

BRIDGET SPIRO [2.4] HEPTANE DERIVATIVES AS ALX RECEPTOR AND/OR FPRL2 AGONISTS

The present invention relates to bridged spiro[2.4]heptane derivatives of formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including
5 processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and especially their use as ALX receptor and/or FPRL2 agonists.

ALXR (alias Lipoxin A4 Receptor, FPRL1, FPR2; disclosed in WO2003/082314 as nucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO:2) is a member
10 of the G-protein coupled receptor family. ALXR was found to mediate calcium mobilisation in response to high concentration of the formyl-methionine-leucyl-phenylalanine peptide. Furthermore, a lipid metabolite, lipoxin A4 (LXA4), and its analogues, were found to bind ALXR with high affinity and increase arachidonic acid production and G-protein activation in ALXR transfected cells (Chiang *et al.*, Pharmacol. Rev., 2006, 58, 463-487). The effects
15 of LXA4 have been evaluated in a variety of animal models of diseases; and LXA4 was demonstrated to have potent anti-inflammatory and pro-resolution activities. The disease models where LXA4, or derivatives, or stable analogs, demonstrated *in vivo* activities are for example dermal inflammation, dorsal air pouch, ischemia/reperfusion injury, peritonitis, colitis, mesangioproliferative nephritis, pleuritis, asthma, cystic fibrosis, sepsis, corneal
20 injury, angiogenesis, periodontitis, carrageenan-induced hyperalgesia, and graft-vs-host disease (GvHD) (Schwab and Serhan, Current Opinion in Pharmacology, 2006, 414-420). ALXR was also identified as a functional receptor of a various number of peptides, including a fragment of the prion protein, a peptide derived from gp120 of the Human Immunodeficiency Virus (HIV)-1_{LAI} strain, and amyloid-beta 1-42 (Ab42) (for review, Le *et al.*, Protein Pept Lett., 2007, 14, 846-853), and has been suggested to participate in the
25 pathogenesis of Alzheimer's Disease (AD) in several crucial ways (Yazawa *et al.*, FASEB J., 2001, 15, 2454-2462). Activation of ALXR on macrophages and microglial cells initiates a G protein-mediated signalling cascade that increases directional cell migration, phagocytosis, and mediator release. These events may account for the recruitment of
30 mononuclear cells to the vicinity of senile plaques in the diseased areas of AD brain where Ab42 is overproduced and accumulated. Although accumulation of leukocytes at the sites of tissue injury may be considered an innate host response aimed at the clearance of noxious agents, activated mononuclear phagocytes also release a variety of substances such as superoxide anions that may be toxic to neurons. Thus, ALXR may

mediate pro-inflammatory responses elicited by Ab42 in AD brain and exacerbate disease progression. It was also reported that humanin (HN), a peptide with neuroprotective capabilities, shares the human ALXR with Ab42 on mononuclear phagocytes and neuronal cell lines and it has been suggested that the neuroprotective activity of HN may
5 be attributed to its competitive occupation of ALXR (Ying *et al.*, J. Immunol., 2004, 172, 7078-7085).

FPRL2 (alias Formyl Peptide Receptor Like-2, FPR3; disclosed in US2006/0078559 as nucleotide sequence SEQ ID NO:1 and amino acid sequence SEQ ID NO: 2) is a member of the G-protein coupled receptor family. The mRNA of FPRL2 was detected in various
10 tissues, including heart, aorta, vein, spleen, lung, trachea, liver, pancreas, adrenal gland, cervix, rectum, small intestine, ileum chronic inflammation, placenta, spinal cord, lymph node, dorsal root ganglia, pons, cerebral meninges, postcentral gyrus, Alzheimer brain frontal lobe and breast tumor. FPRL2 is expressed in human monocytes, macrophages, myeloid dendritic cells, plasmacytoid dendritic cells, eosinophils, but not in neutrophils
15 (Migeotte *et al.*, J. Exp. Med., 2005, 201, 83-89; Devosee *et al.*, J. Immunol., 2009, 4974-4984). Humanin, and its analogues, were found to bind FPRL2 with high affinity (Harada *et al.*, Biochem. Biophys. Res. Commun., 2004, 324, 255-261). Humanin was found to protect neuronal cells from a number of toxic insults. This includes neurotoxicity mediated by three mutant genes that cause FAD as well as Abeta⁺ (Hashimoto *et al.*, Biochem.
20 Biophys. Res. Commun., 2001, 283, 460-468). Humanin has also been reported to have protective activity for neurons against serum deprivation (Takahashi *et al.*, Neuroreport, 2002, 13, 903-907) and against excitotoxic death (Caricasole *et al.*, FASEB J., 2002, 1331-1333). Humanin has also been shown to rescue cortical neurons from prion-peptide-induced apoptosis. Humanin has been further shown to improve learning and memory
25 impairment in mice, thereby evidencing utility as a beneficial agent for the prevention or treatment of learning or memory impairment (Mamiya *et al.*, 2001, Br. J. Pharmacol., 134, 1597-1599). Humanin has also been shown to be protective for muscle cells and rescues human cerebrovascular smooth muscle cells from Abeta-induced toxicity. Furthermore, FPRL2 was found to recognize F2L, a Heme Binding Protein (HBP)
30 polypeptide (Migeotte *et al.*, US2006/0078559). Migeotte *et al.* (J. Exp. Med., 2005, 201, 83-89) suggested that F2L could be released from HBP after cell suffering or cell death. This molecule would thereafter mediate the recruitment of monocytes and Dendritic cells via FPRL2. Immature and mature dendritic cells (iDC and mDC, respectively) migrate to different anatomical sites, e.g., sites of antigen (Ag) deposition and secondary lymphoid

organs, respectively, to fulfill their roles in the induction of primary, Ag-specific immune responses. The trafficking pattern of iDC and mDC is based on their expression of functional chemotactic receptors and the in vivo sites expressing the corresponding ligands including chemokines and/or classical chemoattractants. FPRL2 expressed by DC
5 must be functional and mediate the effect of some known ligands on DC, suggesting that the interaction of FPRL2 and its endogenous ligand(s) may be involved in regulating DC trafficking during Ag uptake and processing in the periphery as well as the T cell-stimulating phase of the immune responses. Kang *et al.* (J. Immunol, 2005, 175, 685-692) demonstrated that FPRL2 ligands, *Helicobacter pylori*-derived peptide Hp(2-20) and F2L,
10 inhibited IL-12 production in Monocyte-derived DC (MoDC) induced by LPS, supporting the notion that FPRL2 participates in the inhibition of MoDC maturation by LPS. Therefore, FPRL2 might be involved in the initiation of a variety of inflammatory diseases based on cell death and could represent an attractive target for therapeutic approaches.

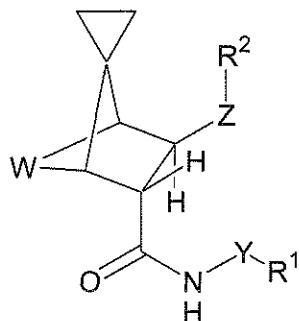
The biological properties of ALXR agonists include, but are not limited to,
15 monocyte/macrophage/microglia/dendritic cell migration/activation, neutrophil migration/activation, regulation of lymphocyte activation, proliferation and differentiation, regulation of inflammation, regulation of cytokine production and/or release, regulation of proinflammatory mediator production and/or release, regulation of immune reaction.

The biological properties of FPRL2 agonists include, but are not limited to,
20 monocyte/macrophage/microglia migration/activation, regulation of lymphocyte activation, proliferation and differentiation, maturation and migration of dendritic cells, regulation of inflammation, regulation of cytokine production and/or release, regulation of proinflammatory mediator production and/or release, regulation of immune reaction.

The present invention provides bridged spiro[2.4]heptane derivatives, which are non-peptide agonists of human ALX and/or FPRL2 receptor. Different bridged spiro[2.4]heptane derivatives have been disclosed in WO9502587. The compounds are useful for the prevention or treatment of diseases, which respond to the modulation of the ALX receptor and/or FPRL2 such as inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer's disease); in addition they are useful for the prevention or treatment of autoimmune diseases and for the modulation of immune responses (especially those elicited by vaccination).
30

Various embodiments of the invention are presented hereafter:

1) In one aspect, there is provided compounds of the formula (I),



(I)

5 wherein

W represents -CH₂CH₂- or -CH=CH-;

Y represents a bond or a (C₁-C₄)alkandiyl group and R¹ represents

- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen; or
- benzo[d][1,3]dioxolyl; or
- aryloxy; or
- a cyclohexyl- or a cyclohexenyl-group, which groups are independently unsubstituted or mono-substituted with (C₁-C₄)alkyl; or
- (C₁-C₂)alkyl-carbonyl; or
- (C₁-C₄)alkoxy-carbonyl;

or Y represents together with R¹ a (C₄-C₆)alkyl group or a amino-(C₄-C₆)alkyl group;

20 Z represents -C(O)NR³-* or -CH₂NR⁴C(O)-*,
wherein the asterisks indicate the bond which is linked to R²;

R² represents

- (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy, hydroxy-methyl, R⁵R⁶N-CH₂-, heterocyclyl-methyl or -CONH₂; or
- (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶, -

COOH, $-C(O)NR^7R^8$ or optionally mono-substituted (C_1-C_4) alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or

- (C_1-C_6) alkyl (preferably (C_1-C_5) alkyl), which is mono-substituted
 - ◇ with (C_3-C_6) cycloalkyl, which cycloalkyl is unsubstituted or mono-substituted with $-NR^5R^6$ or hydroxy;
 - ◇ with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with (C_1-C_4) alkyl, (C_1-C_2) alkyl-carbonyl or *tert*-butoxycarbonyl, and/or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen, (C_1-C_4) alkyl and (C_1-C_2) alkoxy- (C_1-C_2) alkyl; or
 - ◇ with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl, $-CH_2NHR^9$, $-SO_2NH_2$ and phenyl; or
- (C_3-C_5) fluoroalkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted (preferred) or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen and (C_1-C_4) alkyl; or
- heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C_1-C_6) alkyl, benzyl or *tert*-butoxycarbonyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl; or
- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl and phenyl; or
- a group selected from 1-carbamoyl-2-phenyl-ethyl, 1-methoxymethyl-2-phenyl-ethyl, 2-morpholino-2-phenyl-ethyl, 2-phenyl-vinyl, 2,2-dichloro-1-methyl-cyclopropyl;

R^3 represents hydrogen, (C_1-C_3) alkyl or 2-methoxy-ethyl; or

R^2 and R^3 form, together with the nitrogen that carries them, a ring of 5 to 7 members, which ring is substituted with amino- (C_1-C_4) alkyl;

R^4 represents hydrogen or methyl;

R^5 represents hydrogen, (C_1-C_3) alkyl or *tert*-butoxycarbonyl;

R^6 represents hydrogen or (C_1-C_3) alkyl;

R^7 and R^8 represent independently from each other hydrogen or methyl; or R^7 and R^8 form, together with the nitrogen that carries them, a pyrrolidine or piperidine ring; and

R^9 represents hydrogen or *tert*-butoxycarbonyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

In another aspect, there is provided a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for use as medicament.

In yet another aspect, there is provided a pharmaceutical composition containing, as active principle, a compound of formula (I) as defined above or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

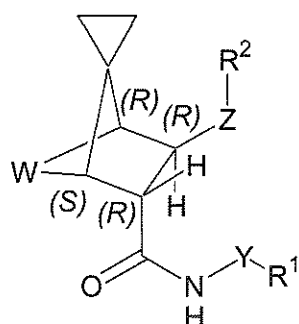
In still another aspect, there is provided the use of a compound of formula (I) as defined above, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

For avoidance of any doubt, the term " Z represents $-C(O)NR^3-$ ", wherein the asterisk indicates the bond which is linked to R^2 " means that the residue R^2 is linked to the nitrogen atom of the amide moiety.

The configuration of compounds of formula (I) according to embodiment 1) is such that the substituent $R^1-Y-NH-C(O)-$ is in relative proximity to the group W (*endo*-position), whereas the substituent R^2-Z- is in relative proximity to the cyclopropyl-moiety (*exo*-position).

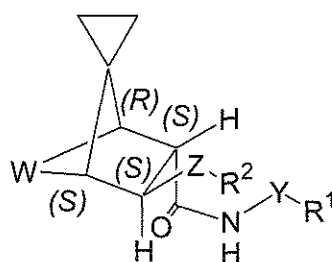
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Formula I comprises compounds of formula I_{St1} and of formula I_{St2} and mixtures thereof.



(I_{St1})

(4*S*,5*R*,6*R*,7*R*)



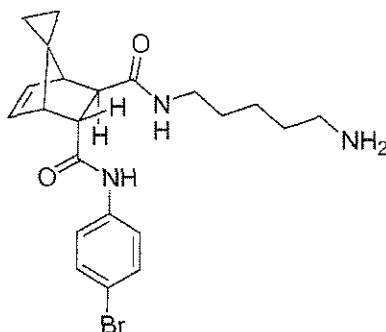
(I_{St2})

(4*R*,5*S*,6*S*,7*S*)

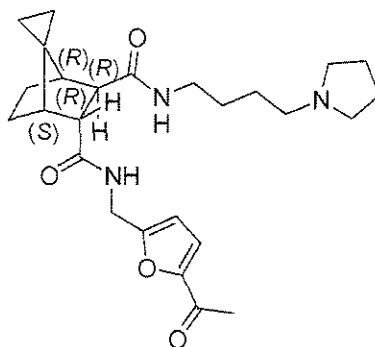
For avoidance of any doubt, compounds of formula (I) are denominated in analogy to the following examples:

a mixture of enantiomers of structure

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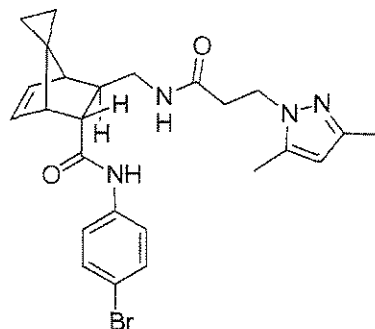
is denominated (5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(5-amino-pentyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
the pure stereoisomer of structure



5

is denominated (5*R*)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide; and

a mixture of enantiomers of structure



10

is denominated (5*R*^{*})-*N*⁵-(4-Bromo-phenyl)-(6*R*^{*})-6-[(3-(3,5-dimethyl-pyrazol-1-yl)-propionylamino)-methyl]-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide.

The compounds of formula (I) according to embodiment 1) may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms.

15 Substituents at a double bond may be present in the (*Z*)- or (*E*)-configuration unless indicated otherwise. The compounds of formula (I) may thus be present as mixtures of

stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a
5 broader or narrower definition.

The term "alkyl", used alone or in combination, refers to a straight or branched chain alkyl group containing one to six carbon atoms. The term "(C_x-C_y)alkyl" (x and y each being an integer), refers to an alkyl group as defined before containing x to y carbon atoms. For
10 example a (C₁-C₆)alkyl group contains from one to six carbon atoms. Representative examples of alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. The alkyl group may be unsubstituted or substituted as explicitly defined.

In case a (C₁-C₄)alkyl group is a substituent to an aryl-, a heteroaryl- or a heterocyclyl-group, the term "(C₁-C₄)alkyl" means (C₁-C₄)alkyl groups as defined above. Examples of
15 said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. Preferred are methyl, ethyl and *iso*-butyl, and most preferred is methyl.

In case a (C₁-C₆)alkyl group is a substituent to a heterocyclyl-group, the term "(C₁-C₆)alkyl" means (C₁-C₆)alkyl groups as defined above. Examples of said groups are
20 methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are methyl, ethyl and 3-methyl-but-1-yl. Most preferred is 3-methyl-but-1-yl.

In case a (C₁-C₄)alkyl group is a substituent to a cyclohexyl- or a cyclohexenyl-group, the term "(C₁-C₄)alkyl" means (C₁-C₄)alkyl groups as defined above. Examples of said groups
25 are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. Preferred are methyl and *tert*-butyl, and most preferred is methyl.

In case "**R**²" represents "(C₁-C₆)alkyl which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶, -COOH, -C(O)NR⁷R⁸ or optionally mono-substituted (C₁-C₄)alkoxy, wherein the
30 substituent is selected from hydroxy and heterocyclyl" the term "(C₁-C₆)alkyl" means (C₁-C₆)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, 2,2-dimethyl-prop-1-yl, 3-methyl-but-1-yl, 3,3-dimethyl-but-1-yl, pent-1-yl, pent-2-yl, 4-methyl-pent-2-yl

and hex-1-yl. Most preferred are methyl, ethyl, *n*-propyl, *n*-butyl, *iso*-butyl, 2,2-dimethyl-prop-1-yl and pent-1-yl. The above-mentioned (C₁-C₆)alkyl groups are unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶, -COOH, -C(O)NR⁷R⁸ or optionally mono-substituted (C₁-C₄)alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl. Preferably the substituent is selected from the group consisting of fluorine, trifluoromethyl, methoxy, ethoxy, ethylthio, hydroxy, cyano, -NR⁵R⁶ or -C(O)NR⁷R⁸.

In the other case wherein "R²" represents "(C₁-C₆)alkyl" the term means (C₁-C₆)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are methyl, ethyl, *n*-propyl, *n*-butyl and *n*-pentyl. More preferred are *n*-butyl and *n*-pentyl and most preferred is *n*-butyl. The above-mentioned (C₁-C₆)alkyl groups are mono-substituted with (C₃-C₆)cycloalkyl, which cycloalkyl is unsubstituted or mono-substituted with -NR⁵R⁶ or hydroxy; with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl, (C₁-C₂)alkyl-carbonyl or *tert*-butoxycarbonyl, and/or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen, (C₁-C₄)alkyl and (C₁-C₂)alkoxy-(C₁-C₂)alkyl; or with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. In a preferred embodiment the (C₁-C₆)alkyl groups are substituted with a heterocyclyl group, which is unsubstituted, mono-substituted at a nitrogen atom with methyl or ethyl or mono-substituted at a carbon atom with fluorine. In another preferred embodiment the (C₁-C₆)alkyl groups are substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, methyl, ethyl, -CH₂NH₂ and -SO₂NH₂.

In case "R³" represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

In case "R⁵" represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

In case " R^6 " represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

5 The term "(C₁-C₄)alkandiyl group" as used in **Y** refers to a carbon chain containing from one to four carbon atoms, which is attached to the residue R^1 and to the amide-nitrogen atom of the rest of the molecule as depicted in formula (I). The respective two residues may be attached to the same or to different carbon atoms of the alkandiyl group. Preferred examples of (C₁-C₄)alkandiyl groups are methandiyl, ethan-1,1-diyl, ethan-1,2-diyl, propan-1,3-diyl and butan-1,4-diyl. More preferred are methandiyl and ethan-1,2-diyl.
10 Most preferred is methandiyl.

In case "**Y** together with R^1 " represents "(C₄-C₆)alkyl" the term means (C₄-C₆)alkyl groups as defined above. Examples of said groups are *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are *n*-butyl, 3-methyl-butyl, 2-ethyl-butyl and *n*-pentyl. Most preferred is *n*-pentyl.

15 In case "**Y** together with R^1 " represents a "amino-(C₄-C₆)alkyl" group the term means a (C₄-C₆)alkyl group as defined above in which one hydrogen atom has been replaced with an amino group. Examples of said groups are 4-amino-butyl, 5-amino-pentyl and 6-amino-hexyl. Most preferred are 4-amino-butyl and 5-amino-pentyl.

20 The term "amino-(C₁-C₄)alkyl" refers to an (C₁-C₄)alkyl group as defined above in which one hydrogen atom has been replaced with an amino group. A preferred example is amino-methyl.

25 The term "(C₃-C₆)cycloalkyl", alone or in combination, means a cycloalkyl group with 3 to 6 carbon atoms. Examples of (C₃-C₆)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The (C₃-C₆)cycloalkyl group may be unsubstituted or substituted as explicitly defined.

In case " R^2 " represents "(C₃-C₆)cycloalkyl" the term means (C₃-C₆)cycloalkyl groups as defined above. Examples of said groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred are cyclopropyl, cyclopentyl and cyclohexyl. Most preferred are cyclopentyl and cyclohexyl. The above-mentioned (C₃-C₆)cycloalkyl groups are
30 unsubstituted or mono-substituted with hydroxy, hydroxy-methyl, $R^5R^6N-CH_2-$, heterocyclyl-methyl or -CONH₂ (preferably with hydroxy or pyrrolidin-1-yl-methyl).

In case " R^2 " represents "(C₁-C₆)alkyl, which is mono-substituted with (C₃-C₆)cycloalkyl" the term "(C₃-C₆)cycloalkyl" means the above-mentioned groups. Preferred are cyclopropyl and cyclohexyl. The above-mentioned (C₃-C₆)cycloalkyl groups are unsubstituted or mono-substituted with -NR⁵R⁶ or hydroxy (preferably with hydroxy).

- 5 The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term "(C_x-C_y)alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C₁-C₄)alkoxy group contains from one to four carbon atoms. Representative examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-
10 butoxy and *tert*-butoxy. The alkoxy group may be unsubstituted or substituted as explicitly defined.

In case a (C₁-C₄)alkoxy group is a substituent to an aryl- or a heteroaryl-group, the term "(C₁-C₄)alkoxy" means (C₁-C₄)alkoxy groups as defined above. Examples of said groups are methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-
15 butoxy. Preferred are methoxy, ethoxy and *iso*-propoxy. Most preferred is methoxy.

In case " R^2 " represents "(C₁-C₆)alkyl which is mono-substituted with optionally mono-substituted (C₁-C₄)alkoxy" the term "optionally mono-substituted (C₁-C₄)alkoxy" means a (C₁-C₄)alkoxy group as defined above, which is unsubstituted or mono-substituted. Examples of said groups are methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-
20 butoxy, *sec*-butoxy and *tert*-butoxy. Preferred are methoxy and ethoxy. The above-mentioned (C₁-C₄)alkoxy group is unsubstituted or mono-substituted with hydroxy or heterocyclyl and preferably unsubstituted or mono-substituted with heterocyclyl.

The term "(C₁-C₂)alkoxy-(C₁-C₂)alkyl" refers to an (C₁-C₂)alkyl group as defined above in which one hydrogen atom has been replaced with an (C₁-C₂)alkoxy group as defined
25 above. Examples of (C₁-C₂)alkoxy-(C₁-C₂)alkyl groups are methoxy-methyl, methoxy-ethyl, ethoxy-methyl and ethoxy-ethyl. Preferred is methoxy-methyl.

The term "alkylthio", used alone or in combination, refers to an alkyl-S- group wherein the alkyl group is as defined before. The term "(C_x-C_y)alkylthio" (x and y each being an integer) refers to an alkylthio group as defined before containing x to y carbon atoms. For
30 example a (C₁-C₄)alkylthio group contains from one to four carbon atoms. Representative examples of alkylthio groups include methylthio, ethylthio, *n*-propylthio, *iso*-propylthio, *n*-butylthio, *iso*-butylthio, *sec*-butylthio and *tert*-butylthio. Preferred are methylthio and ethylthio. Most preferred is ethylthio.

The term “(C₁-C₂)alkyl-carbonyl”, used alone or in combination, refers to a (C₁-C₂)alkyl-C(O)- group wherein the (C₁-C₂)alkyl group is as defined before. Representative examples of (C₁-C₂)alkyl-carbonyl groups include methyl-carbonyl (acetyl) and ethyl-carbonyl (propionyl). Preferred is acetyl.

- 5 The term “(C₁-C₄)alkoxy-carbonyl”, used alone or in combination, refers to a (C₁-C₄)alkoxy-C(O)- group wherein the (C₁-C₄)alkoxy group is as defined before. Representative examples of (C₁-C₄)alkoxy-carbonyl groups include methoxy-carbonyl, ethoxy-carbonyl, *n*-propoxy-carbonyl, *iso*-propoxy-carbonyl, *n*-butoxy-carbonyl, *iso*-butoxy-carbonyl, *sec*-butoxy-carbonyl and *tert*-butoxy-carbonyl. Preferred are methoxy-carbonyl and *tert*-butoxy-carbonyl. Most preferred is methoxy-carbonyl.
- 10

The term “(C_x-C_y)fluoroalkyl” (x and y each being an integer) refers to an alkyl group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The fluoroalkyl group may be unsubstituted or substituted as explicitly defined.

- 15 In case a (C₁-C₂)fluoroalkyl group is a substituent to an aryl- or a heteroaryl-group, the term “(C₁-C₂)fluoroalkyl” means (C₁-C₂)fluoroalkyl groups as defined above. Examples of said groups are trifluoromethyl, difluoromethyl and 2,2,2-trifluoroethyl. Preferred are trifluoromethyl and 2,2,2-trifluoroethyl. Most preferred is trifluoromethyl.

- In case “R²” represents “(C₃-C₅)fluoroalkyl” the term means a (C₃-C₅)fluoroalkyl group as defined above. Examples of said groups are 2-fluoro-propyl, 2,2-difluoro-propyl, 2-fluoro-butyl, 2,2-difluoro-butyl, 3-fluoro-butyl, 3,3-difluoro-butyl, 2-fluoro-pentyl, 2,2-difluoro-pentyl, 3-fluoro-pentyl, 3,3-difluoro-pentyl, 4-fluoro-pentyl and 4,4-difluoro-pentyl. Preferred are 3-fluoro-butyl and 3,3-difluoro-butyl. Most preferred is 3-fluoro-butyl. The above-mentioned (C₃-C₅)fluoroalkyl groups are mono-substituted with heterocyclyl.
- 20

- 25 The term “(C_x-C_y)fluoroalkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. For example a (C₁-C₂)fluoroalkoxy group contains from one to two carbon atoms in which one to five hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy and 2,2,2-trifluoroethoxy. Preferred are (C₁)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy. Most preferred is trifluoromethoxy.
- 30

The term halogen means fluoro, chloro, bromo or iodo.

In case the halogen is a substituent to an aryl- or a heteroaryl-group, the term means preferably fluoro, chloro or bromo and most preferably chloro or bromo.

In case the halogen is a substituent to a heterocyclyl-group, the term means most preferably fluoro.

5

The term "aryl", used alone or in any combination, means a phenyl or a naphthyl group. Preferred is a phenyl group. The aryl group may be unsubstituted or substituted as explicitly defined.

In case R^1 represents "aryl" the term means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted, mono- or di-substituted and most preferably mono- or di-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Preferably the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, trifluoromethyl and trifluoromethoxy (and most preferably from fluoro, bromo, methoxy and trifluoromethyl). Examples of such aryl groups are phenyl, 4-methyl-phenyl, 2,4-dimethyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-methoxy-phenyl, 4-methoxy-phenyl, 2,4-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 4-ethoxy-phenyl, 2-*iso*-propoxy-phenyl, 4-*iso*-propoxy-phenyl, 3-acetyl-phenyl, 4-acetyl-phenyl, 4-trifluoromethyl-phenyl, 3-difluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl, 4-fluoro-phenyl, 2,3,5-trifluoro-phenyl, 2,4,6-trifluoro-phenyl, 4-chloro-phenyl, 2,4-dichloro-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-iodo-phenyl, 3-chloro-2-fluoro-phenyl, 2-chloro-3,6-difluoro-phenyl, 2-bromo-4-fluoro-phenyl, 3-bromo-4-fluoro-phenyl, 4-bromo-2-fluoro-phenyl, 4-bromo-3-fluoro-phenyl, 4-bromo-2,3-difluoro-phenyl, 4-bromo-2,5-difluoro-phenyl, 4-bromo-2,6-difluoro-phenyl, 4-bromo-3,5-difluoro-phenyl, 4-bromo-3-chloro-phenyl, 5-methyl-2-methoxy-phenyl, 4-bromo-2-methyl-phenyl, 2-chloro-6-fluoro-3-methyl-phenyl, 2,3-difluoro-4-methoxy-phenyl, 2,6-difluoro-4-methoxy-phenyl, 3,5-difluoro-4-methoxy-phenyl, 3-fluoro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 3-bromo-4-methoxy-phenyl, 2-fluoro-3-trifluoromethyl-phenyl, 2-fluoro-5-trifluoromethyl-phenyl, 3-fluoro-5-trifluoromethyl-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl and 4-bromo-3-trifluoromethyl-phenyl (and preferably 4-methoxyphenyl, 4-trifluoromethylphenyl, 2,4-dichloro-phenyl, 4-bromophenyl, 4-bromo-2-fluoro-phenyl, 4-bromo-3-fluoro-phenyl and 4-bromo-2,6-difluoro-phenyl).

In case R^2 represents "aryl" the term means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably mono- or di-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl (and preferably from halogen). Examples of such aryl groups are 4-bromophenyl and 2-chloro-3-fluorophenyl.

In case R^2 represents "(C₁-C₆)alkyl, which is mono-substituted with an aryl group" the term "aryl" means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted or mono-substituted and most preferably mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. Preferably the substituents are independently selected from the group consisting of halogen, -CH₂NHR⁹ and -SO₂NH₂ (and most preferably from -CH₂NH₂ and -SO₂NH₂). Examples of such aryl groups are 4-fluorophenyl, 2-chlorophenyl, 3-aminomethyl-phenyl, 4-aminomethyl-phenyl, 3-(*tert*-butoxycarbonylamino-methyl)-phenyl, 4-(*tert*-butoxycarbonylamino-methyl)-phenyl and 4-sulfamoyl-phenyl (and preferably 3-aminomethyl-phenyl, 4-aminomethyl-phenyl and 4-sulfamoyl-phenyl).

The term "aryloxy", used alone or in combination, refers to an aryl-O- group wherein the aryl group is as defined before. A preferred example of an aryloxy group is phenoxy.

The term "heteroaryl", used alone or in any combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzo[2,1,3]oxadiazolyl, benzo[2,1,3]thiadiazolyl, benzo[1,2,3]thiadiazolyl, quinoliny, isoquinoliny, naphthyridiny, cinnoliny, quinazolinyl, quinoxaliny and phthalazinyl. The heteroaryl group may be unsubstituted or substituted as explicitly defined.

In case R^1 represents "heteroaryl" the term means the above-mentioned groups. Preferred heteroaryl groups as used in R^1 are furanyl (notably furan-2-yl), oxazolyl (notably oxazol-2-yl and oxazol-5-yl), isoxazolyl (notably isoxazol-3-yl), oxadiazolyl (notably [1,2,5]oxadiazolyl), thienyl (notably thiophen-2-yl and thiophen-3-yl), thiazolyl (notably thiazol-2-yl, thiazol-4-yl and thiazol-5-yl), thiadiazolyl (notably [1,2,4]thiadiazol-5-yl and [1,3,4]thiadiazol-5-yl), imidazolyl (notably imidazol-1-yl and imidazol-2-yl), pyridyl (notably

pyridin-2-yl and pyridin-3-yl), pyrimidyl (notably pyrimidin-5-yl), pyrazinyl (notably pyrazin-2-yl), indolyl (notably indol-1-yl and indol-5-yl), benzimidazolyl (notably benzimidazol-2-yl), benzoxazolyl (notably benzoxazol-6-yl), benzothiazolyl (notably benzothiazol-2-yl and benzothiazol-5-yl), benzoisothiazolyl (notably benzoisothiazol-5-yl) and benzo[2,1,3]oxadiazolyl (notably benzo[2,1,3]oxadiazol-4-yl). Most preferred heteroaryl groups are furanyl (notably furan-2-yl), thiazolyl (notably thiazol-2-yl), pyridyl (notably pyridin-2-yl and pyridin-3-yl), pyrazinyl (notably pyrazin-2-yl) and benzothiazolyl (notably benzothiazol-5-yl). The above-mentioned heteroaryl groups as used in **R**¹ are unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Preferably the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Most preferably the substituents are independently selected from halogen, methyl and acetyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups as used in **R**¹ are furan-2-yl, 5-acetyl-furan-2-yl (preferred), 5-methyl-furan-2-yl, 4-methyl-oxazol-2-yl, 2-acetyl-oxazol-4-yl, 2-acetyl-oxazol-5-yl, 4-acetyl-oxazol-2-yl, 5-methyl-isoxazol-3-yl, 5-*iso*-butyl-isoxazol-3-yl, 5-*tert*-butyl-isoxazol-3-yl, 5-acetyl-thiophen-2-yl, 5-bromo-thiophen-3-yl, 5-chloro-thiazol-2-yl, 2-bromo-thiazol-5-yl, 4-bromo-thiazol-2-yl, 5-bromo-thiazol-2-yl (preferred), 4-methyl-thiazol-2-yl, 5-methyl-thiazol-2-yl, 4,5-dimethyl-thiazol-2-yl, 4-*tert*-butyl-thiazol-2-yl, 2-acetyl-thiazol-4-yl, 2-acetyl-thiazol-5-yl, 4-acetyl-thiazol-2-yl, 5-acetyl-thiazol-2-yl, 4-trifluoromethyl-thiazol-2-yl, 5-nitro-thiazol-2-yl, 5-cyano-thiazol-2-yl, 4-(4-chloro-phenyl)-thiazol-2-yl, 4-methyl-[1,2,5]oxadiazol-3-yl, 3-phenyl-[1,2,4]thiadiazol-5-yl, 2-trifluoromethyl-[1,3,4]thiadiazol-5-yl, imidazol-1-yl, 4,5-dimethyl-imidazol-2-yl (preferred), pyridin-2-yl, 2-methoxy-pyridin-4-yl, 2,6-dichloro-pyridin-4-yl, 5-bromo-pyridin-2-yl (preferred), 5-methyl-pyridin-2-yl (preferred), 5-trifluoromethyl-pyridin-2-yl, 6-chloro-pyridin-3-yl (preferred), 6-bromo-pyridin-3-yl (preferred), 6-bromo-5-fluoro-pyridin-3-yl, 6-methoxy-pyridin-3-yl, 6-trifluoromethyl-pyridin-3-yl, 2-chloro-pyrimidin-5-yl, 5-bromo-pyrazin-2-yl (preferred), indol-1-yl, 2-methyl-indol-1-yl, indol-5-yl, 1-methyl-benzimidazol-2-yl, benzoxazol-6-yl, benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, benzothiazol-5-yl (preferred), 2-methyl-benzothiazol-5-yl, 3-methyl-benzoisothiazol-5-yl and benzo[2,1,3]oxadiazol-4-yl.

In case R^2 represents "heteroaryl" the term means the above-mentioned groups. Preferred heteroaryl groups as used in R^2 are isoxazolyl (notably isoxazol-4-yl), pyrazolyl (notably pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl) and pyridyl (notably pyridin-3-yl). The above-mentioned heteroaryl groups as used in R^2 are unsubstituted, mono-, di- or tri-substituted (preferably mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl. Preferably the substituents are independently selected from the group consisting of methyl and phenyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups as used in R^2 are 5-phenyl-isoxazol-4-yl (preferred), 1,5-dimethyl-pyrazol-3-yl, 5-chloro-1,3-dimethyl-pyrazol-4-yl, 1-phenyl-pyrazol-5-yl (preferred) and 4-methyl-pyridin-3-yl.

In case R^2 represents "(C₁-C₆)alkyl, which is mono-substituted with a heteroaryl group" the term "heteroaryl" means the above-mentioned groups. Preferred heteroaryl groups are furanyl (notably furan-3-yl), isoxazolyl (notably isoxazol-4-yl), thiazolyl (notably thiazol-4-yl), imidazolyl (notably imidazol-1-yl and imidazol-2-yl), pyrazolyl (notably pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl), triazolyl (notably [1,2,4]triazol-1-yl), pyridyl (notably pyridin-2-yl and pyridin-3-yl), indolyl (notably indol-3-yl) and benzimidazolyl (notably benzimidazol-2-yl). The above-mentioned heteroaryl groups are unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted, mono- or disubstituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. Preferably the substituents are independently selected from the group consisting of (C₁-C₄)alkyl and phenyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups are furan-3-yl, 5-methyl-3-phenyl-isoxazol-4-yl, 2-methyl-thiazol-4-yl, 2,5-dimethyl-thiazol-4-yl, imidazol-1-yl (preferred), 4,5-dimethyl-imidazol-2-yl (preferred), pyrazol-1-yl (preferred), 3,5-dimethyl-pyrazol-1-yl (preferred), 1-ethyl-5-methyl-pyrazol-3-yl (preferred), 5-methyl-pyrazol-4-yl, 1-ethyl-3-methyl-pyrazol-5-yl, [1,2,4]triazol-1-yl (preferred), pyridin-2-yl, pyridin-3-yl, indol-3-yl, benzimidazol-2-yl (preferred) and 1-methyl-benzimidazol-2-yl.

The term "heterocyclyl", used alone or in combination, means a 4- to 7-membered (notably 4- to 6-membered) saturated monocyclic ring containing 1 or 2 heteroatoms independently selected from the group consisting of sulfur, oxygen and nitrogen (preferably oxygen and nitrogen), wherein one or two methylene groups adjacent to a nitrogen atom are optionally replaced by carbonyl groups. Examples of such heterocyclyl groups are azetidiny, oxetany, pyrrolidiny, pyrrolidinonyl, tetrahydrofurany, tetrahydrothiopheny, imidazolidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl,

thiazolidinonyl, piperidinyl, piperidonyl, piperazinyl, piperazinonyl, piperazine-dionyl, tetrahydro-2*H*-pyranyl, morpholinyl, morpholinonyl, thiomorpholinyl, thiomorpholinonyl, dioxanyl, 1,4-diazepanyl and 1,4-diazepanonyl. Preferred examples are azetidiny, pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, imidazolidinonyl, piperidinyl, piperidonyl, piperazinyl, tetrahydro-2*H*-pyranyl, morpholinyl, dioxanyl and 1,4-diazepanyl. The heterocyclyl group may be unsubstituted or substituted as explicitly defined.

In case **R²** represents "(C₃-C₆)cycloalkyl, which is mono-substituted with heterocyclyl-methyl" the term "heterocyclyl" means the above-mentioned groups. Preferred heterocyclyl groups are azetidiny (notably azetidin-1-yl), pyrrolidinyl (notably pyrrolidin-1-yl) and piperidinyl (notably piperidin-1-yl). Most preferred is pyrrolidinyl (notably pyrrolidin-1-yl).

In case **R²** represents "heterocyclyl" the term means the above-mentioned groups. Preferred heterocyclyl groups as used in **R²** are azetidiny (notably azetidin-3-yl), pyrrolidinyl (notably pyrrolidin-3-yl), piperidinyl (notably piperidin-3-yl and piperidin-4-yl) and tetrahydro-2*H*-pyranyl (notably tetrahydro-2*H*-pyran-3-yl). Most preferred are pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl and tetrahydro-2*H*-pyran-3-yl. The above-mentioned heterocyclyl groups are unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl. Examples of such unsubstituted or mono-substituted heterocyclyl groups are azetidin-3-yl, 1-*tert*-butoxycarbonyl-azetidin-3-yl, pyrrolidin-3-yl (preferred), 1-*tert*-butoxycarbonyl-pyrrolidin-3-yl, piperidin-3-yl (preferred), 1-*tert*-butoxycarbonyl-piperidin-3-yl, piperidin-4-yl (preferred), 1-methyl-piperidin-4-yl, 1-ethyl-piperidin-4-yl, 1-(3-methyl-butyl)-piperidin-4-yl, 1-benzyl-piperidin-4-yl, 1-*tert*-butoxycarbonyl-piperidin-4-yl and 6-(pyrrolidin-1-ylmethyl)-tetrahydro-2*H*-pyran-3-yl.

In case **R²** represents "(C₁-C₆)alkyl, which is mono-substituted with heterocyclyl" the term "heterocyclyl" means the above-mentioned groups. Preferred heterocyclyl groups are azetidiny (notably azetidin-1-yl), pyrrolidinyl (notably pyrrolidin-1-yl and pyrrolidin-2-yl), pyrrolidinonyl (notably pyrrolidin-2-on-1-yl), tetrahydrofuranyl (notably tetrahydrofuran-2-yl), imidazolidinonyl (notably imidazolidin-2-on-1-yl), piperidinyl (notably piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and piperidin-4-yl), piperazinyl (notably piperazin-1-yl), morpholinyl (notably morpholin-4-yl), dioxanyl (notably 1,4-dioxan-2-yl) and 1,4-diazepanyl (notably 1,4-diazepan-1-yl). Most preferred are azetidiny (notably azetidin-1-yl), pyrrolidinyl (notably pyrrolidin-1-yl and pyrrolidin-2-yl), tetrahydrofuranyl (notably tetrahydrofuran-2-yl), imidazolidinonyl (notably imidazolidin-2-on-1-yl), piperidinyl (notably piperidin-1-yl, piperidin-2-yl and piperidin-4-yl), piperazinyl (notably piperazin-1-yl),

morpholinyl (notably morpholin-4-yl) and 1,4-diazepanyl (notably 1,4-diazepan-1-yl). The above-mentioned heterocyclyl groups are unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl, (C₁-C₂)alkyl-carbonyl or *tert*-butoxycarbonyl, and/or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen, (C₁-C₄)alkyl and (C₁-C₂)alkoxy-(C₁-C₂)alkyl. Preferably the heterocyclyl groups are unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl (notably methyl or ethyl), or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from fluorine, methyl and methoxymethyl. Examples of such unsubstituted or substituted heterocyclyl groups are azetidin-1-yl, pyrrolidin-1-yl, 3-fluoro-pyrrolidin-1-yl (notably (R)-3-fluoro-pyrrolidin-1-yl and (S)-3-fluoro-pyrrolidin-1-yl), 3,3-difluoro-pyrrolidin-1-yl, 2,5-dimethyl-pyrrolidin-1-yl, 2-methoxymethyl-pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, 1-ethyl-pyrrolidin-2-yl, 1-*tert*-butoxycarbonyl-pyrrolidin-2-yl, pyrrolidin-2-on-1-yl, tetrahydrofuran-2-yl, imidazolidin-2-on-1-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, 1-*tert*-butoxycarbonyl-piperidin-3-yl, piperidin-4-yl, 1-*tert*-butoxycarbonyl-piperidