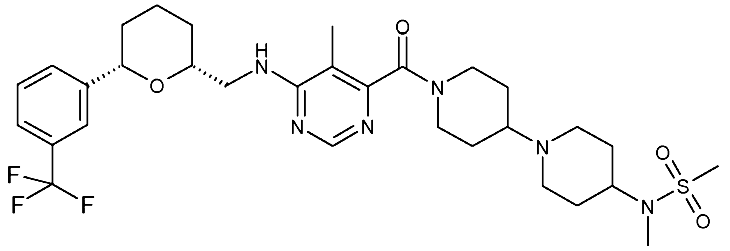
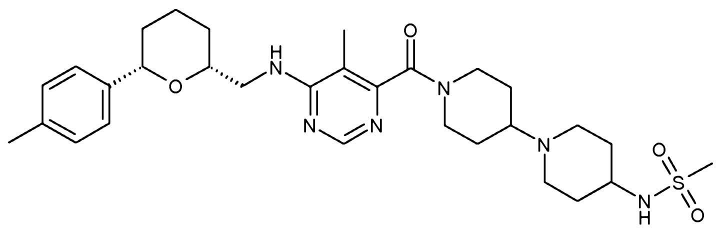
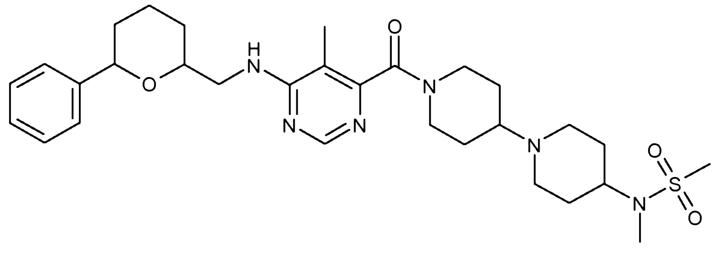
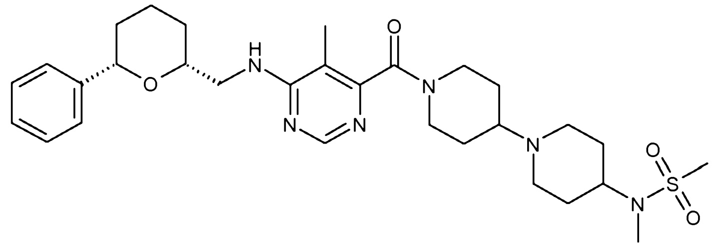
Intermediate 26b (60 mg, 0.14 mmol) , Intermediate 17a (28.6 mg, 0.14 mmol) and N,N-diisopropyl-ethyl amine (0.05 ml, 0.31 mmol) in 0.5 ml of dry 1,4-dioxane were mixed in a microwave vial and reacted in the following conditions: Power 100, Ramp 5 min, Hold 2h, Temperature 150°C, Pressure 150 psi, Stirring. The reaction mixture was concentrated under vacuum and diluted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 40 mg (0.07 mmol) of the desired product were obtained.

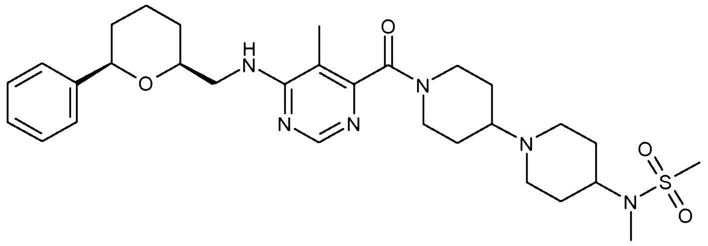
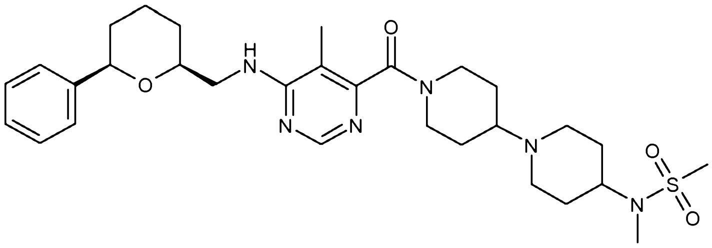
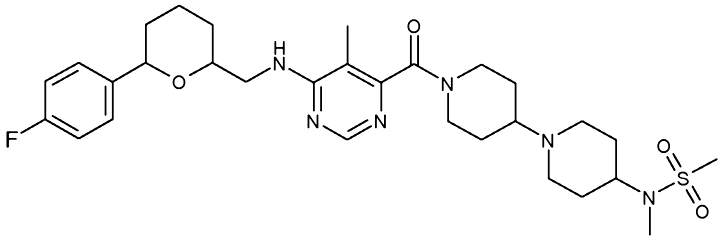
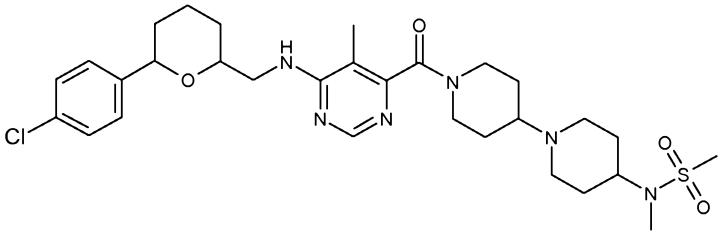
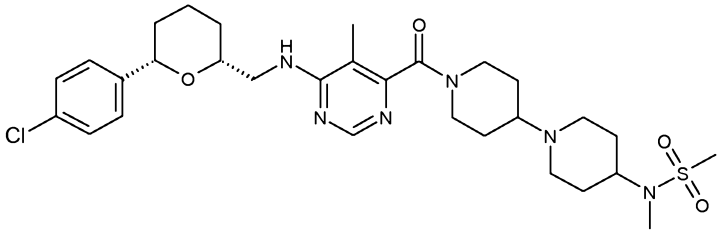
HPLC (Method 2M): R_t. (min) = 6.00

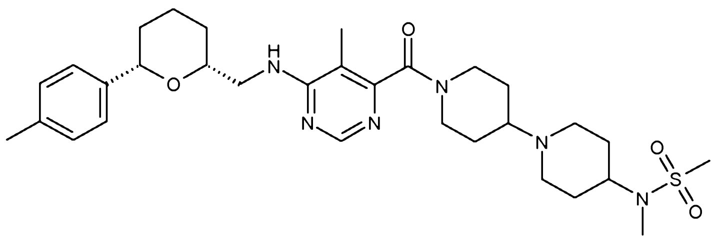
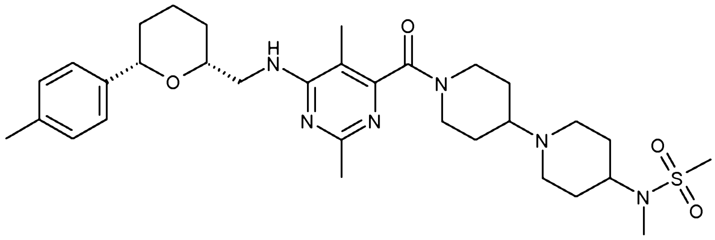
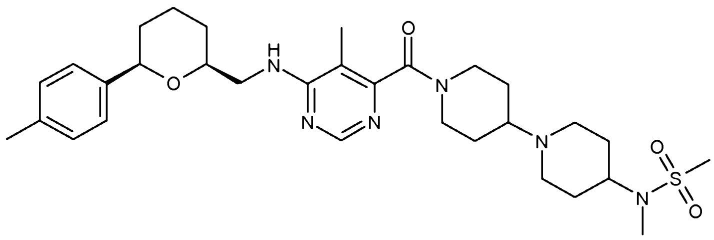
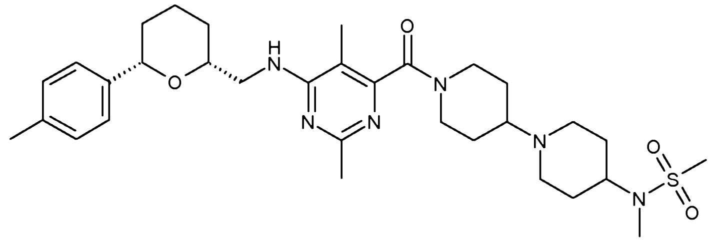
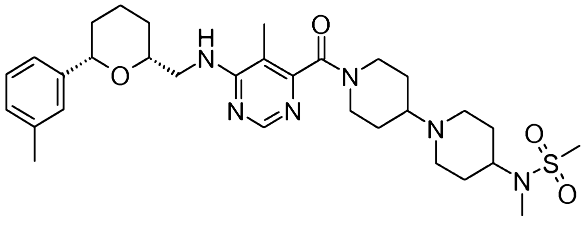
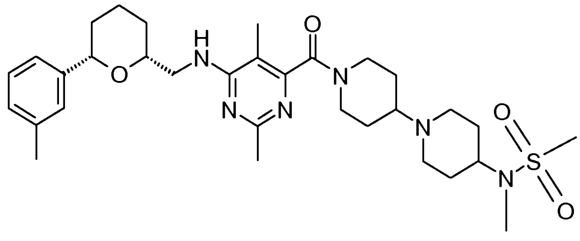
$[M+H]^+$= 599

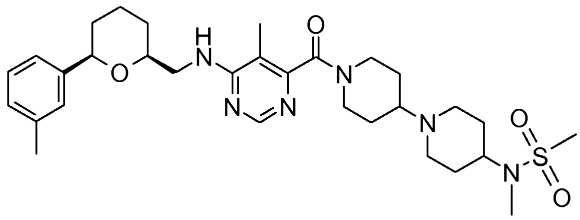
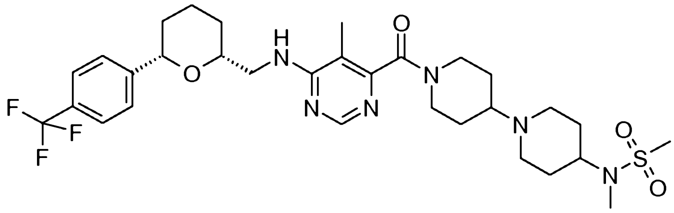
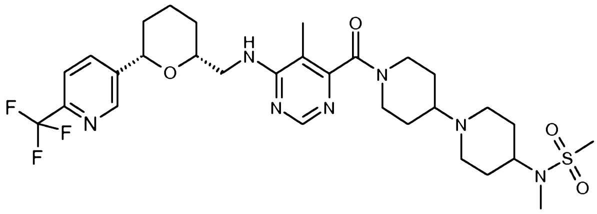
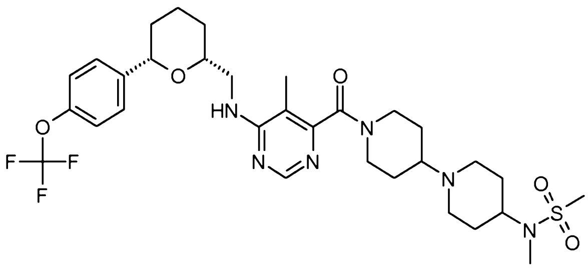
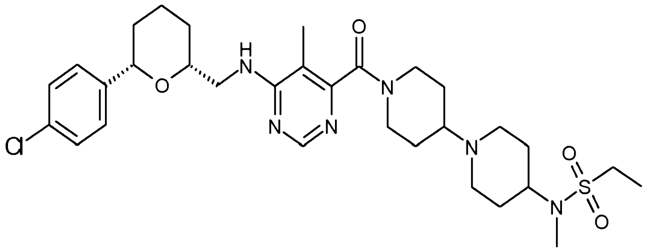
The following examples were synthesized in analogy to the preparation of Example 1

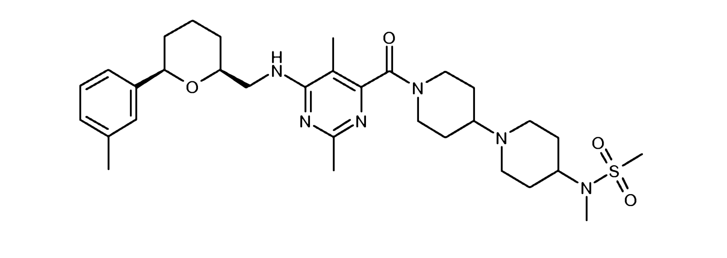
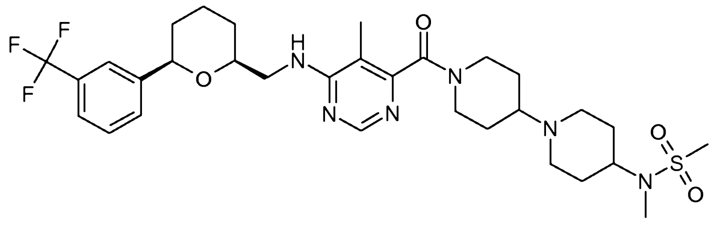
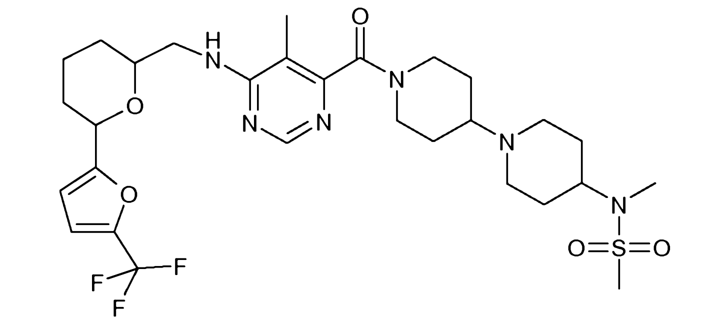
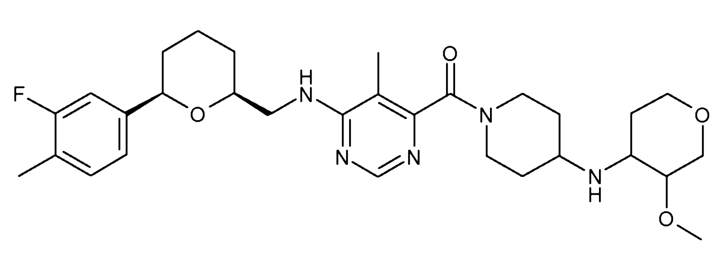
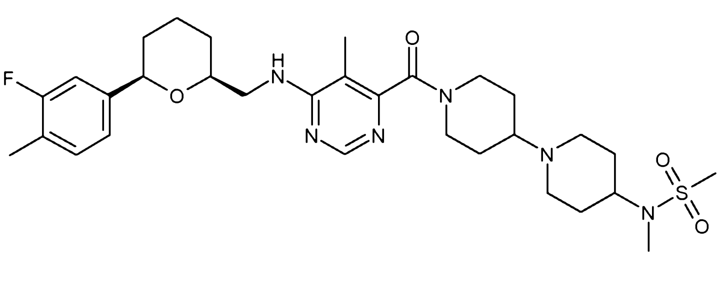
Ex #	MOLSTRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t. (min)	Method
2		26b	17b	653	9.53	1E (Hydro)
3		26c	15f	576	10.62	1E (Hydro)
4		26c	15b	576	10.96	1E (Hydro)
5		26b	16d	619	9.81	1E (Hydro)
6		26b	17d	619	9.85	1E (Hydro)

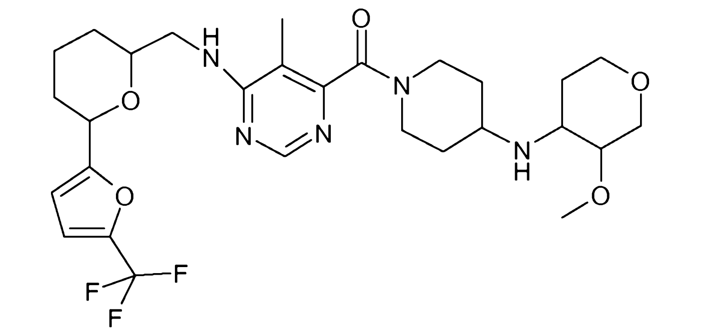
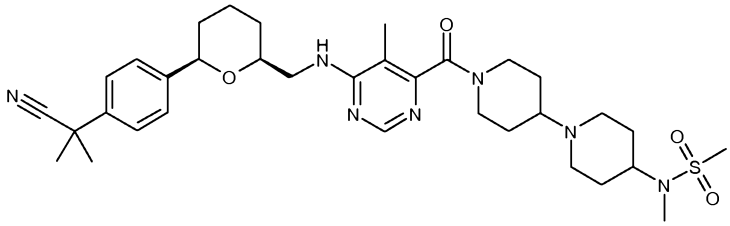
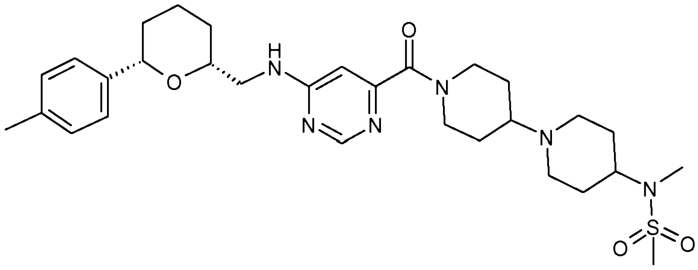
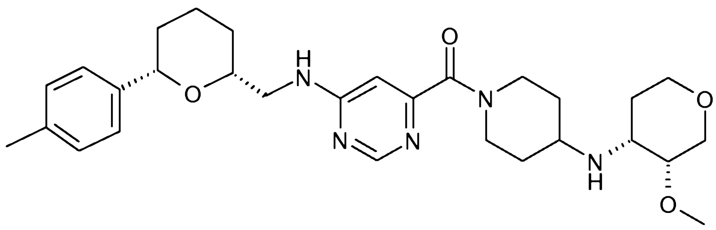
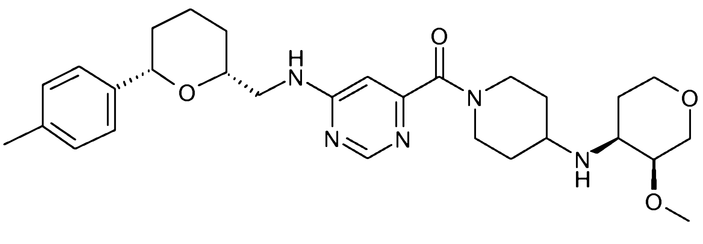
7		26b	16f	653	7.21	2F
8		26b	17f	653	7.09	2F
9		26c	17a	585	9.24	1E (Hydro)
10		26b	14c	585	8.62 and 9.08	1E (hydro)
11		26b	15c	585	9.03	1E (Hydro)

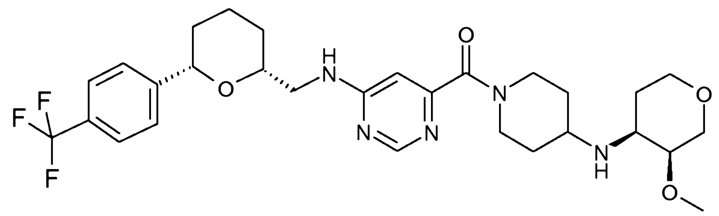
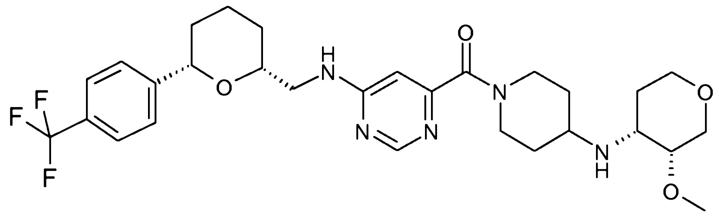
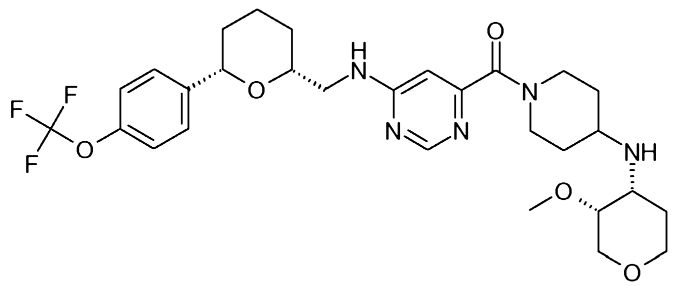
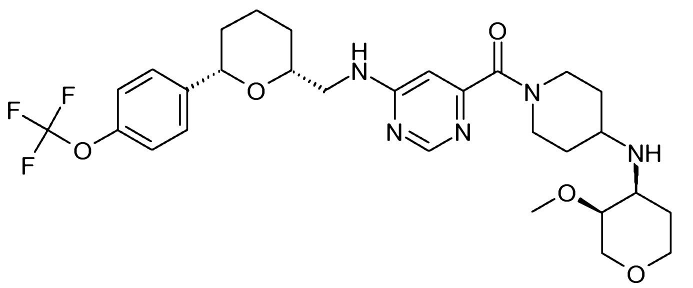
12 *		26b	15c	585	8.95	1E (Hydro)
13 *		26b	15c	585	8.72	1E (Hydro)
14		26b	14i	603	8.6	1E (Hydro)
15		26b	14d	619	9.18 and 9.68	1E (Hydro)
16		26b	15d	619	9.77	1E (Hydro)

17		26b	15a	599	8.98	1E (Hydro)
18		26d	15a	613	9.90	1E (Hydro)
19		26b	16a	599	9.4	1E (Hydro)
20		26d	17a	613	9.79	1E (Hydro)
21		26b	17e	599	9.48	1E (Hydro)
22		26d	17e	613	9.98	1E (Hydro)

23		26b	16e	599	9.53	1E (Hydro)
24		26b	16b	653	9.53	1E (Hydro)
25		26b	15g	654	8.83	1E (Hydro)
26		26b	15h	669	10.38	1E (Hydro)
27		26e	15d	633	9.47	1E (Hydro)

28		26d	16e	613	9.98	1E (Hydro)
28 a		26b	15b	653	9.79	1E (Hydro)
28 b		26b	33c	643	8.95 and 9.28	1E (Hydro)
28 c		26i	33b	556	10.08	1E (Hydro)
28 d		26b	33b	617	10.05	1E (Hydro)

28e		26i	33c	582	8.70 and 9.07	1E (Hydro)
28f		26b	33b	652	9.48	1E (Hydro)
28g		26f	17a	585	1.83	2Ha
28h		26g	17a	524	1.77	2Ha
28i		26h	17a	524	1.78	2Ha

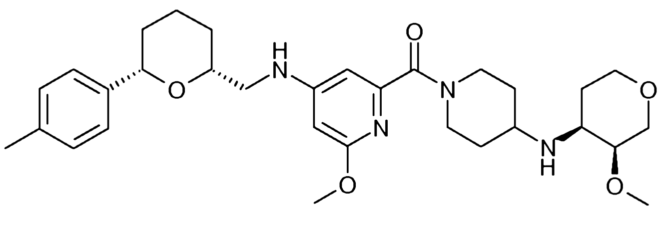
28 j		26h	16b	578	1.91	2Ha
28 k		26g	16b	578	1.95	2Ha
28 l		26g	16h	594	1.96	2Ha
28 m		26h	16h	594	1.96	2Ha

*Ex 12 and 13 were obtained by chiral HPLC separation of ex 11:

Ex 12: Chiral HPLC (method 2Ic isocratic): R_t = 10.94 min

Ex 13: Chiral HPLC (method 2Ic isocratic): R_t = 12.93 min

<u>Example 28n</u>

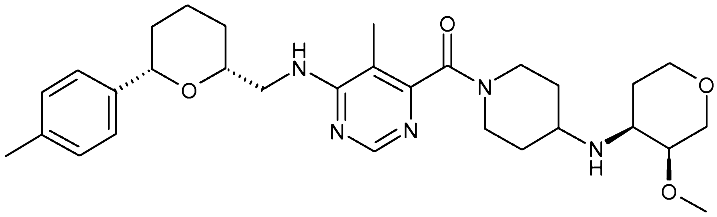


Intermediate 17a (35 mg, 170 µmol) and intermediate 26j (127 mg, 256 µmol) were added to 1.5 ml toluene and 0.5 ml dioxane. Then, caesium carbonate (94 mg, 290 µmol), tris(dibenzylideneacetone)dipalladium (15 mg, 17 µmol) and XPhos (34 mg, 71 µmol) were added and the reaction mixture was stirred over night at 110°C under argon atmosphere. The reaction mixture was diluted with ethyl acetate, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product (35 mg).

HPLC (Method 2HA): R_t. (min) = 1.18

$[M+H]^+$= 553

Example 29

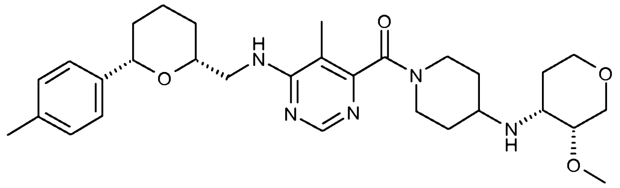
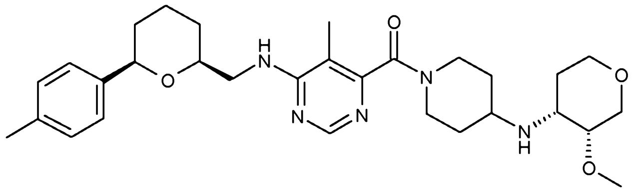
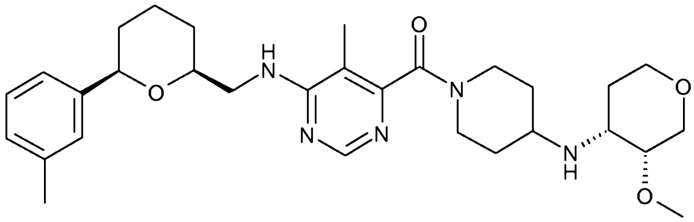
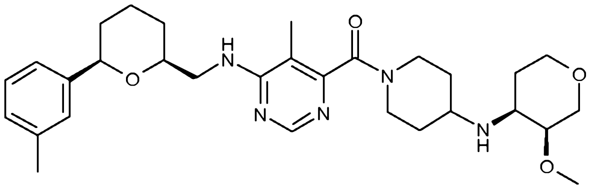
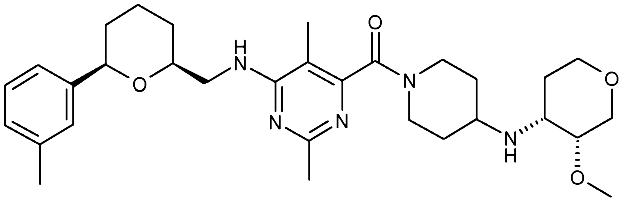


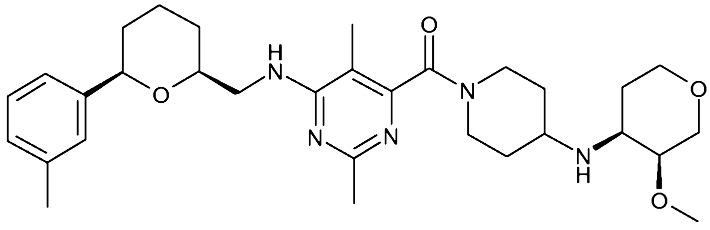
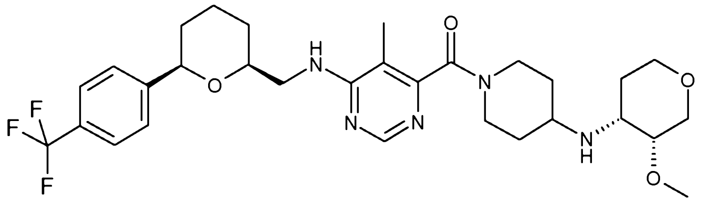
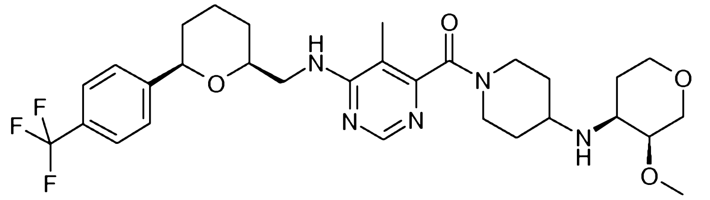
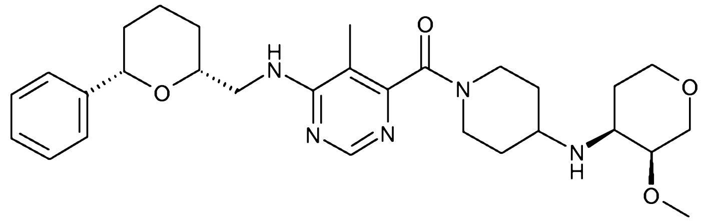
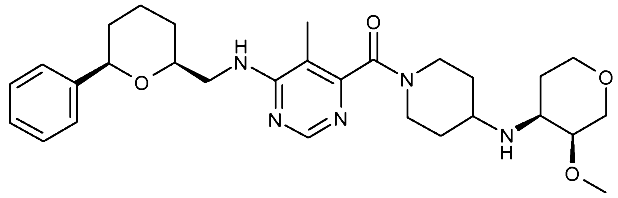
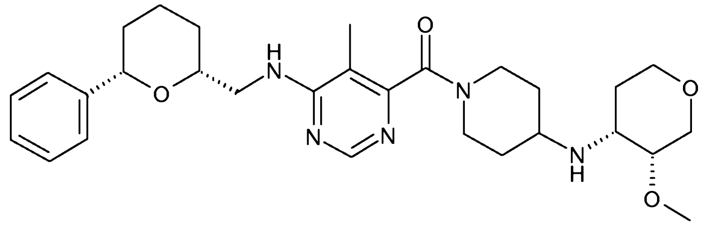
Intermediate 28a (70 mg, 0.21 mmol), TBTU (65.8 mg, 0.20 mmol) and N,N-diisopropyl-ethylamine (0.11 ml, 0.62 mmol) in 5 ml DMF were stirred at room temperature for 5 min. Intermediate 21c (59 mg, 0.21 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture 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: dichloromethane/MeOH=96/4%). 45 mg (0.08 mmol) of the desired product were obtained.

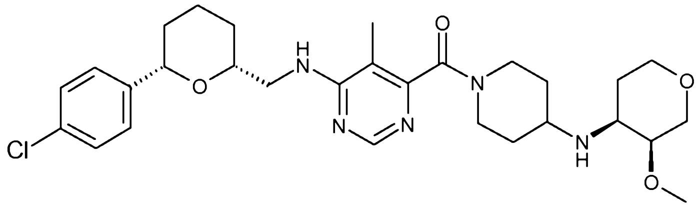
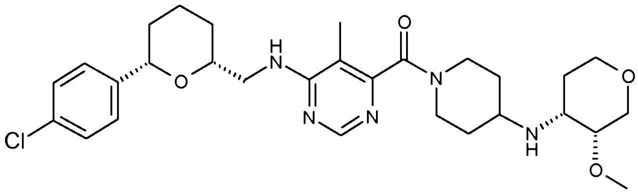
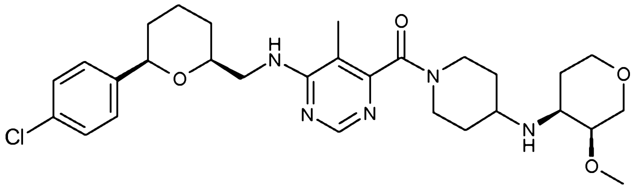
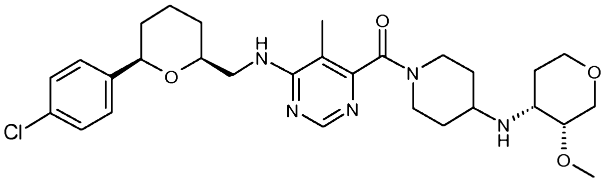
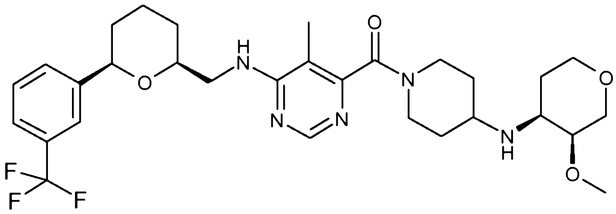
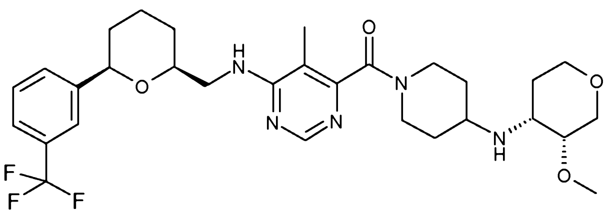
HPLC (Method 1E Hydro): R_t. (min) = 8.50

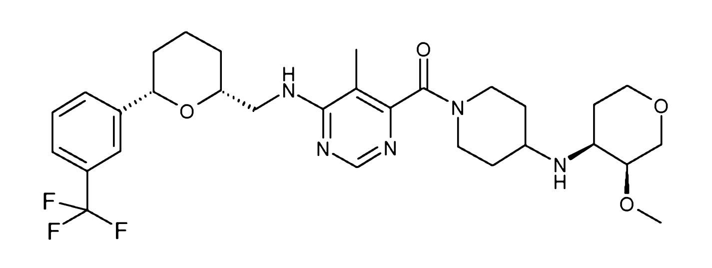
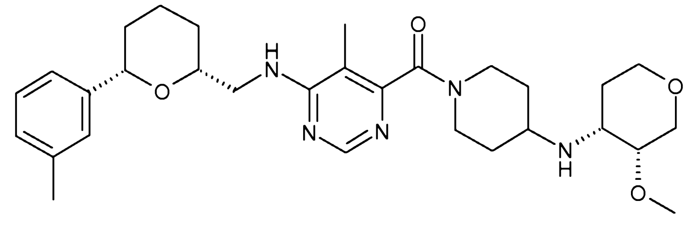
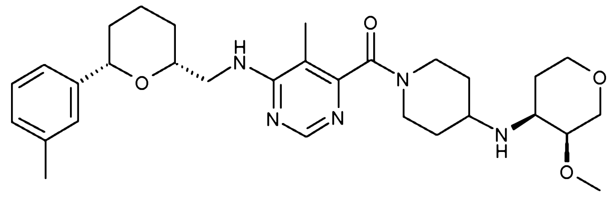
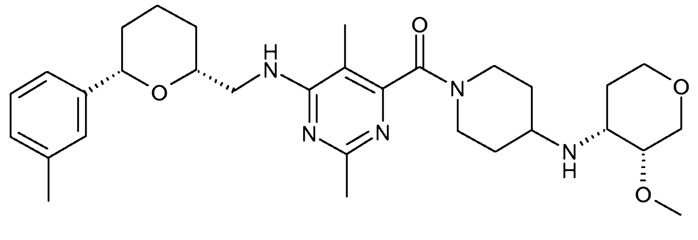
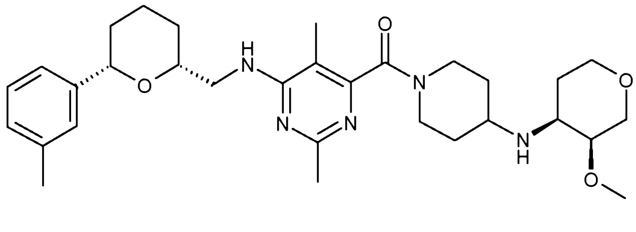
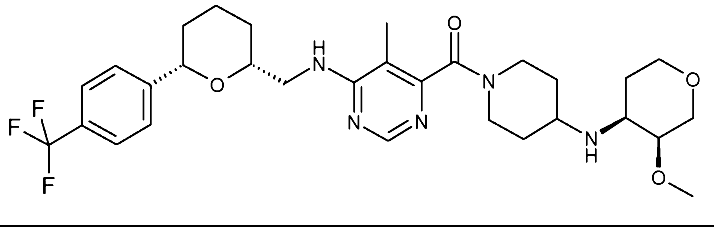
$[M+H]^+$= 538

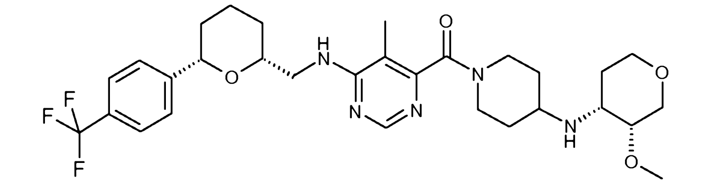
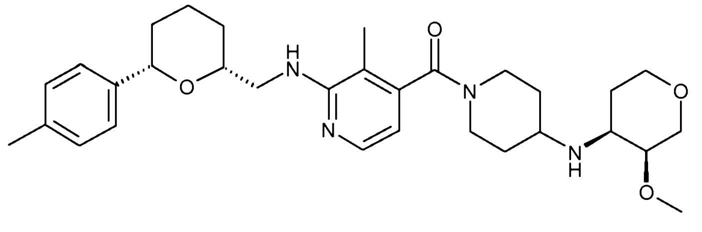
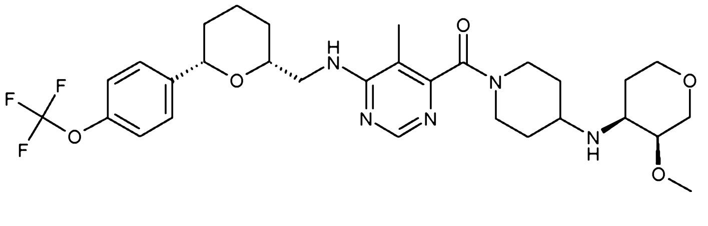
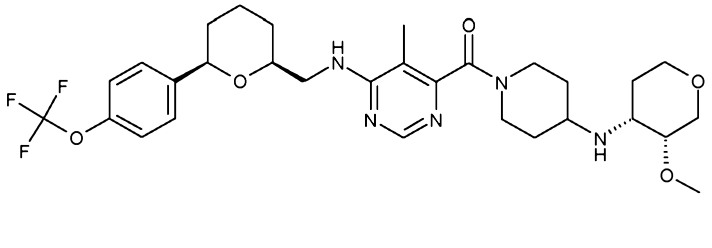
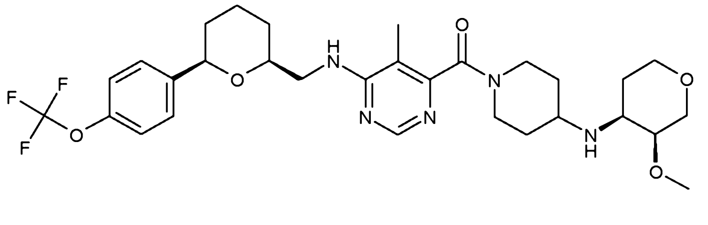
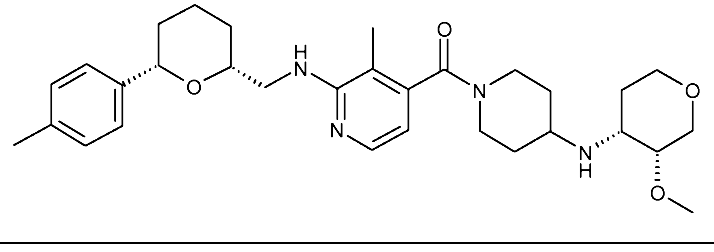
The following examples were synthesized in analogy to the preparation of Example 29.

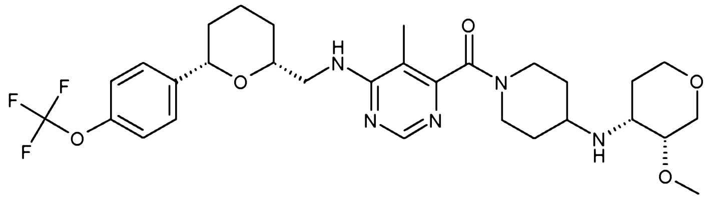
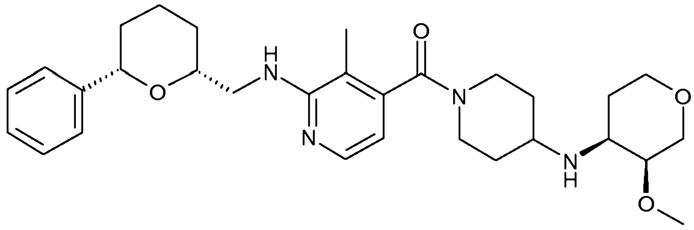
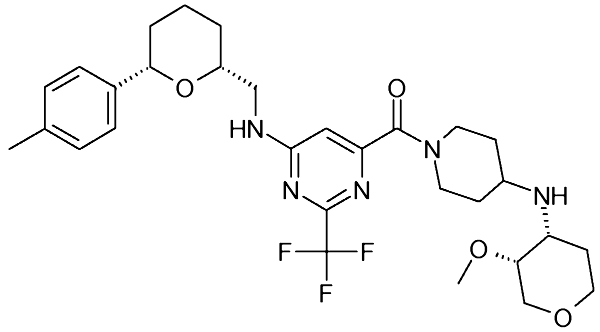
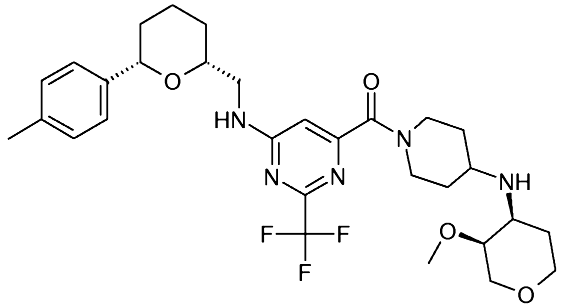
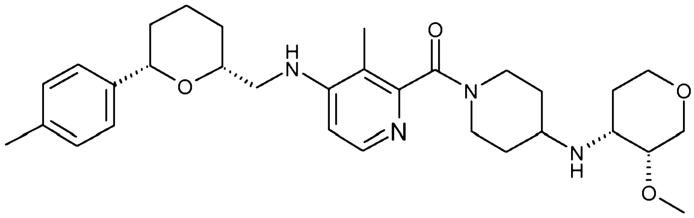
Ex #	STRUCTURE	Intermediate	Amine	$[M+H]^+$	HPLC R_t (min)	Method
30		28a	21b	538	9.33	1E (Hydro)
31		28b	21b	538	9.55	1E (Hydro)
32		28i	21b	538	9.75	1E
33		28i	21c	538	9.76	1E
34		28k	21b	552	9.79	1E (Hydro)

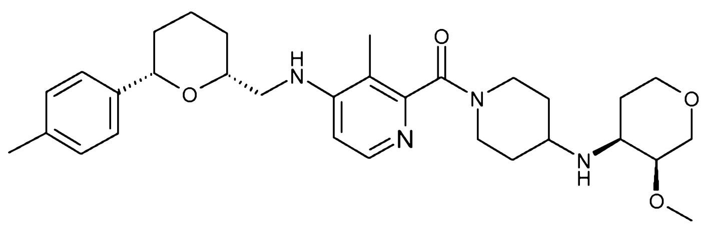
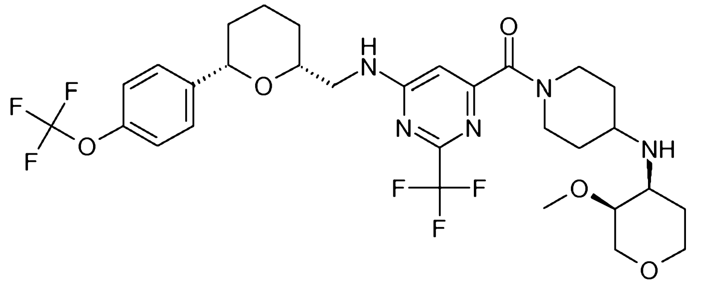
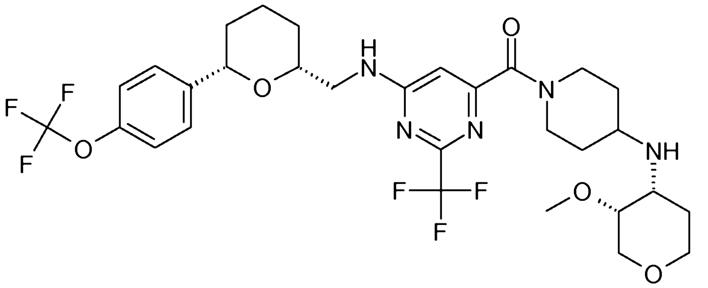
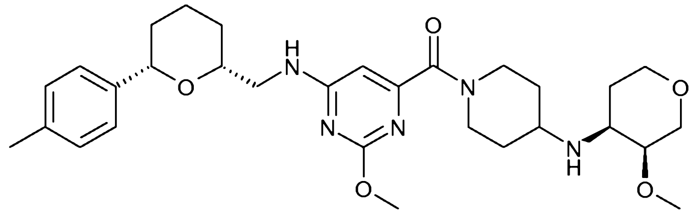
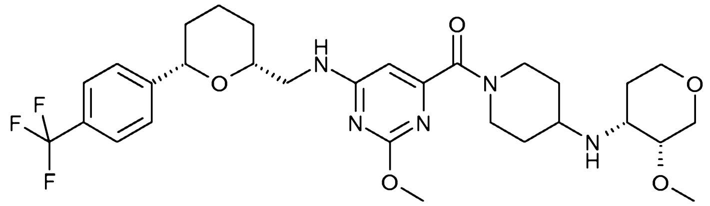
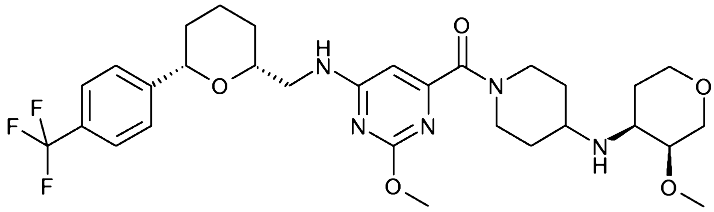
35		28k	21c	552	10.2	1E
36		28d	21b	592	9.27	1E (Hydro)
37		28d	21c	592	9.28	1E (Hydro)
38		28e	21c	524	8.64	1E (Hydro)
39		28f	21c	524	8.47	1E (Hydro)
40		28e	21b	524	8.66	1E (Hydro)

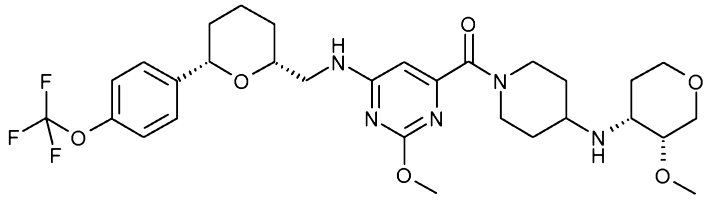
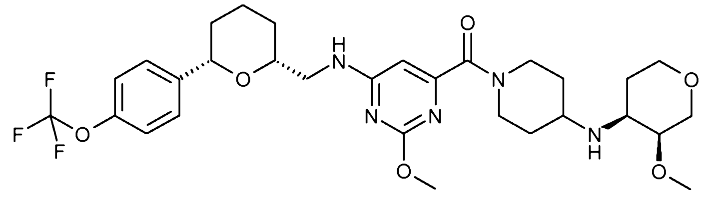
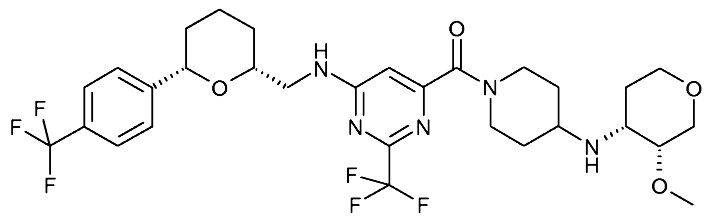
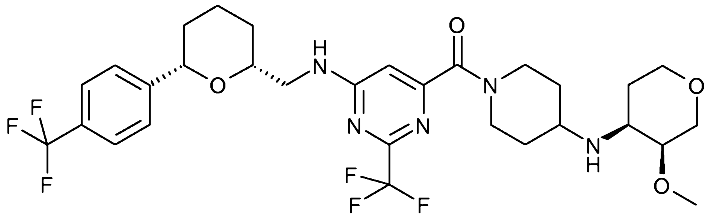
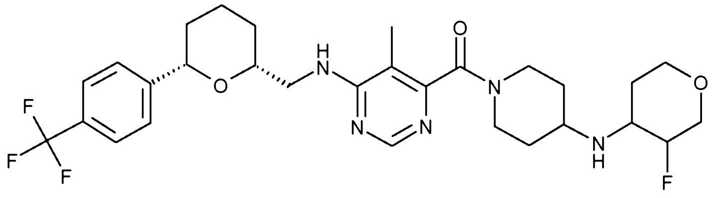
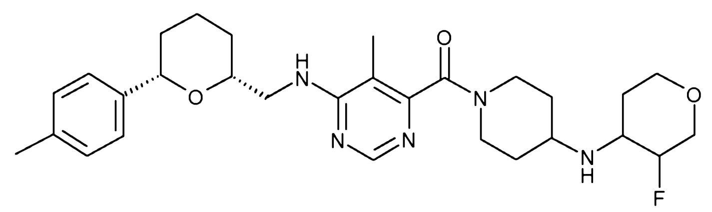
41		28g	21c	558	7.14	2F
42		28g	21b	558	7.04	2F
43		28h	21c	558	7.17	2F
44		28h	21b	558	7.17	2F
45		28m	21c	592	9.89	1E (Hydro)
46		28m	21b	592	9.73	1E (Hydro)

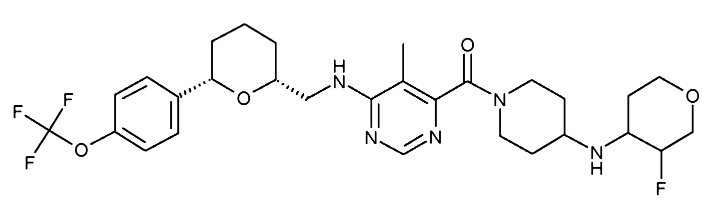
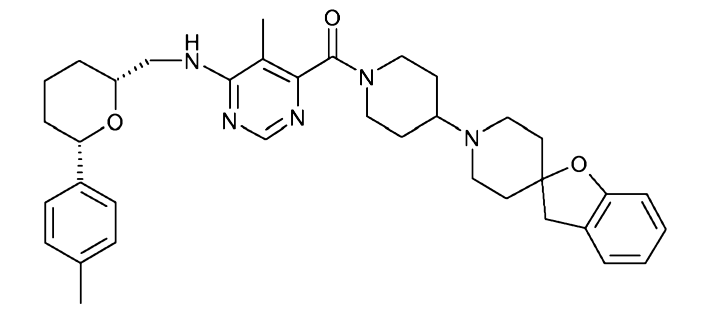
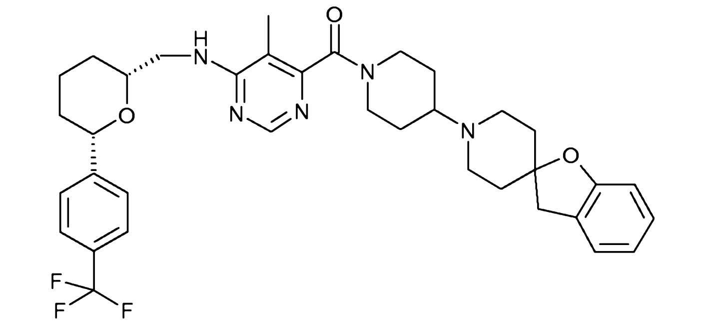
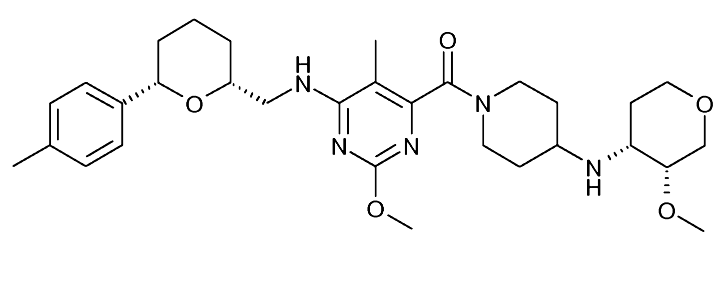
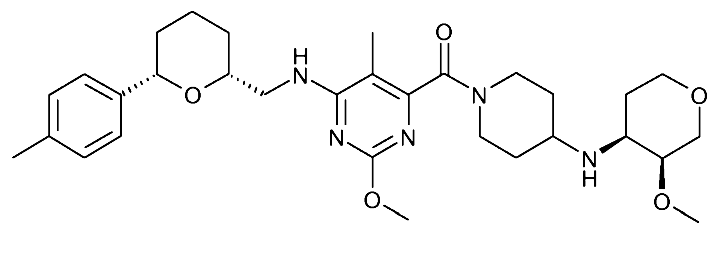
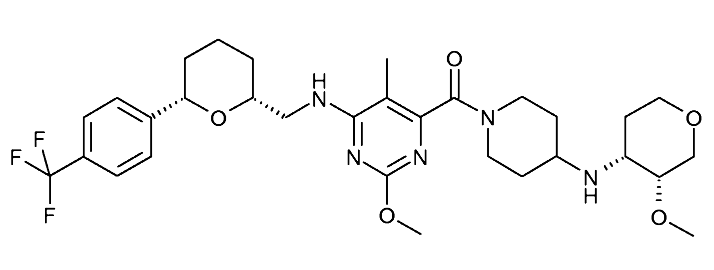
47		28n	21c	592	9.65	1E (Hydro)
48		28j	21b	538	9.70	1E
49		28j	21c	538	9.63	1E
50		28l	21b	552	10.1	1E
51		28l	21c	552	10.18	1E
52		28c	21c	592	9.30	1E (Hydro)

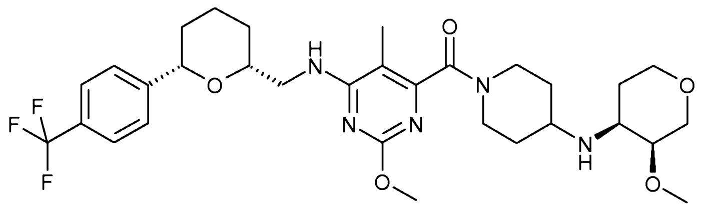
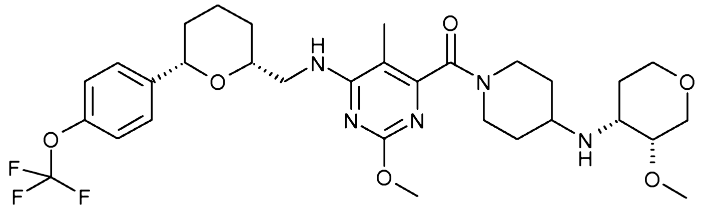
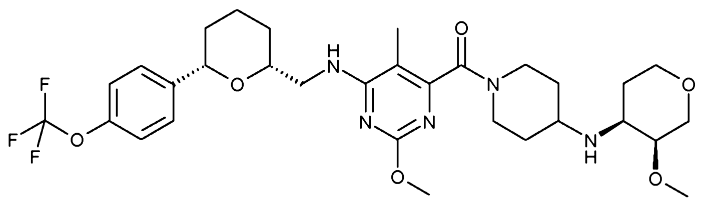
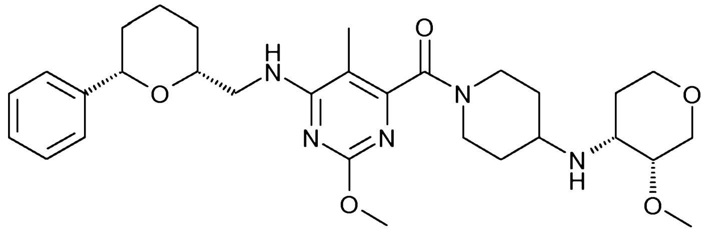
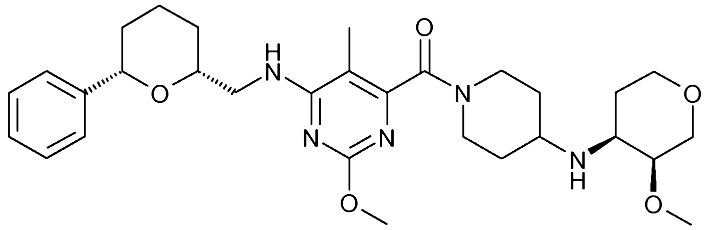
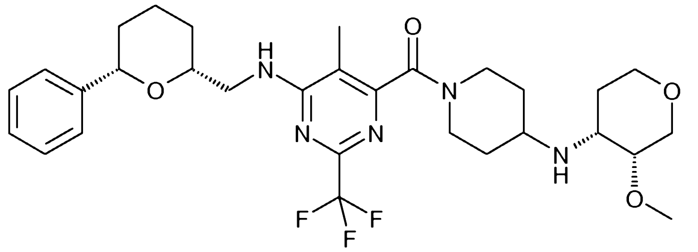
53		28c	21b	592	9.30	1E (Hydro)
53a		28q	21c	537	10.28	1E
53b		28o	21c	607	7.59	2F
53c		28p	21b	608	7.47	2F
53d		28p	21c	608	7.59	2F
53e		28q	21b	537	10.32	1E

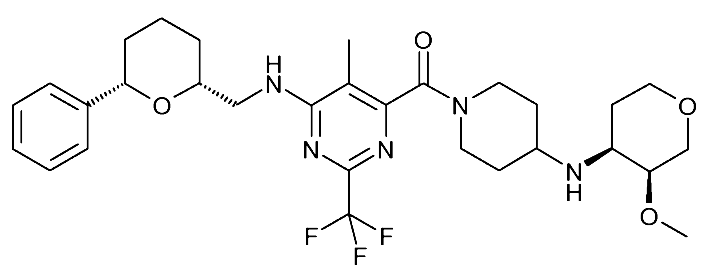
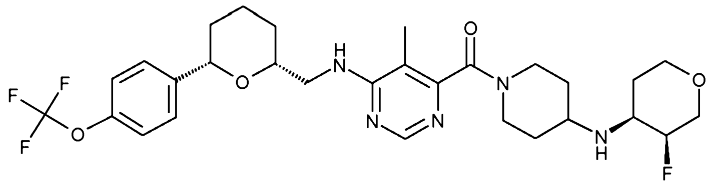
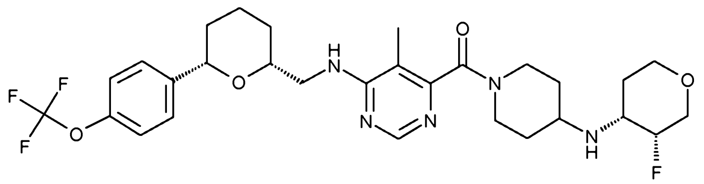
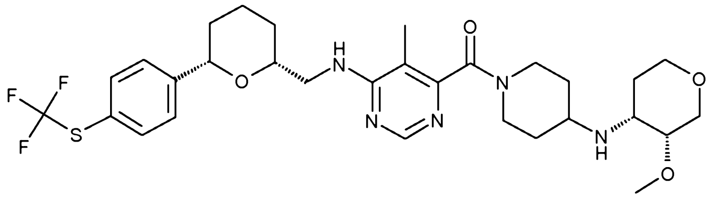
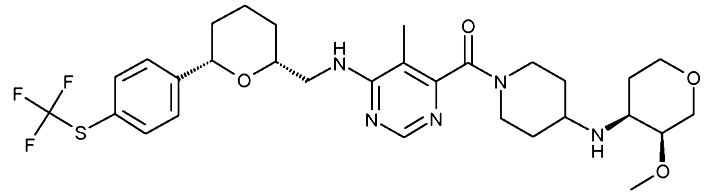
53f		28o	21b	608	7.59	2F
53g		28r	21c	523	9.18	1E (Hydro)
53h		35	21b	592	2.18	2Ha
53i		35	21c	592	2.17	2Ha
53j		36	21b	537	10.03	1E (Hydro)

53k		36	21c	537	10.05	1E (Hydro)
53l		35a	21c	662	2.30	2Ha
53 m		35a	21b	662	2.29	2Ha
53n		35c	21c	554	1.96	2Ha
53o		35d	21b	608	2.06	2Ha
53p		35d	21c	608	2.07	2Ha

53q		35e	21b	624	2.08	2Ha
53r		35e	21c	624	2.09	2Ha
53s		35b	21b	646	2.29	2Ha
53t		35b	21c	646	2.29	2Ha
53u		28c	21f	580	9.33	1E (Hydro)
53v		28a	21f	526	8.85	1E (Hydro)

53w		28o	21f	596	9.5	1E (Hydro)
53x		28a	21g	596	7.75	2FF
53y		28c	21g	650	8.14	2FF
53z		35f	21b	568	1.9	2Ha
53aa		35f	21c	568	1.88	2Ha
53ab		35g	21b	622	2.04	2Ha

53ac		35g	21c	622	2.04	2Ha
53ad		35h	21b	638	2.06	2Ha
53ae		35h	21c	638	2.07	2Ha
53af		35i	21b	554	1.77	2Ha
53ag		35i	21c	554	1.77	2Ha
53ah		35j	21b	592	2.03	2Ha

53ai		35j	21c	592	2.03	2Ha
53aj *		-	-	596	9.52	1E (Hydro)
53ak*		-	-	596	9.53	1E (Hydro)
53al		28pa	21b	624	2.00	2Ha
53am		28pa	21c	624	1.99	2Ha

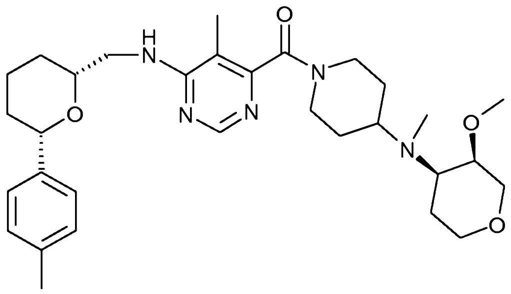
* Ex 53aj and 53ak were obtained by chiral HPLC separation of example 53w:

Ex 53aj: Chiral HPLC (method 2Ja): R_t = 13.35 min

Ex 53ak: Chiral HPLC (method 2Ja): R_t = 15.28 min

Relative stereochemistry of 3-fluoro-tetrahydro-pyran-4-ylamine assigned as cis by 1H-NMR.

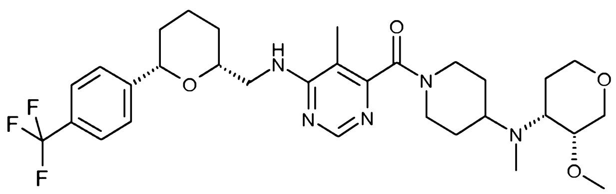
Example 54



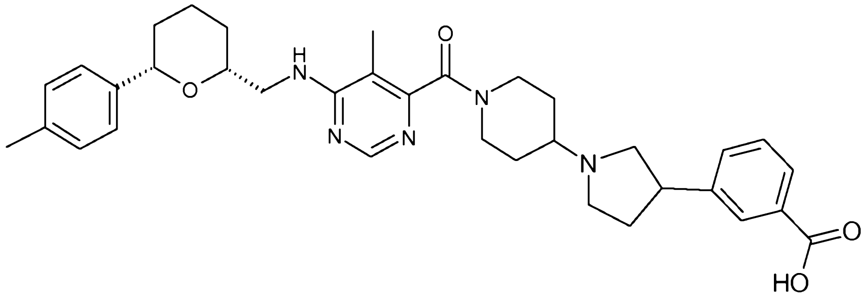
Example 30 (95 mg, 0.14 mmol), formaldehyde (0.027 ml, 0.34 mmol), N,N-diisopropyl-ethylamine (0.034 ml, 0.2 mmol) and trifluoroacetic acid (0.017 ml, 0.22mmol) in 3 ml methanol were stirred at room temperature for 5 min. Sodium cyanoborohydride (43 mg, 0.68 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 43 mg (0.08 mmol) of the desired product were obtained as solid.

HPLC (Method 1E Hydro): R_t. (min) = 9.56
$[M+H]^+$= 552

The following example was synthesized in analogy to the preparation of Example 54.

Ex #	**STRUCTURE**	**Starting example**	**$[M+H]^+$**	**HPLC R_t. (min)**	**Method**
54a		53	606	7.53	2F

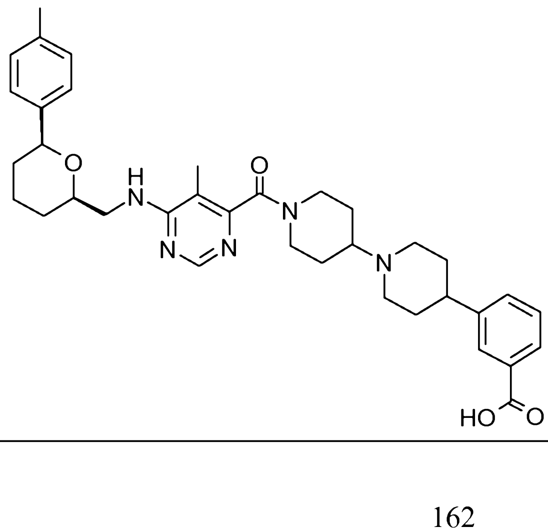
Example 55

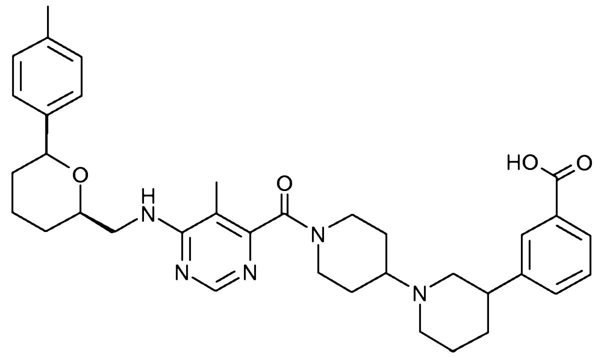
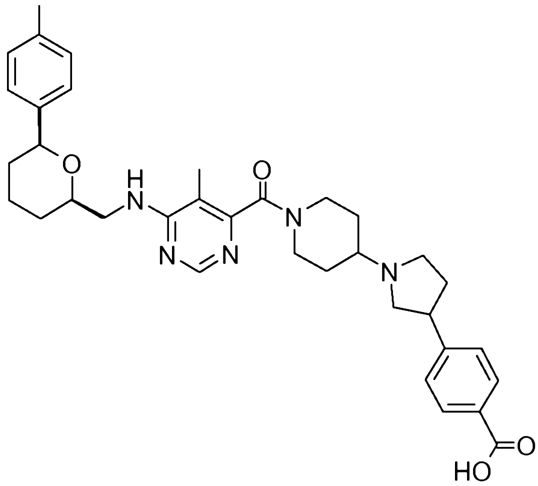
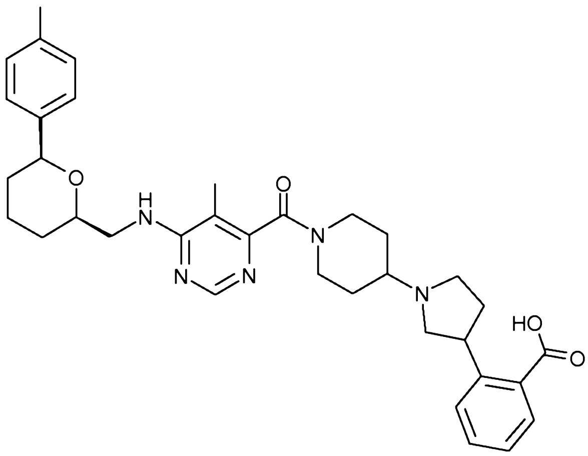


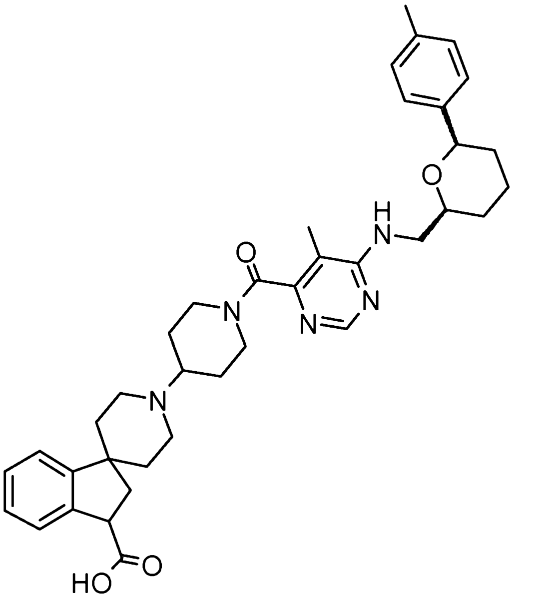
To a solution of commercially available 3-pyrrolidin-3-yl-benzoic acid ethyl ester (43.9 mg 0.2 mmol) in 0.2 DMA, a solution of Intermediate 43 (40.7 mg, 0.1 mmol) in 0.3 ml of DMA and 0.08 ml of acetic acid were added. The reaction mixture was stirred at room temperature for 1h, then, sodium triacetoxyborohydride (25.4 mg, 0.12 mmol) was added. The reaction mixture was stirred at room tempertature for 18h, then it was warmed at 65°C for 6h. 0.4 ml of ethanol and 0.6 ml of an aqueous 10% sodium hydroxide solution were added and the reaction mixture was stirred at 65°C for 18h. 0.5 ml of trifluoroacetic acid were added and the reaction mixture was concentrated under vacuum. The mixture was purified by reverse preparative LC/MS. 23 mg (0.04 mmol) of the desired product were obtained.

HPLC (Method 2Ga): R_t. (min) = 1.34
$[M+H]^+$= 598

The following examples were synthesized in analogy to the preparation of Example 55

Ex #	STRUCTURE	Intermediate	Amino-ester	Source	$[M+H]^+$	HPLC R_t. (min)	Method
56		43	3-piperidin-4yl-benzoic acid methyl ester	Commercially available	612	1.37	2Ga

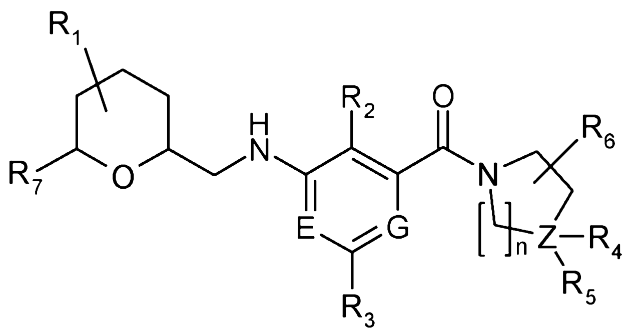
57		43	3-piperidin-3yl-benzoic acid methyl ester	Commercially available	612	1.35	2Ga
58		43	4-pyrrolidin-3yl-benzoic acid methyl ester	Commercially available	598	1.33	2Ga
59		43	2-pyrrolidin-3yl-benzoic acid methyl ester	Commercially available	598	1.46	2Gb

60		43	2,3-dihydrospiro[indene-1,4'-piperidine]-3-carboxylic acid methyl ester	Commercially available	638	1.36	2Ga

2010332969 23 Jan 2015

CLAIMS:

1. A compound of formula (I),



(I)

wherein R_1 is a group selected from among -H, -halogen, -CN, -O-C_1-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_7 is a ring selected from among -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, and -C_5-C_{10}-heteroaryl,
wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF_3, -O-CF_3, -S-CF_3, -CN, -C_1-C_6-alkyl,–$C(CH_3)_2$-CN, and -halogen,
or wherein the ring R_7 is optionally substituted with one or more groups selected from among -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_2-C_6-alkenyl, and -C_2-C_6-alkynyl, optionally being substituted by one or more groups selected from among -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, -methyl, and =O,
or wherein the ring R_7 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 -C_1-C_6-alkylene, -C_2-C_6-alkenylene and -C_4-C_6-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH_2, -C_1-C_3-alkyl, -O-C_1-C_6-alkyl, -CN, -CF_3, -OCF_3, halogen, and =O;

wherein R_2 is selected from among -H, -halogen, -CN, -O-C_2-C_4-alkyl, -C_1-C_4-alkyl, -CH=CH_2, -C≡CH, -CF_3, -OCF_3, -OCF_2H, and -$OCFH_2$;

wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH_3, -CF_3, and –CN;

wherein n is 1, 2 or 3;

2010332969 23 Jan 2015

wherein G and E are independently selected from among C-H or N;

wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,

or wherein Z is N,
and R_4 denotes an electron pair and R_5 is selected from among -H, -C_1-C_6-alkyl, -NH_2, -C_3-C_8-cycloalkyl, -C_3-C_8-heterocyclyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H, and -C_1-C_6-alkyl,

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, -CF_3, -CN, -C_1-C_6-alkyl, -O-C_1-C_6-alkyl, -O-C_3-C_8-cycloalkyl, -O-C_3-C_8-heterocyclyl, -O-C_5-C_{10}-aryl, -O-C_5-C_{10}-heteroaryl, -C_0-C_6-alkylene-CN, -C_0-C_4-alkylene-O-C_1-C_4-alkyl, -C_0-C_4-alkylene-O-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-O-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-O-C_5-C_{10}-aryl, -C_0-C_4-alkylene-O-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-C_0-C_4-alkyl-N(R_9,$R_{9'}$), -C_0-C_4-alkylene-N(R_{10})-Q-C_1-C_4-alkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-N(R_{10})-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-Q-N(R_{11},$R_{11'}$), -C_0-C_4-alkylene-N(R_{12})-Q-N(R_{13},$R_{13'}$), -C_0-C_4-alkylene-R_{14}, -C_0-C_4-alkylene(R_{20},$R_{20'}$), -C_0-C_4-alkylene-Q-C_1-C_6-alkyl, -C_0-C_4-alkylene-Q-C_3-C_8-cycloalkyl, -C_0-C_4-alkylene-Q-C_3-C_8-heterocyclyl, -C_0-C_4-alkylene-Q-C_5-C_{10}-aryl, -C_0-C_4-alkylene-Q-C_5-C_{10}-heteroaryl, -C_0-C_4-alkylene-O-Q-N(R_{15},$R_{15'}$), and -C_0-C_4-alkylene-N(R_{16})-Q-O-(R_{17}),
wherein Q is selected from among -C(O)-, and -SO_2-,
wherein R_{10}, R_{12}, R_{16}, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-cycloalkyl,
wherein R_9, $R_{9'}$, R_{11}, $R_{11'}$, R_{13}, $R_{13'}$, R_{15}, $R_{15'}$, are independently selected from among -H, -C_1-C_6-alkyl, and -C_3-C_6-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 -C_2-C_6-alkylene group,
wherein R_{14} and R_{17} are independently selected from among -H, -C_1-C_6-alkyl, -C_5-C_{10}-aryl, -C_5-C_{10}-heteroaryl, -C_3-C_8-cycloalkyl, and -C_3-C_8-heterocyclyl, wherein said -C_3-C_8-heterocyclyl optionally comprises nitrogen and/or -SO_2- in the ring,

2010332969 23 Jan 2015

and wherein R_{14} and R_{17} are optionally substituted with one or more groups selected from among -OH, $-OCH_3$, $-CF_3$, -COOH, $-OCF_3$, -CN, -halogen, $-C_1-C_4$-alkyl, =O, and $-SO_2-C_1-C_4$-alkyl,
wherein R_{20} and $R_{20'}$ together form a spiro-C_3-C_8-carbocycle or spiro-C_3-C_8-heterocycle comprising one or more group selected from O in the ring, and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among $-C_1-C_6$-alkylene, $-C_2-C_6$-alkenylene, and $-C_4-C_6$-alkynylene and wherein said spirocycle is optionally further substituted with one or more groups selected from among -OH, $-OCH_3$, $-CF_3$, -COOH, $-OCF_3$, -CN, -halogen,

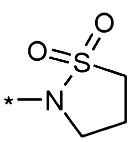
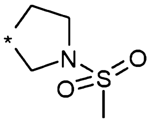
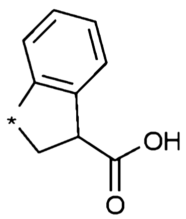
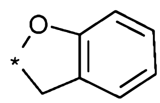
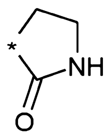
or wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $-L_1-R_{18}$,
wherein L_1 is selected from among -NH-, $-N(C_1-C_4$-alkyl)-, and a bond,
wherein R_{18} is selected from among $-C_5-C_{10}$-aryl, $-C_5-C_{10}$-heteroaryl, $-C_3-C_8$-cycloalkyl, and $-C_3-C_8$-heterocyclyl,
wherein 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,
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 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 $-OCF_3$;

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

2. The compound according to claim 1,

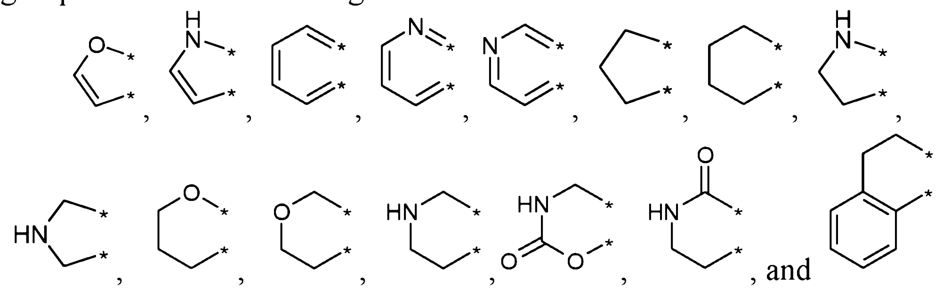
wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidinyl, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8,$R_{8'}$), with R_8 and $R_{8'}$ independently being selected from among -H and -C_1-C_6-alkyl,
wherein R_4 and R_5 if different from -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, -CF_3, -OCF_3, -CN, -O-CH_3, -O-C_2H_5, -O-C_3H_7, -CH_2-CN, -CH_2-O-CH_3, -$(CH_2)_2$-O-CH_3, -C(O)-CH_3, -C(O)-C_2H_5, -C(O)-C_3H_7, -COOH, -C(O)-NH_2, -C(O)-NH-CH_3, -C(O)-$N(CH_3)_2$, -NH-C(O)-CH_3, -N(CH_3)C(O)-CH_3, -NH-C(O)-C_2H_5, -N(CH_3)-C(O)-C_2H_5, -NH-C(O)-C_3H_7, -N(CH_3)-C(O)-C_3H_7, -NH-SO_2-CH_3, -N(CH_3)-SO_2-CH_3, -N(C_2H_5)-SO_2-CH_3, -N(C_3H_7)-SO_2-CH_3, -NH-SO_2-C_2H_5, -N(CH_3)-SO_2-C_2H_5, -N(C_2H_5)-SO_2-C_2H_5, -N(C_3H_7)-SO_2-C_2H_5, -NH-SO_2-C_3H_7, -N(CH_3)-SO_2-C_3H_7, -N(C_2H_5)-SO_2-C_3H_7, -N(C_3H_7)-SO_2-C_3H_7, -NH-SO_2-C_3H_5, -N(CH_3)-SO_2-C_3H_5, -N(C_2H_5)-SO_2-C_3H_5, -N(C_3H_7)-SO_2-C_2H_5, -CH_2-NH-SO_2-CH_3, -CH_2-N(CH_3)-SO_2-CH_3, -CH_2-NH-SO_2-C_2H_5, -CH_2-N(CH_3)-SO_2-C_2H_5, -CH_2-NH-SO_2-C_3H_7, -CH_2-N(CH_3)-SO_2-C_3H_7, -CH_2-NH-SO_2-C_3H_5, -CH_2-N(CH_3)-SO_2-C_3H_5, -NH-C(O)-NH_2, -N(CH_3)-C(O)-NH_2, -NH-C(O)-NH-CH_3, -N(CH_3)-C(O)-NH-CH_3, -NH-C(O)-$N(CH_3)_2$, -N(CH_3)-C(O)-$N(CH_3)_2$, -SO_2-NH_2, -SO_2-NH(CH_3), -SO_2-$N(CH_3)_2$, -C(O)-NH-C_2H_5, -C(O)-N(CH_3)-C_2H_5, -C(O)-N(CH_3)-C_3H_7, -C(O)-N(CH_3)-C_4H_9, -C(O)-NH-CH(CH_3)-C_2H_5, -C(O)-N(CH_3)-CH(CH_3)-C_2H_5, -CH_2-C(O)-NH_2, -CH_2-C(O)-NH-CH_3, -CH_2-C(O)-$N(CH_3)_2$, –N(CH_3)-SO_2-$N(CH_3)_2$, -(C_6-aryl)-COOH, -phenyl, -pyridin-4-yl, -CH_2-3-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,


,

,

,

and

,

or wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure –L_1-R_{18},
wherein L_1 is selected from among -NH-, -N(CH_3)-, and -N(C_2H_5)-,
and wherein R_{18} 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 R_{18} is optionally substituted by one or more groups selected from among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$,

and wherein R_4, R_5 and R_{18} are optionally further bi-valently substituted by one or more groups selected from among



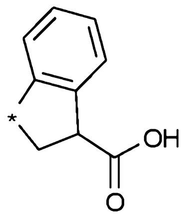
on one ring atom or on two neighboring ring atoms, such that spirocyclic or annellated rings are formed.

3. The compound according to any of the preceding claims, wherein R_7 is selected from among $-C_5-C_6$-aryl, $-C_5-C_6$-heteroaryl, $-C_3-C_8$-cycloalkyl, and $-C_3-C_8$-heterocyclyl wherein the ring R_7 is optionally substituted with one or more groups selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl,$–C(CH_3)_2$-CN, and -halogen.

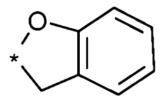
4. The compound according to any of the preceding claims, wherein R_7 is selected from among $-C_5-C_6$-aryl, and $-C_5-C_6$-heteroaryl,
wherein the ring R_7 is optionally substituted with one or more groups selected from among $-CF_3$, $-O-CF_3$, $-S-CF_3$, -CN, -methyl, –F, -Cl, $–C(CH_3)_2$-CN, and -Br.

5. The compound according to any of the preceding claims 1, 3, and 4
wherein Z is C,
and R_4 denotes –H and R_5 is a group of the structure $–L_1-R_{18}$,
wherein L_1 is selected from among -NH- , $-N(CH_3)-$, $-N(C_2H_5)-$, and a bond,
and wherein R_{18} is selected from among $–C_6$-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,
and wherein R_{18} is optionally substituted by one or more groups selected from among among -F, $-CF_3$, $-OCF_3$, -CN, -OH, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$,

or wherein Z is C,
and R_4 and R_5 are independently selected from among -H, -C_1-C_6-alkyl, and -N(R_{19},$R_{19'}$), wherein R_{19} and $R_{19'}$ together form a –C_2-C_6-alkylene group, preferably a –C_4-C_5alkylene group such that a ring is formed,
wherein such ring is optionally substituted by one or more groups selected from among among -F, -CF_3, -OCF_3, -CN, -OH, -O-CH_3, -CH_3, -NH-C(O)-CH_3, -N(CH_3)-C(O)-CH_3, -C(O)-CH_3, -S(O)$_2$-CH_3, -NH-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_3, -N(CH_3)-S(O)$_2$-CH_2-CH_3, -(C_6-aryl)-COOH, -C(O)-O-C_2H_5,



, and



.

6. The compound according to any of the preceding claims, wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH_2, and -C≡CH.

7. The compound according to any of the preceding claims, wherein R_3 is selected from among -H, -CF_3, -O-CH_3, and –methyl.

8. The compound according to any of the preceding claims, wherein R_6 is selected from among -H, -CH_3, -C_2H_5, -O-CH_3, -O-C_2H_5, -F, -CF_3, and -OCF_3.

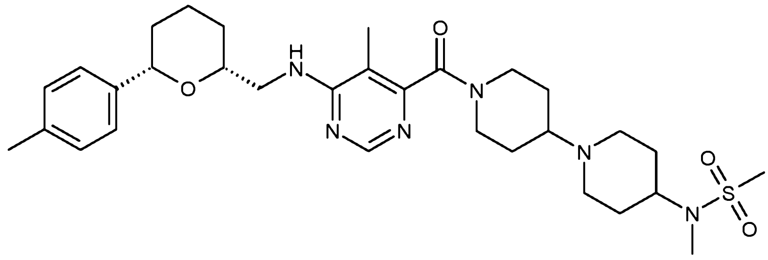
9. The compound according to any of the preceding claims, wherein R_1 is -H.

10. The compound according to any of the preceding claims, wherein n is 2.

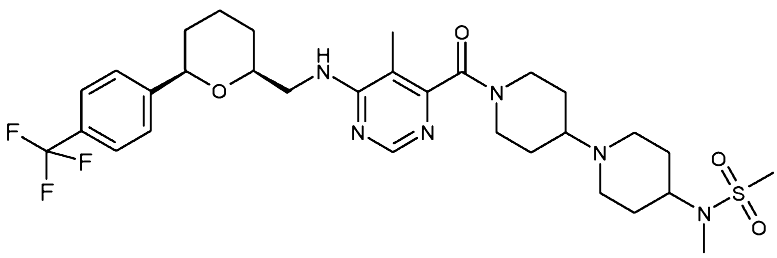
11. The compound according to any of the preceding claims, wherein G and E are N.

12. The compound according to any of the preceding claims, wherein Z is C.

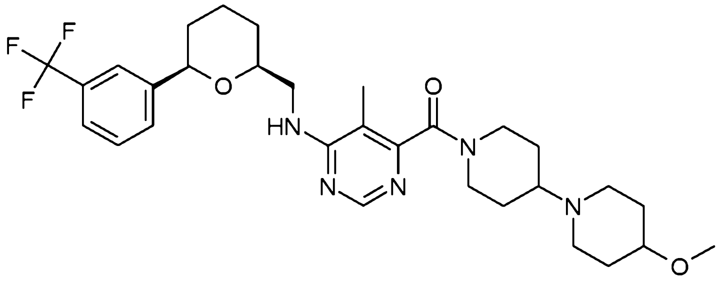
13. The compound according to any of the preceeding claims chosen from the group consisting of



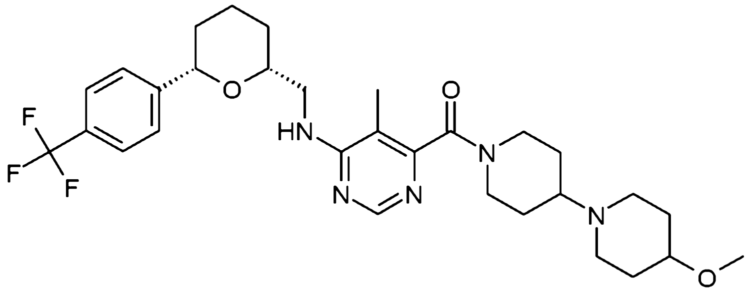
,



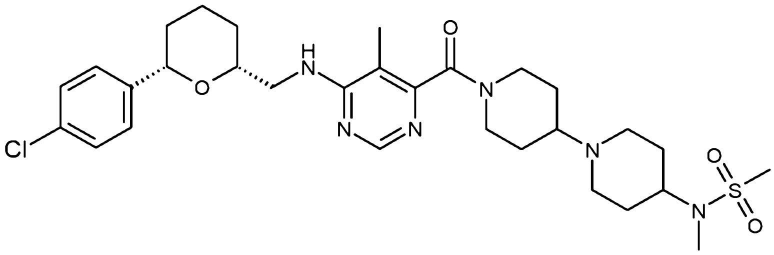
,



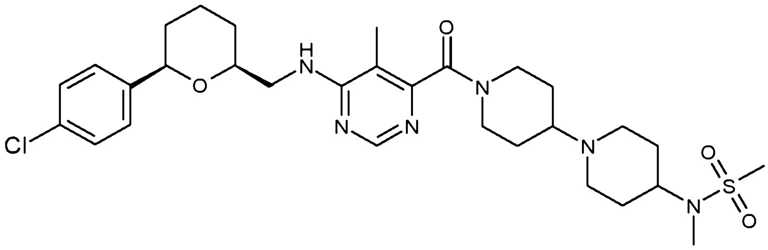
,



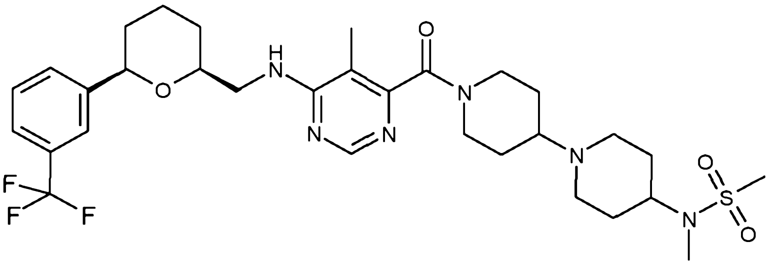
,



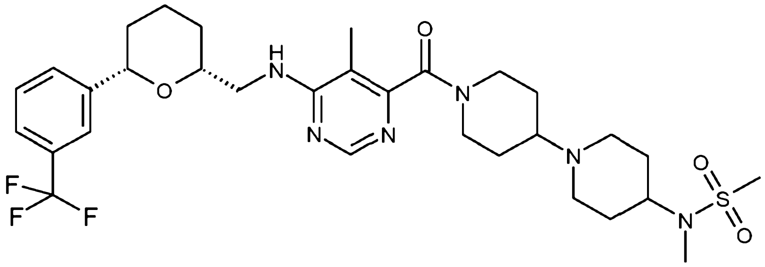
,



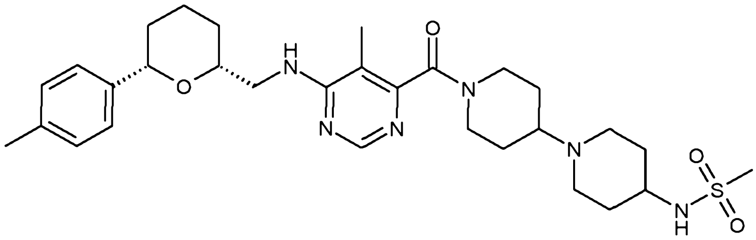
,



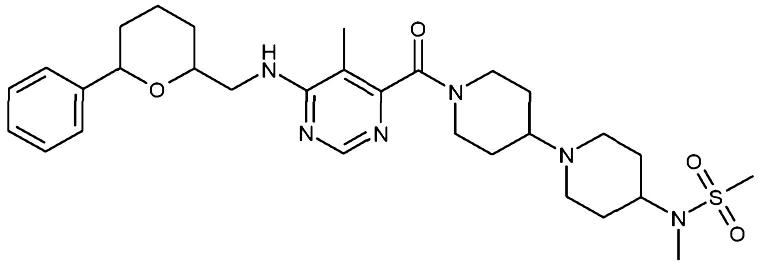
,



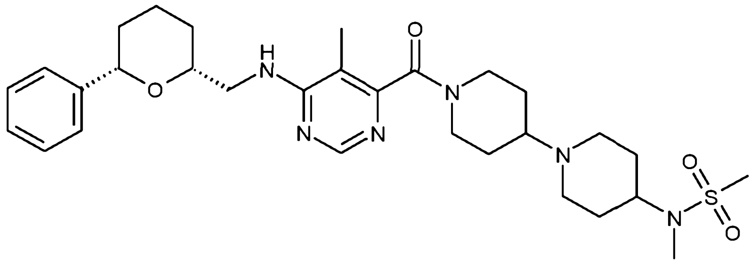
,



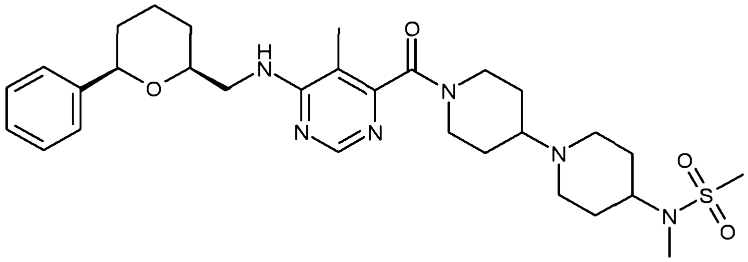
,



,

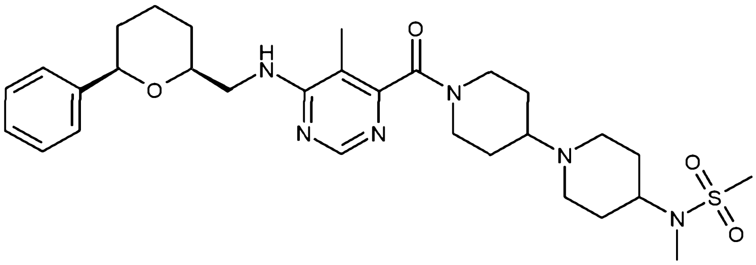


,

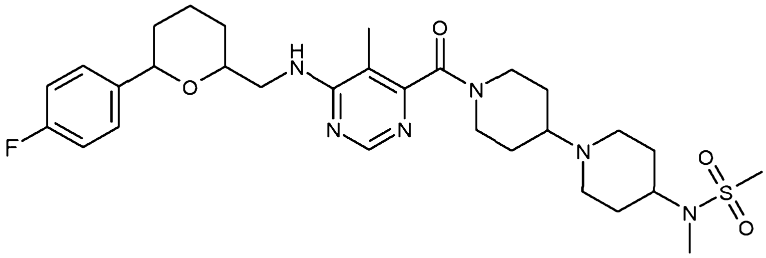


,

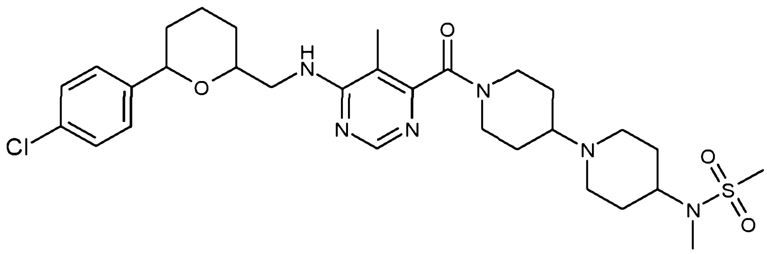
2010332969 23 Jan 2015



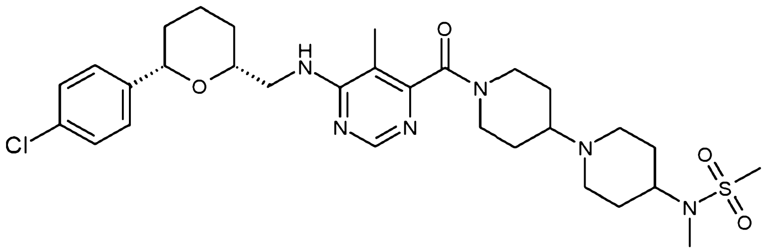
,



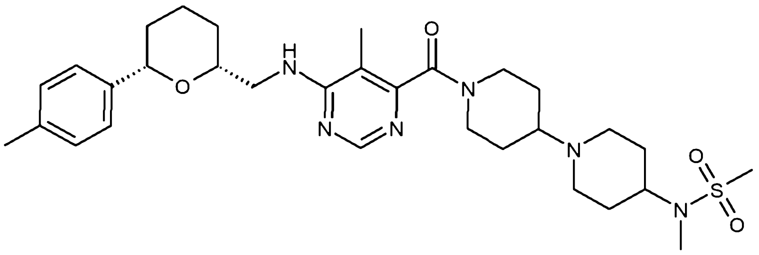
,



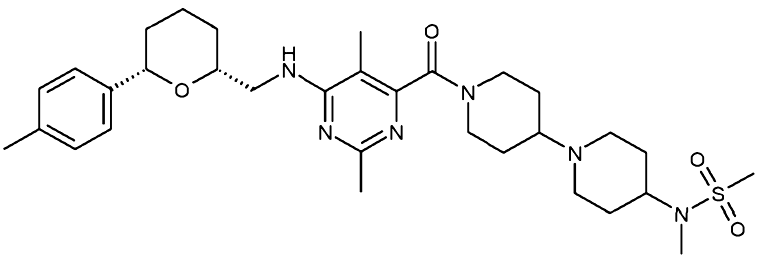
,



,

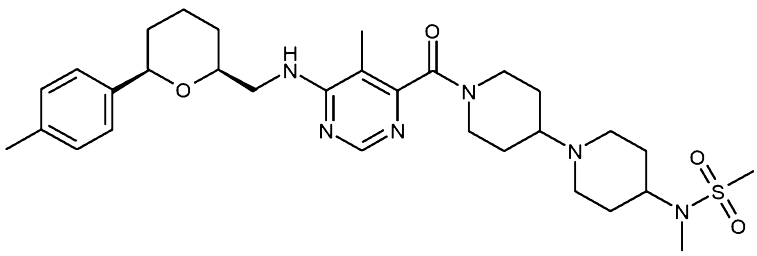


,

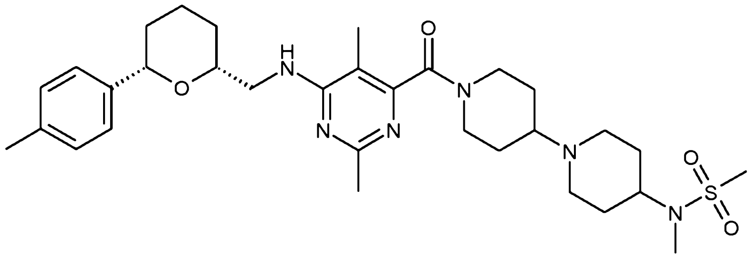


,

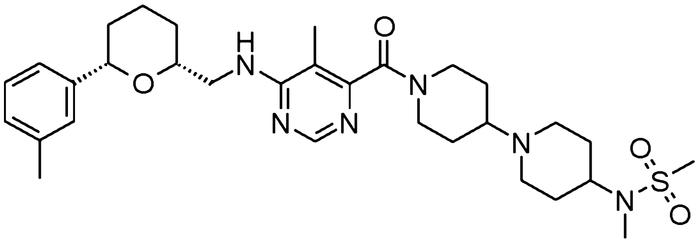
2010332969 23 Jan 2015



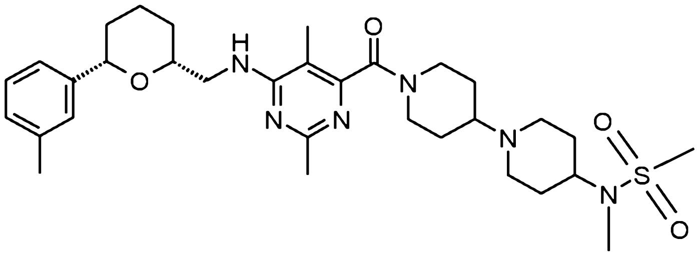
,



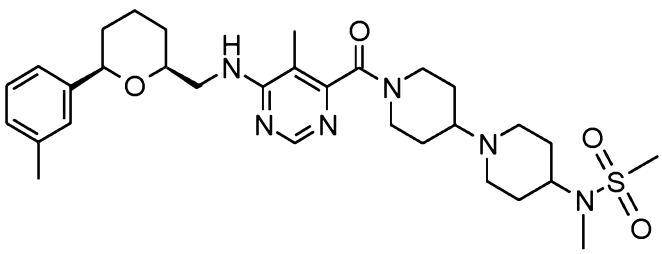
,



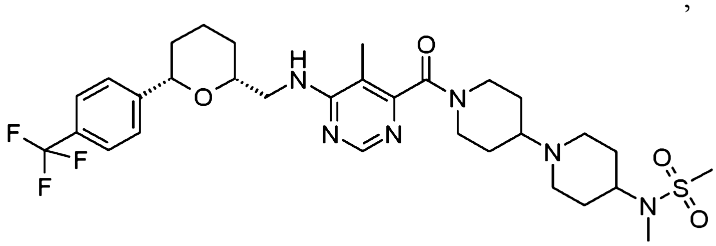
,



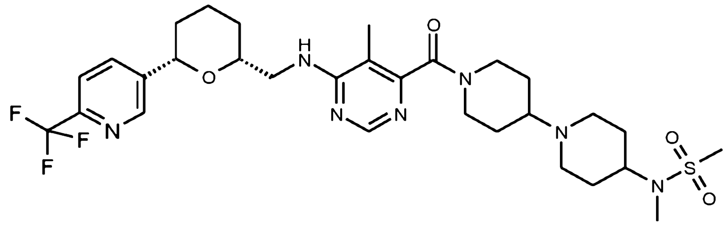
,



,

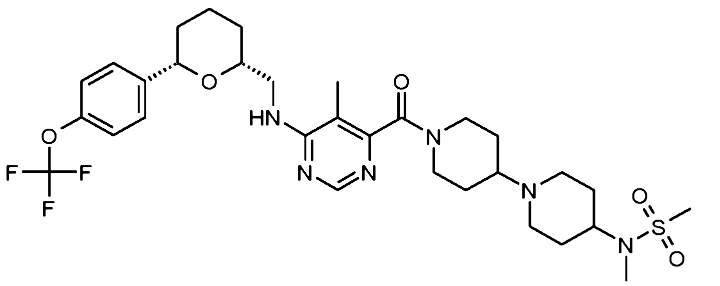


,

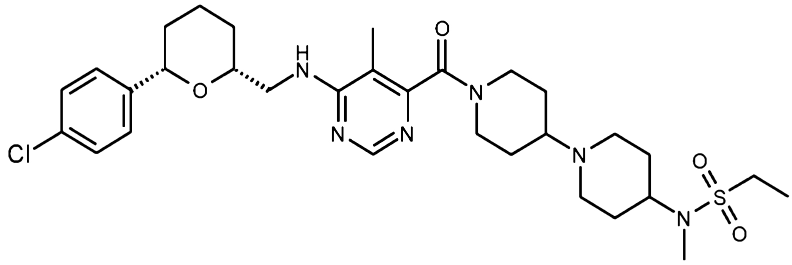


,

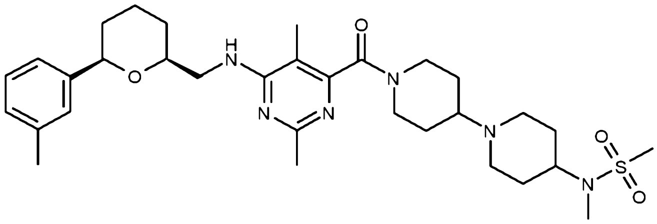
2010332969 23 Jan 2015



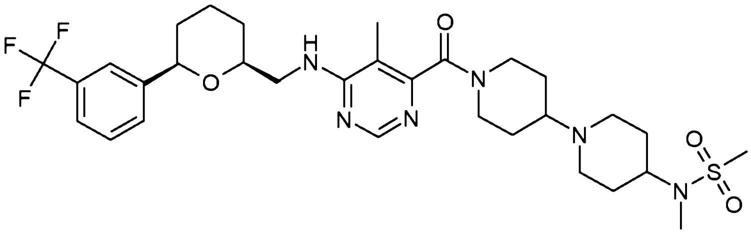
,



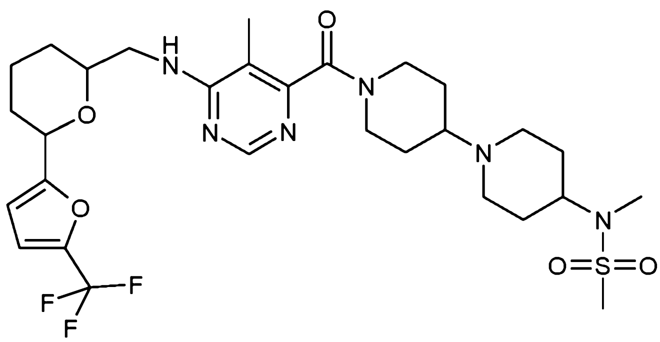
,



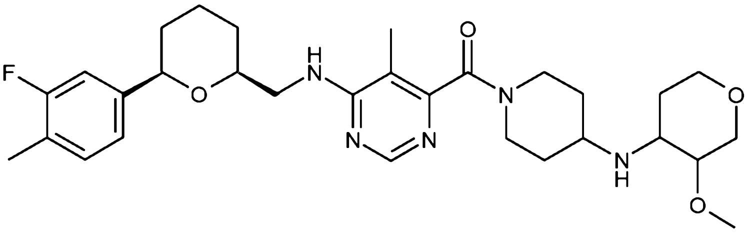
,



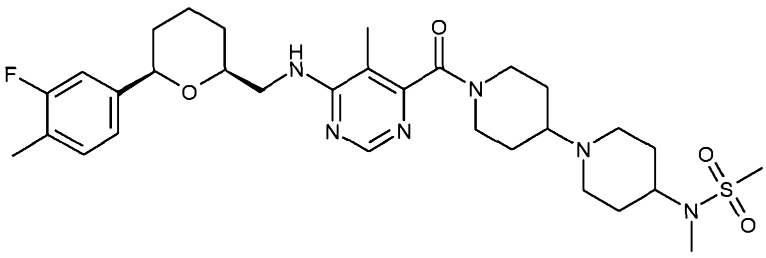
,



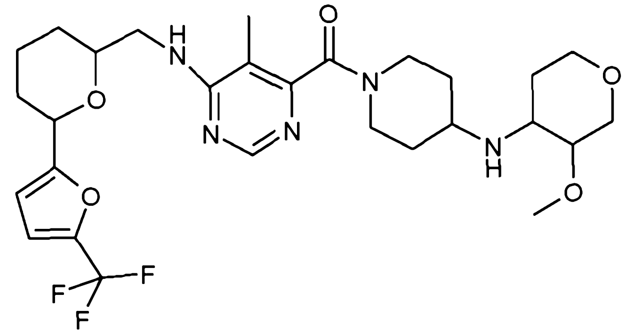
,



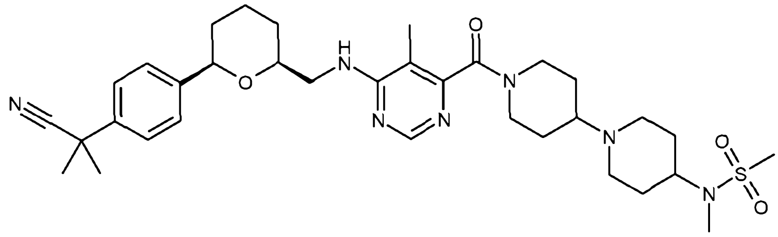
,



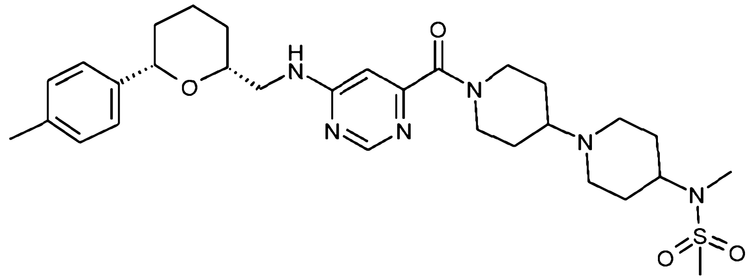
,



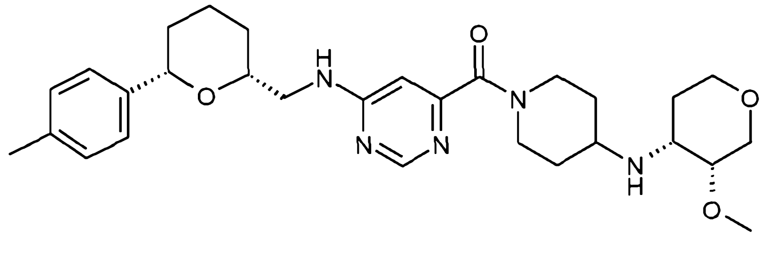
,



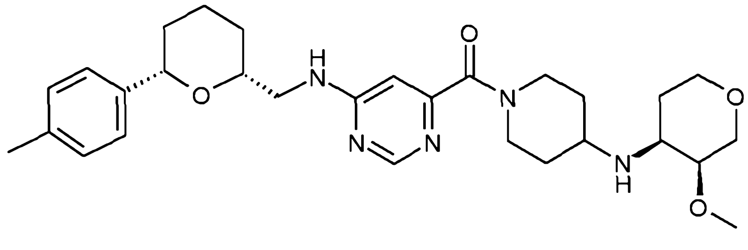
,



,

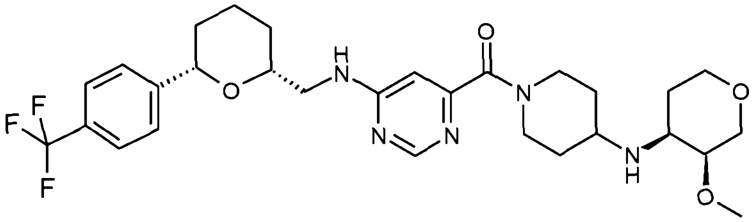


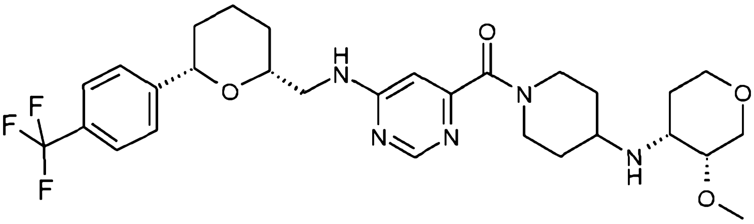
,

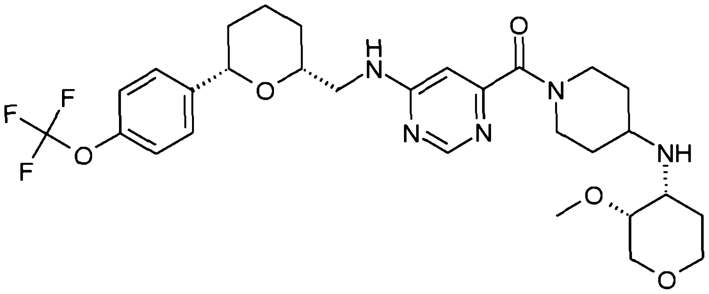


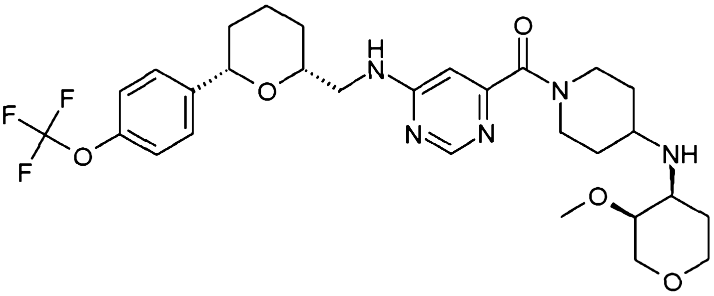
,

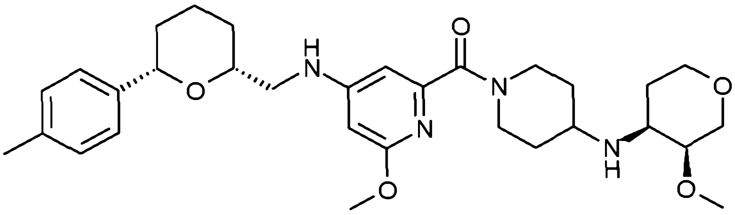
2010332969 23 Jan 2015

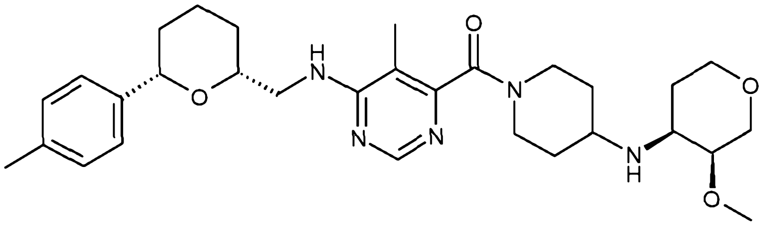

,

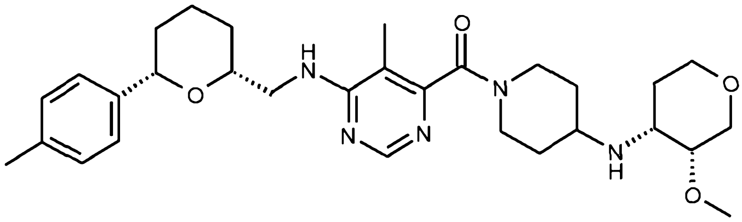

,

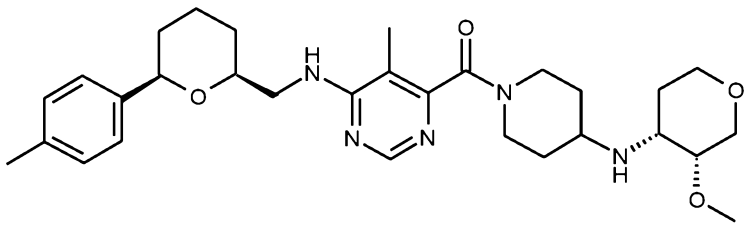

,

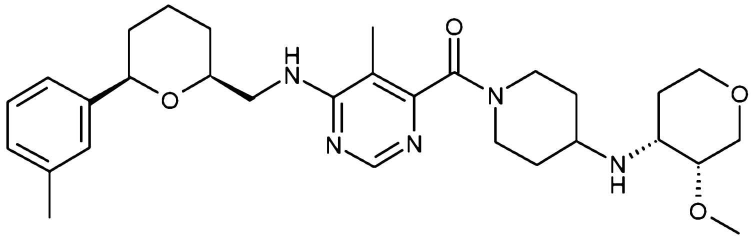

,

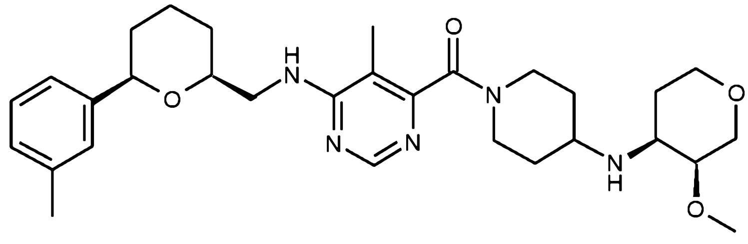

,

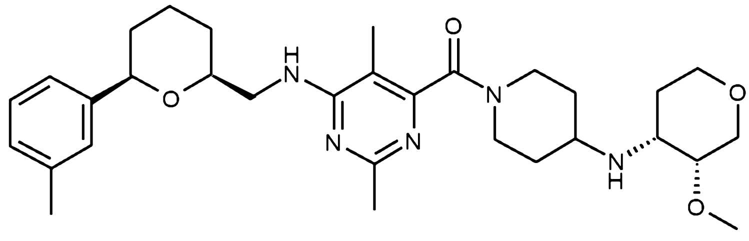

,

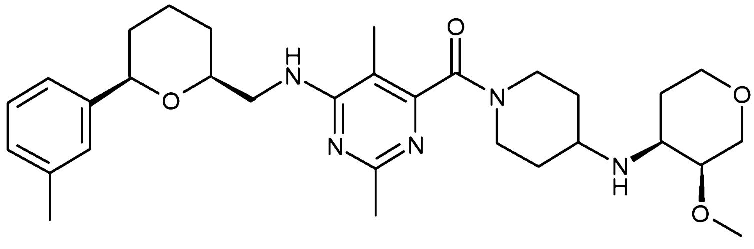

,

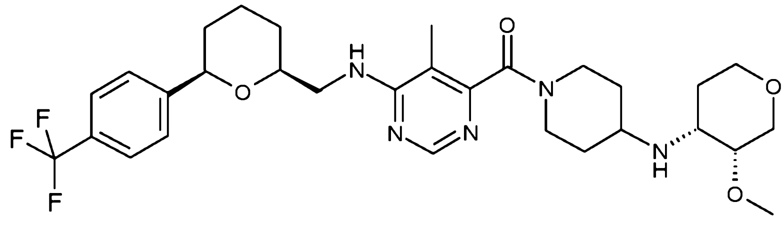

,

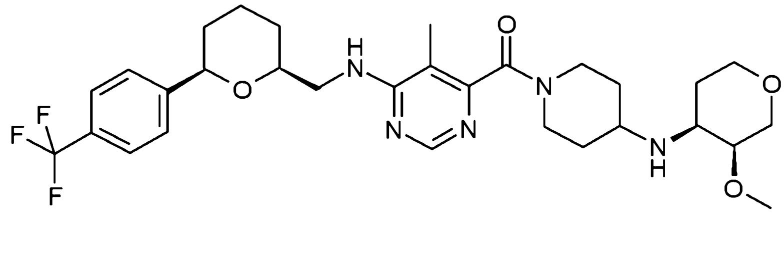

,

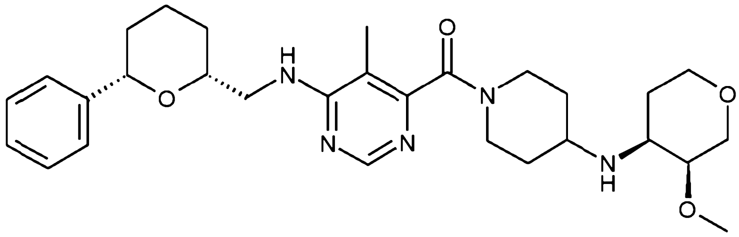

,

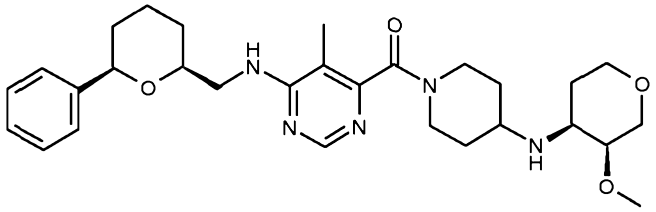

,

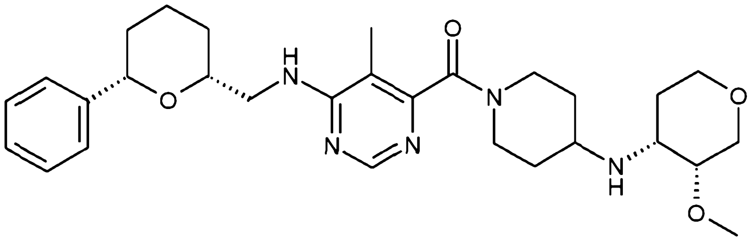

,

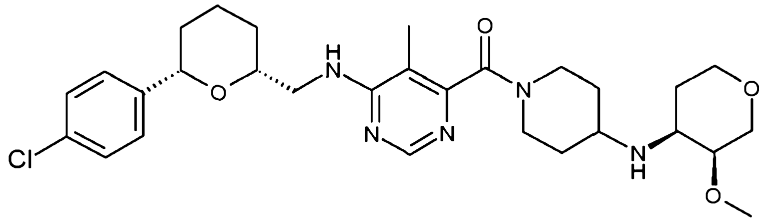

,

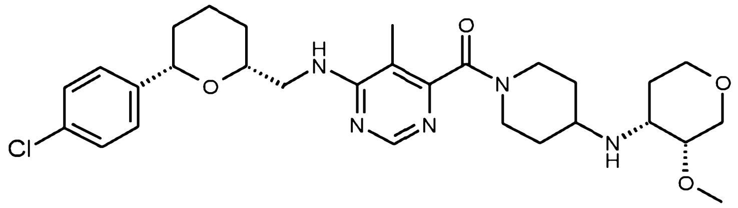

,

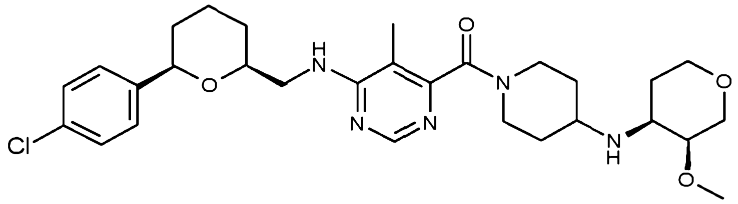

,

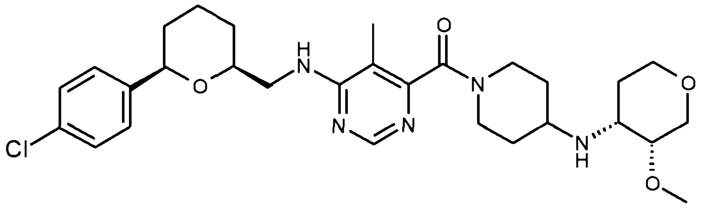

,

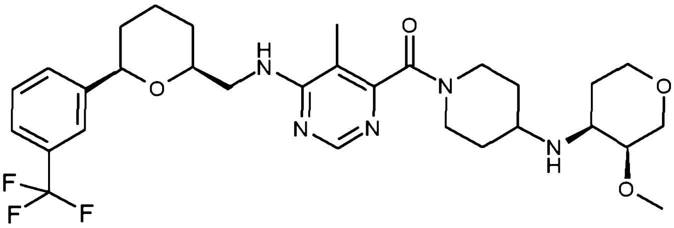

,

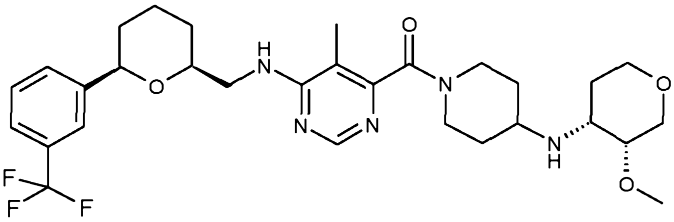

,

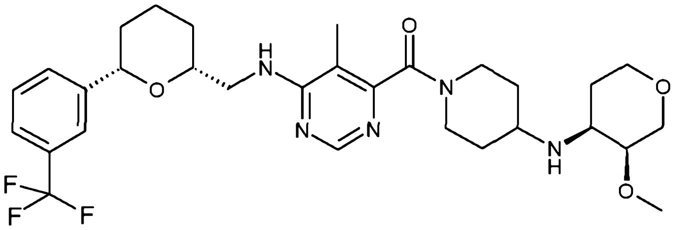

,

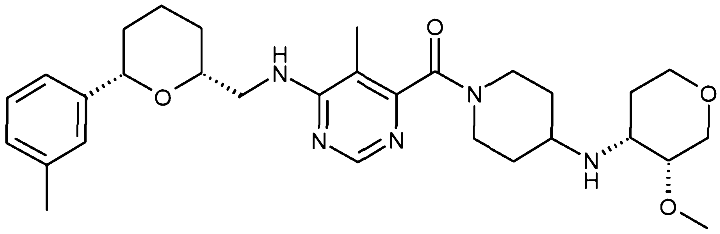

,

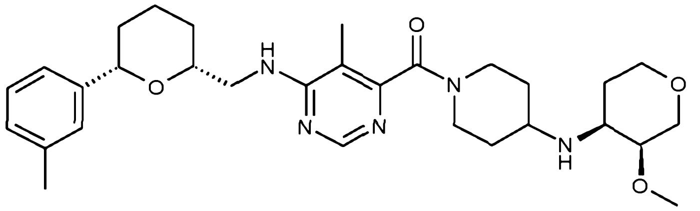

,

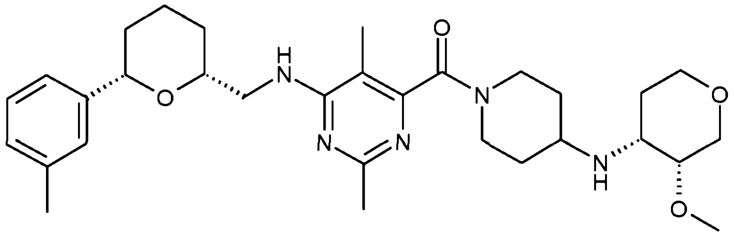

,

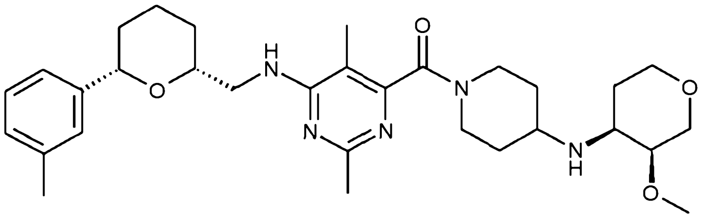

,

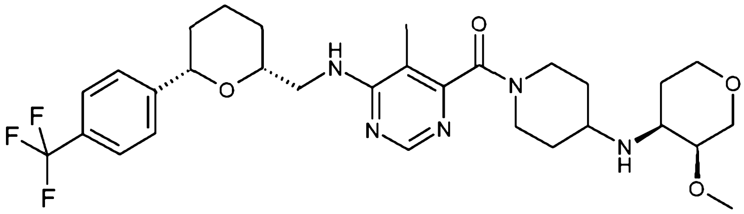

,

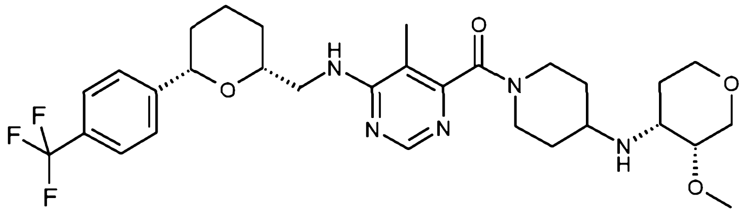

,

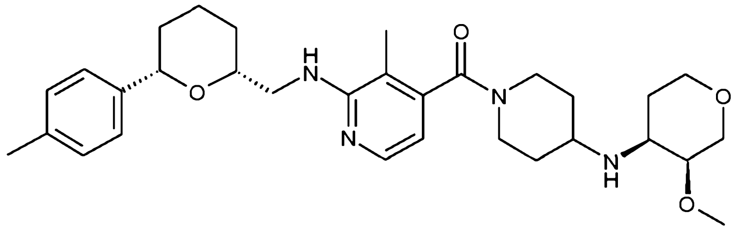

,

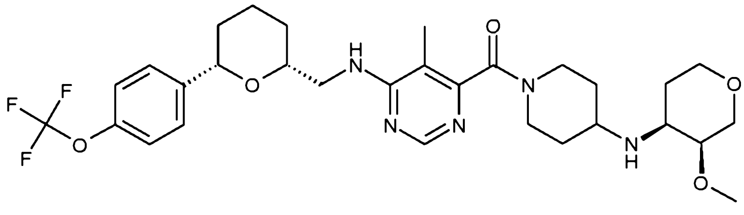

,

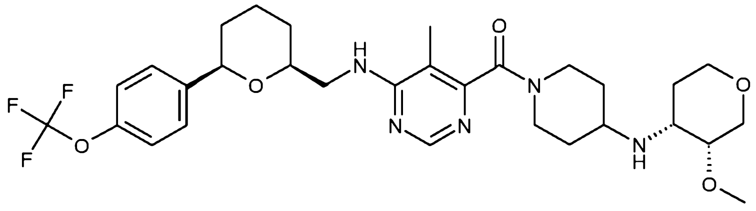

,

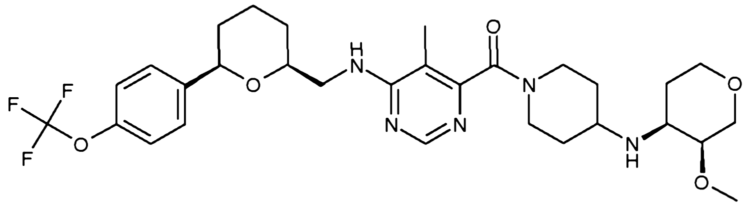

,

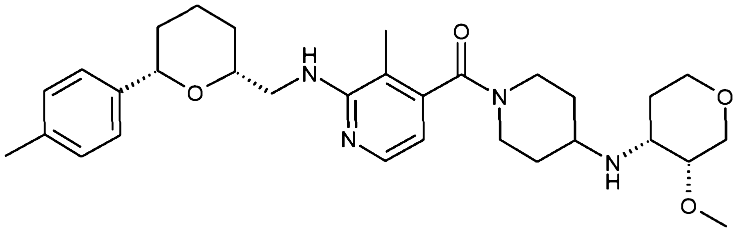

,

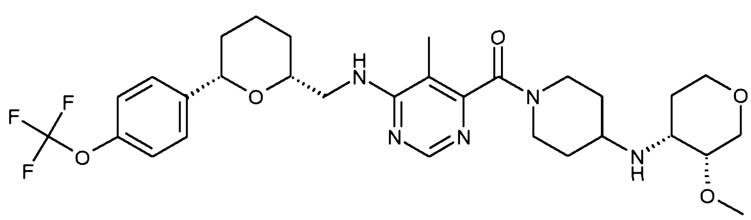

,

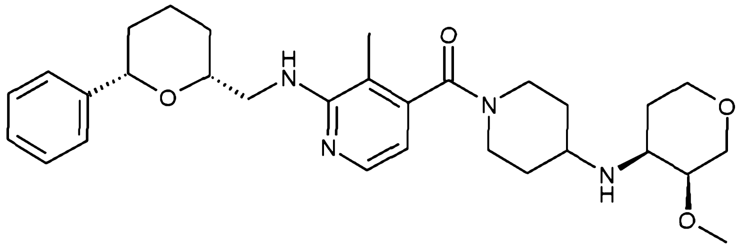

,


,

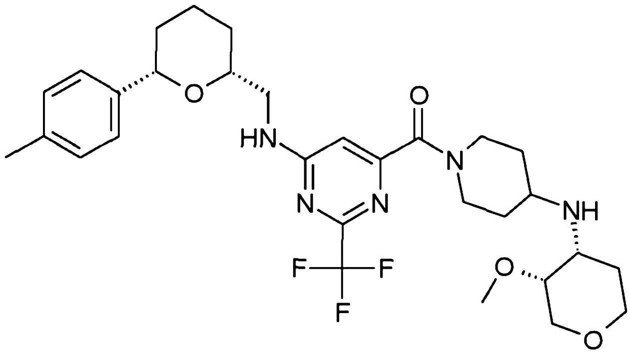

,


,

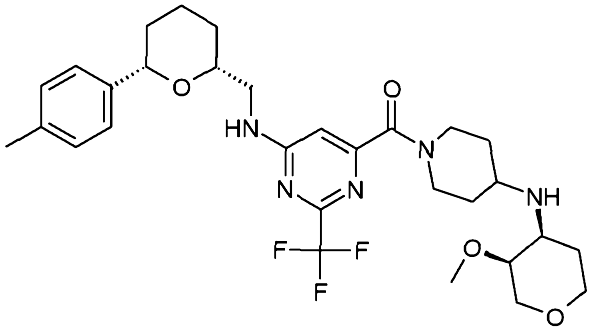

,



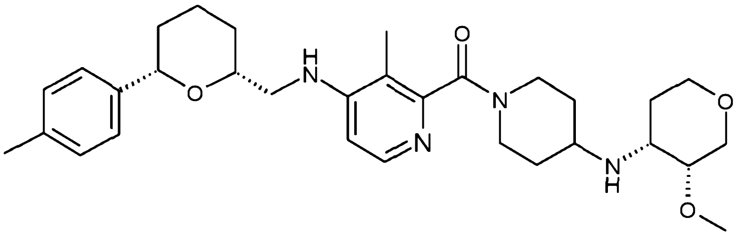
,



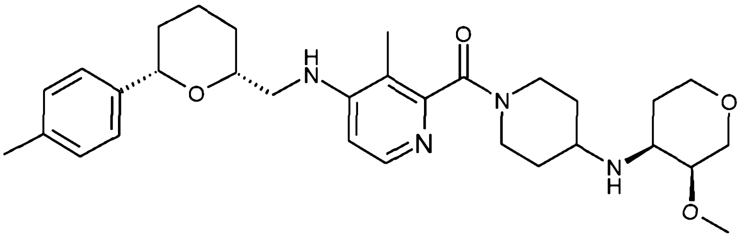
,



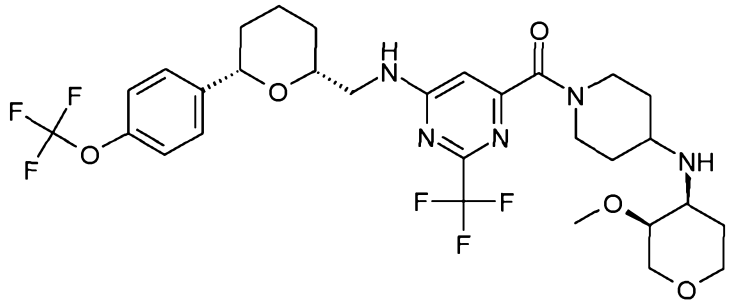
,



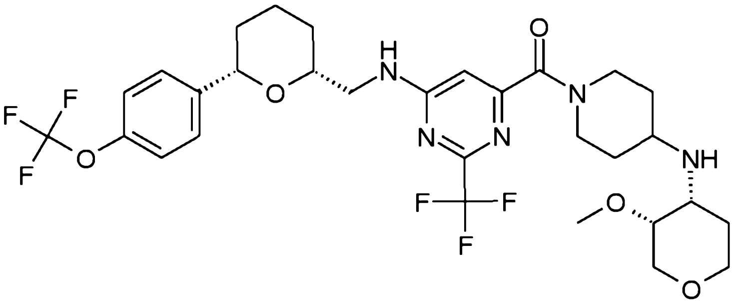
,

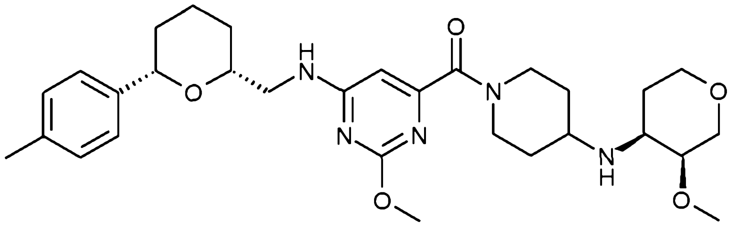


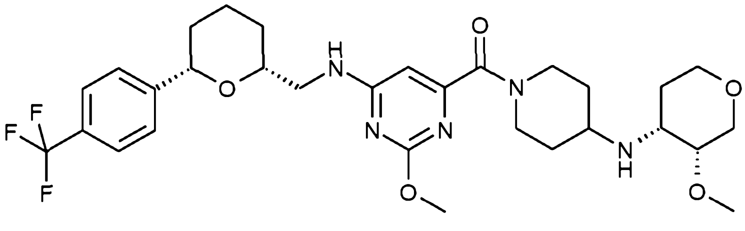
,

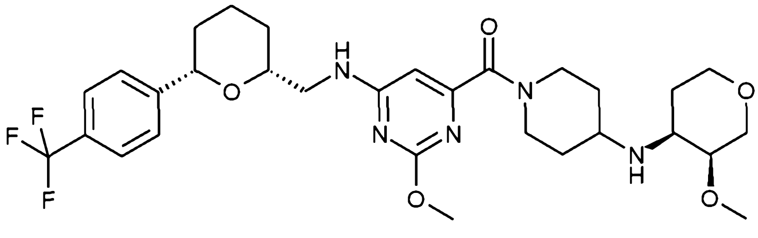


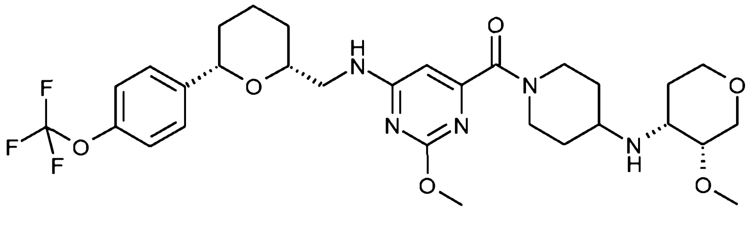
,

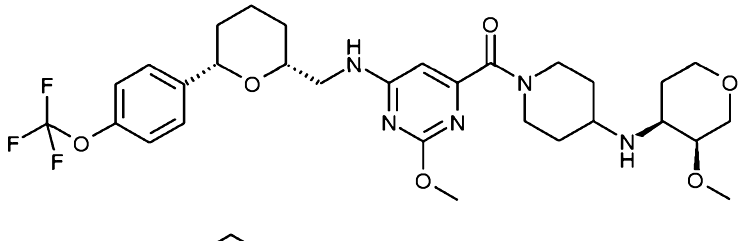

,

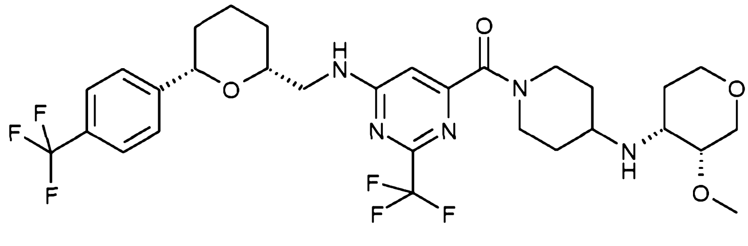

,

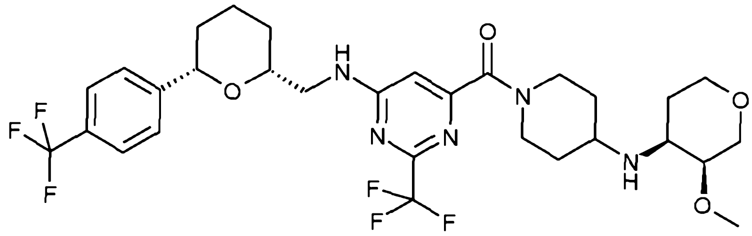

,


,

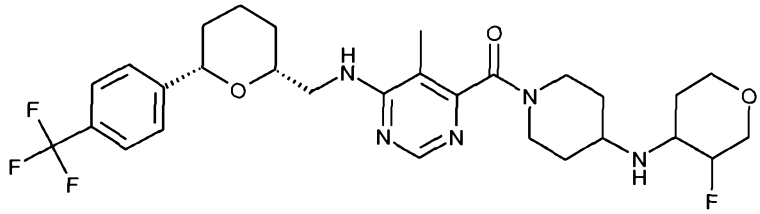

,


,

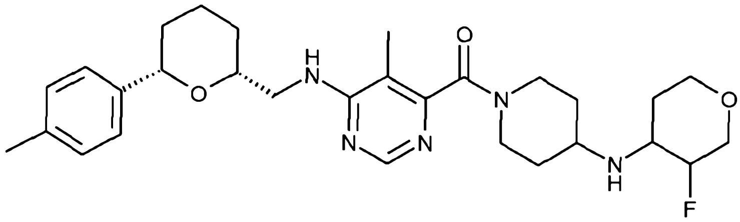

,



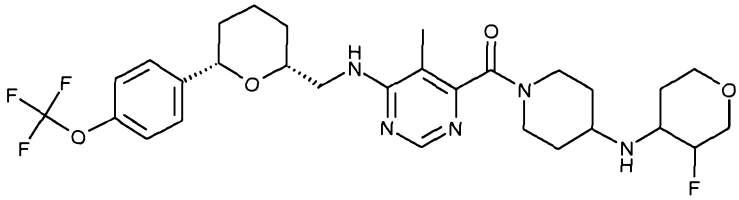
,



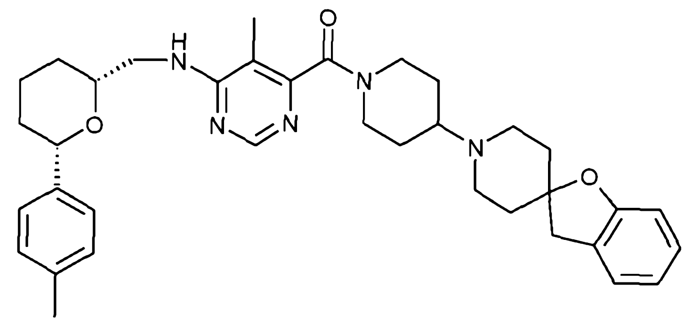
,



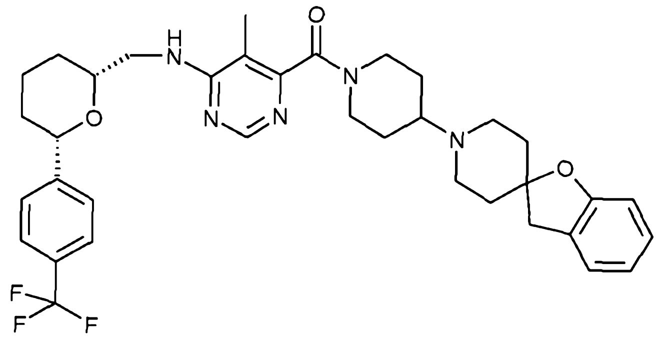
,



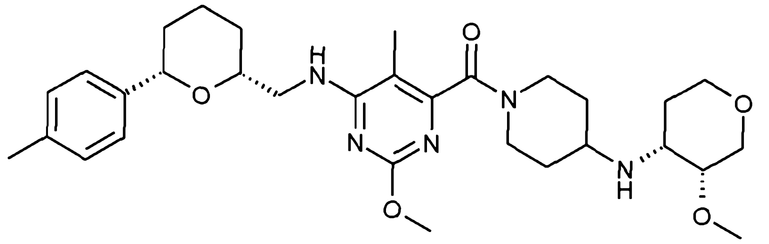
,



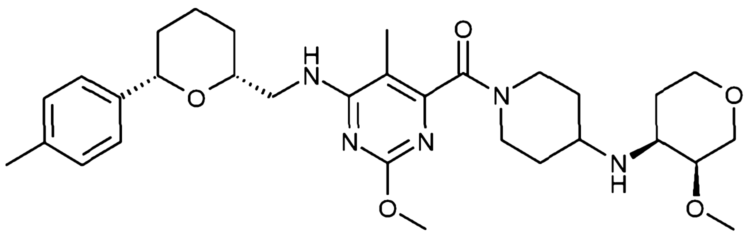
,

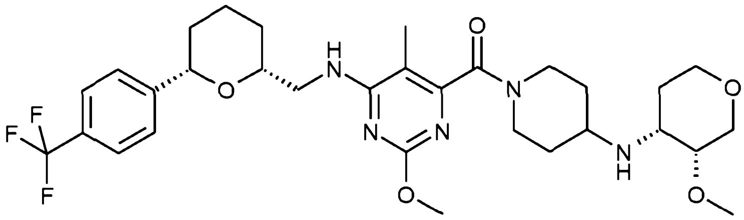


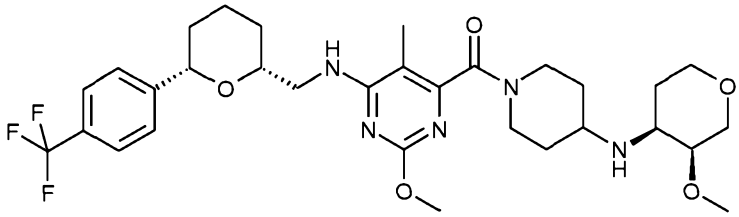
,

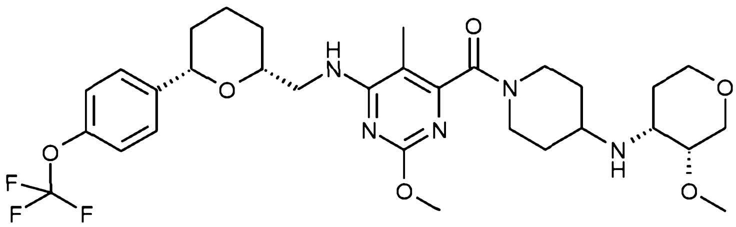


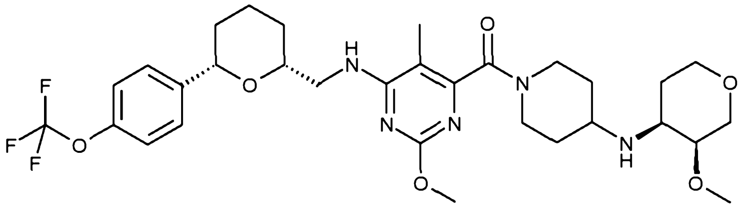
,

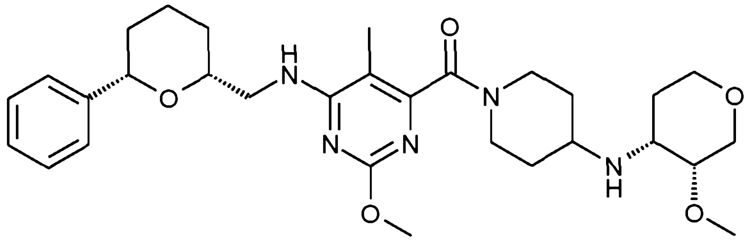

,

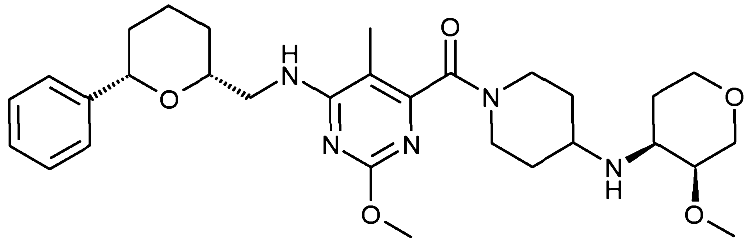

,


,

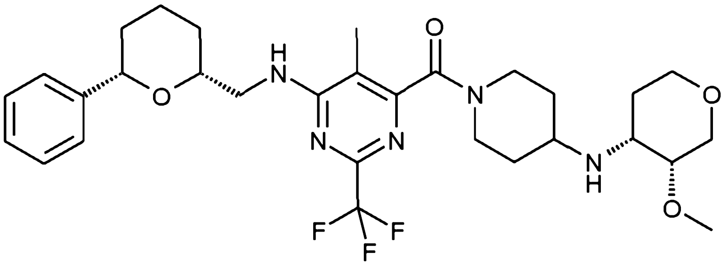

,


,

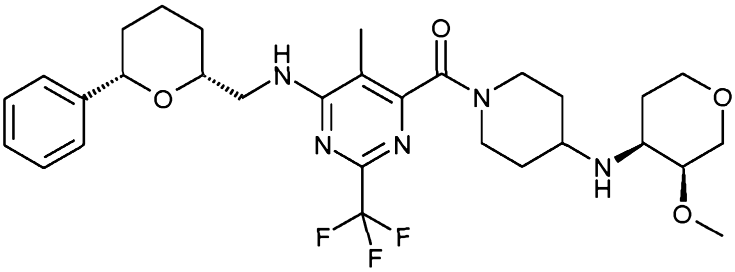

,


,

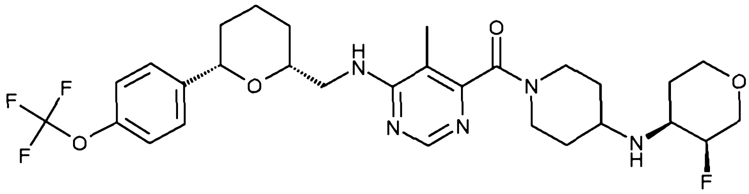
2010332969 23 Jan 2015



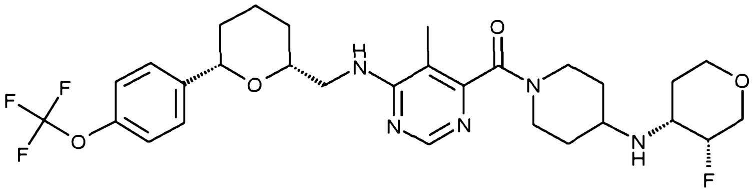
,



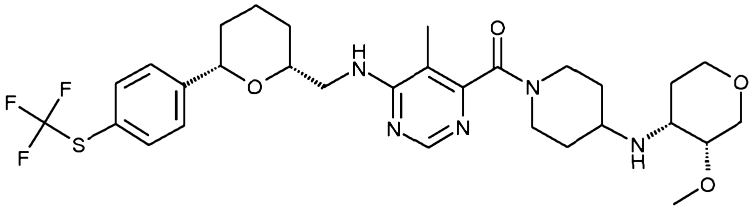
,



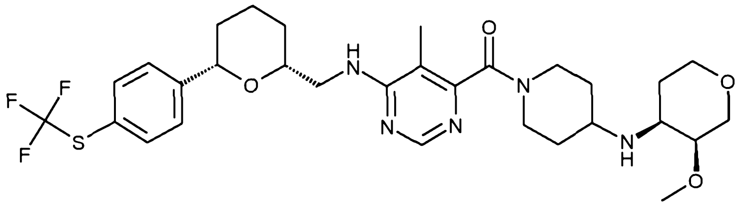
,



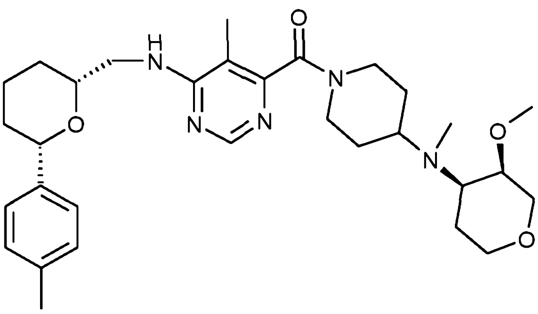
,



,

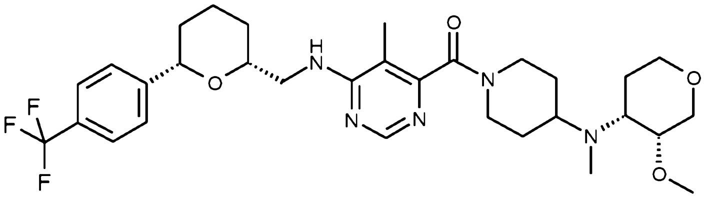


,

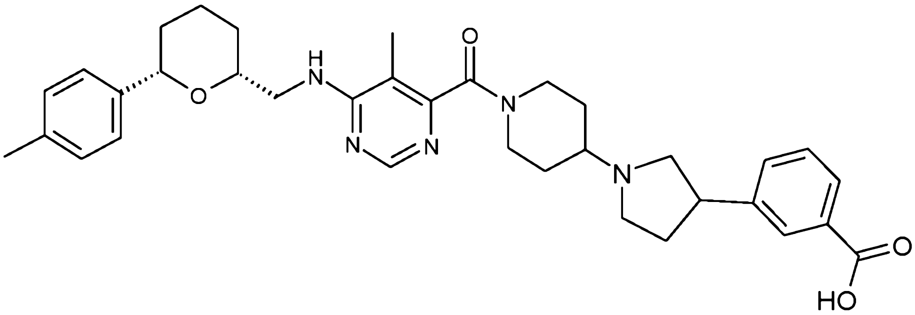


,

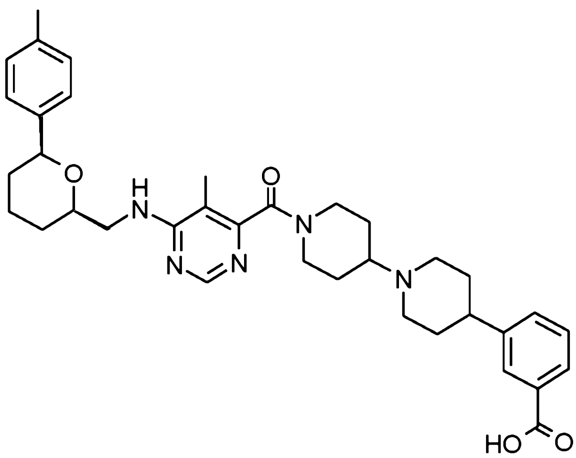
2010332969 23 Jan 2015



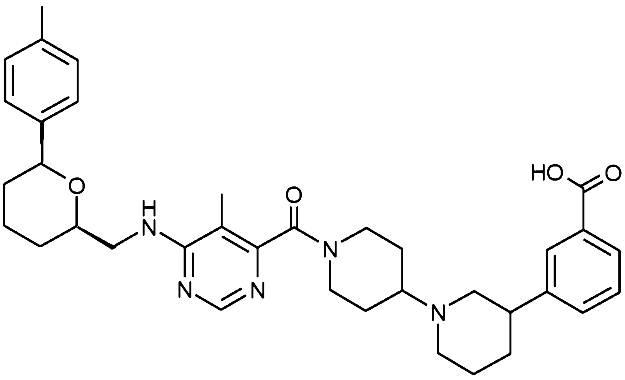
,



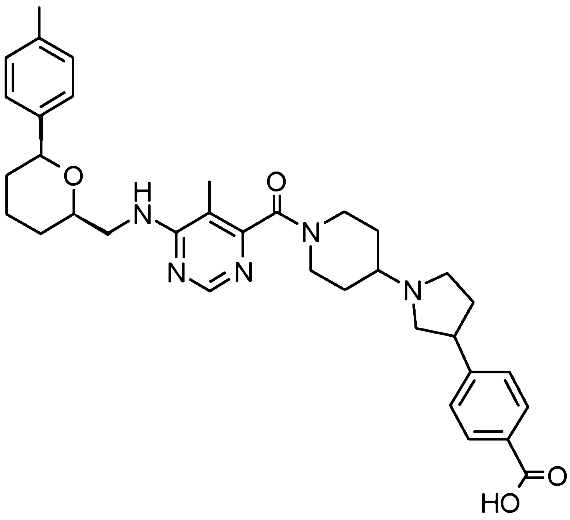
,



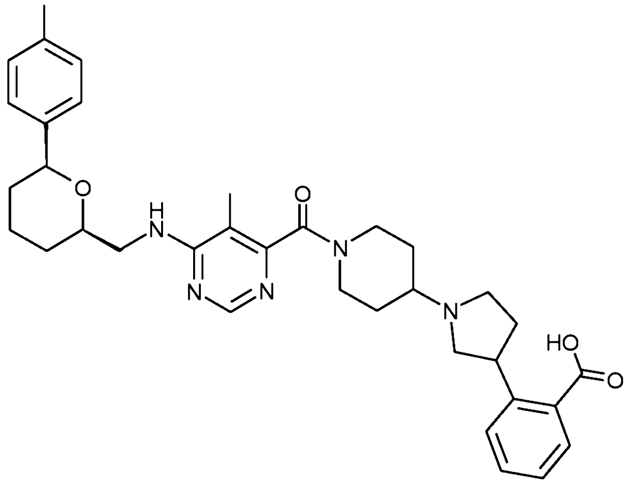
,



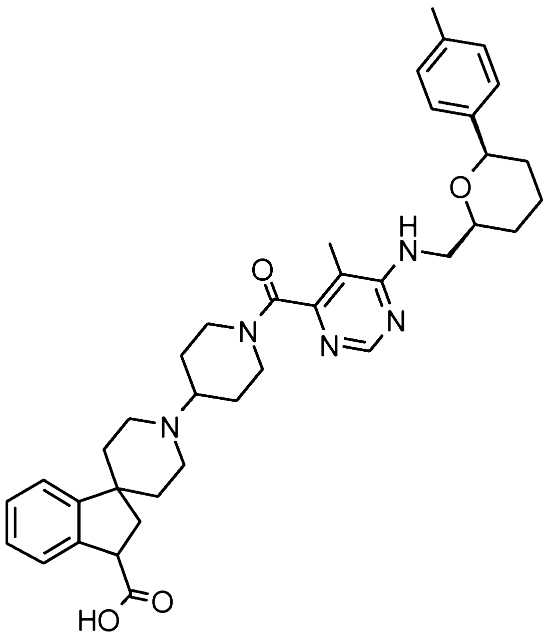
,



,



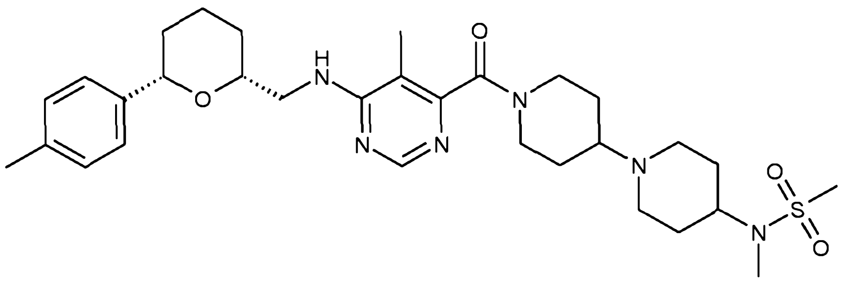
,

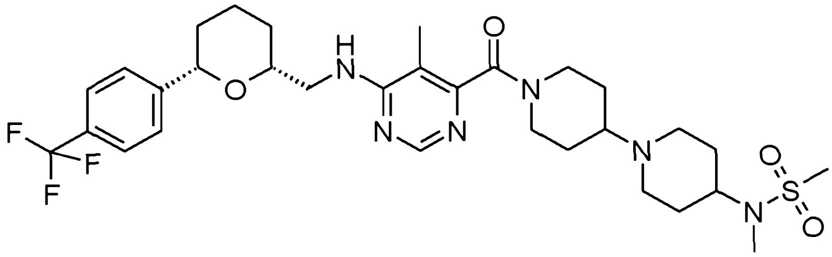


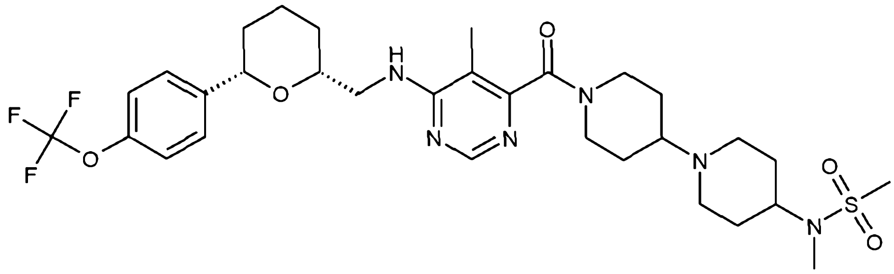
.

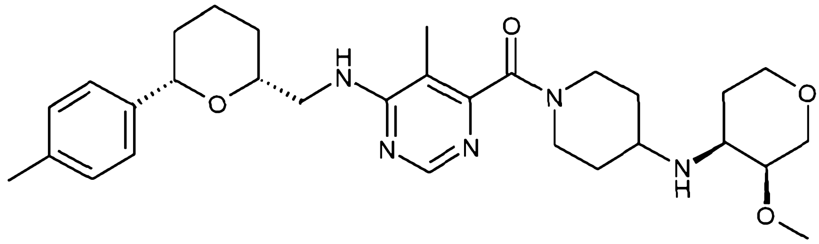
14. The compound according to any of the preceeding claims chosen from the group consisting of

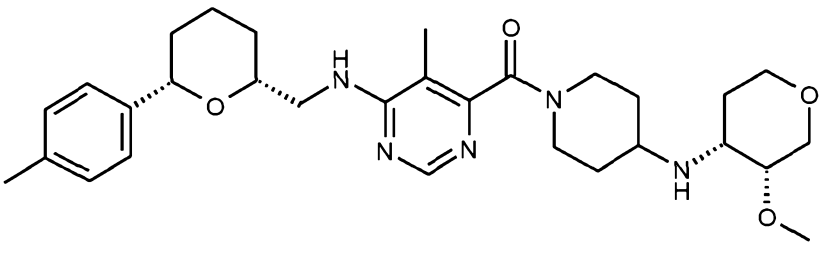
2010332969 23 Jan 2015

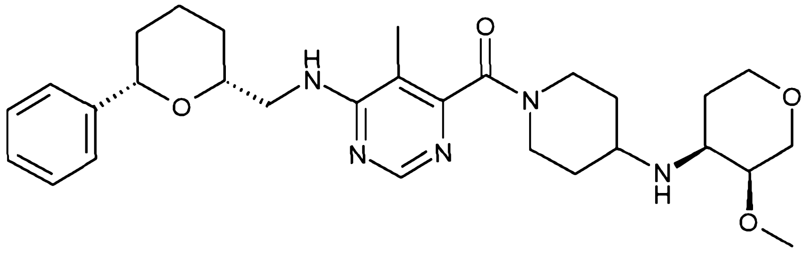

,


,

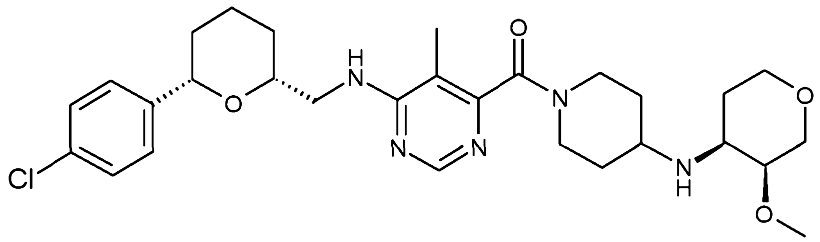

,

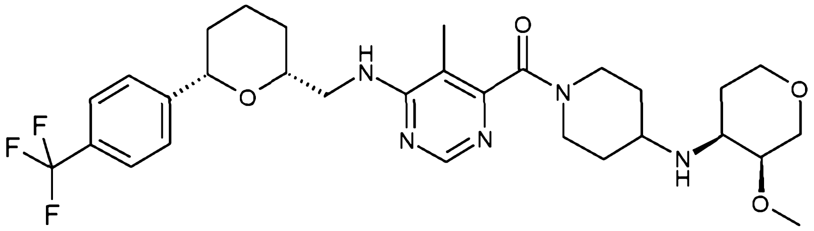

,

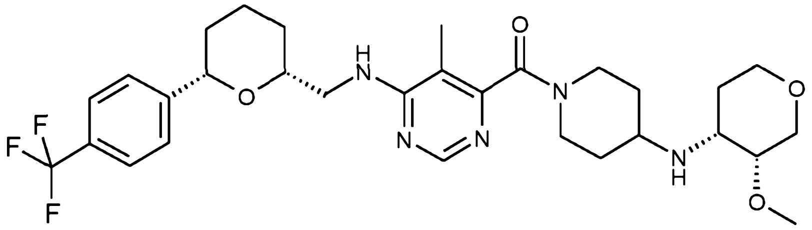

,

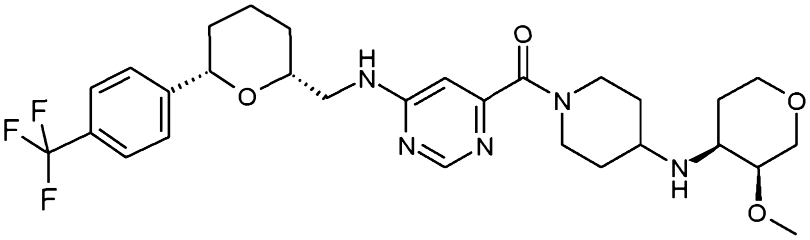

,

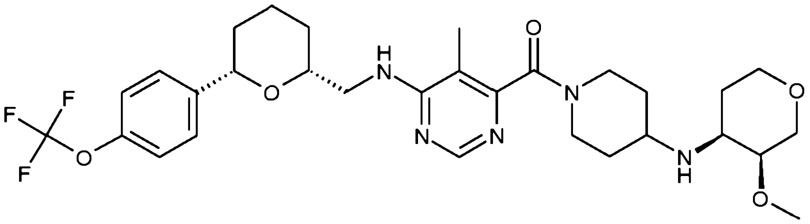
2010332969 23 Jan 2015

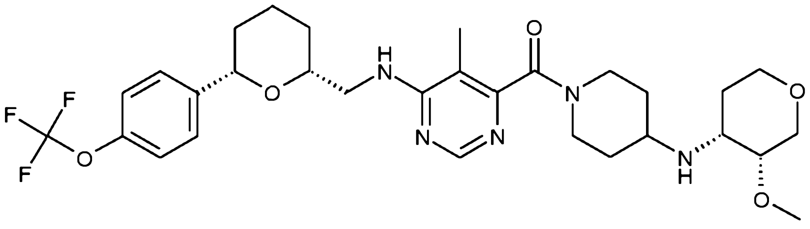

,

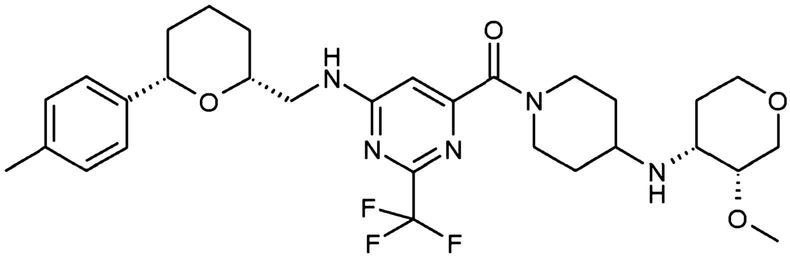

,

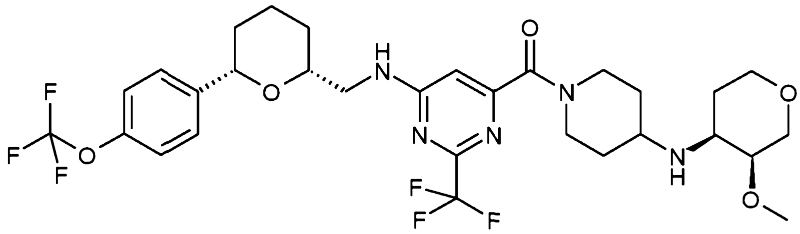

,

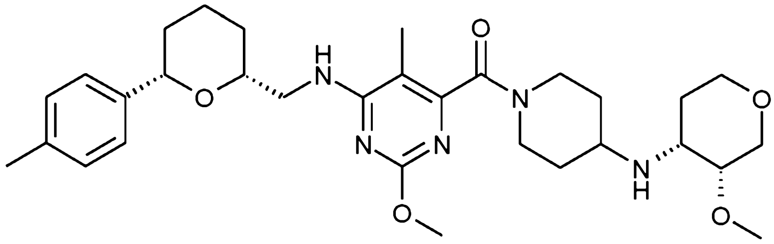

,

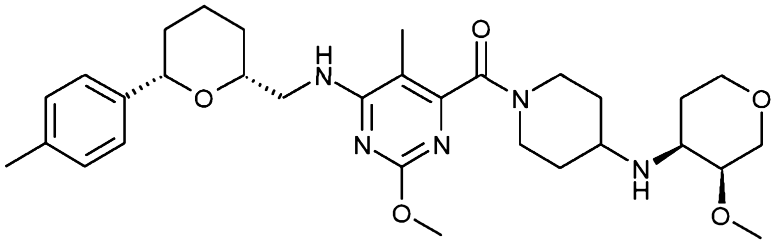

,

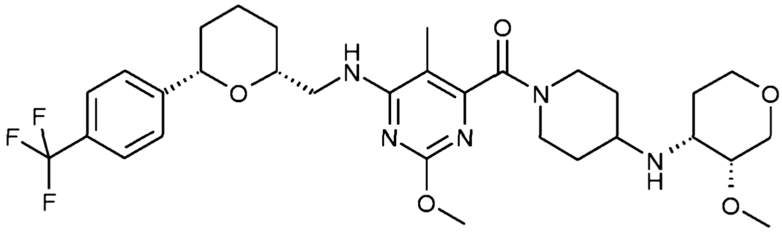

,

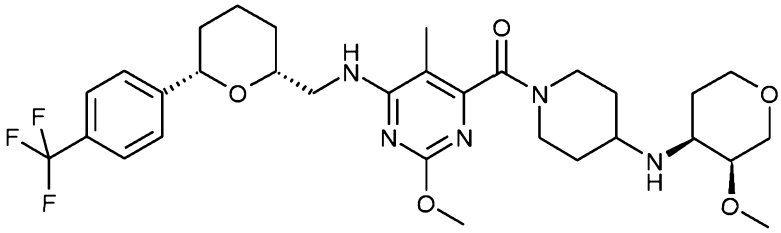

,

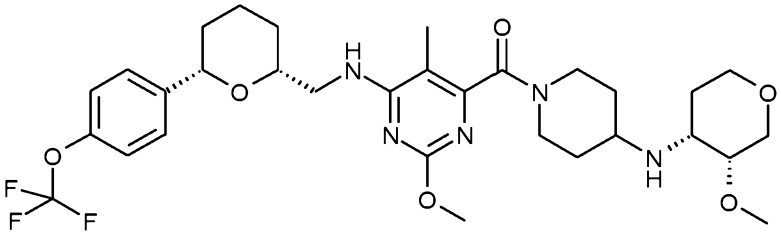

,

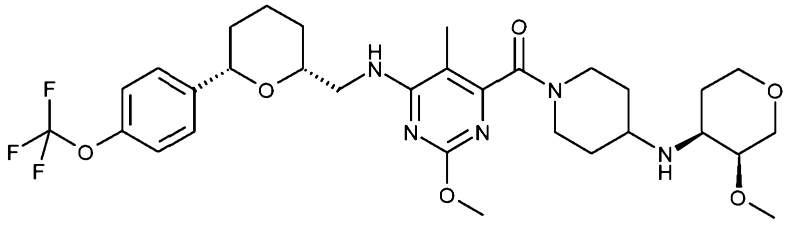

,


,


,


,


,


.

15. The compound according to any of the preceding claims for use as a medicament.

16. The compound according to any of claims 1-14 for use in the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.

17. The compound according to any one of claims 1 to 14 whenever used as a medicament.

18. The compound according to any one of claims 1 – 13 when used for the treatment of osteoarthritis, diabetic nephropathy, low back pain, neuropathic pain or a pain disease.

19. A compound according to claim 1, substantially as hereinbefore described with reference to any one of the Examples of the Specification.

Boehringer Ingelheim International GmbH

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON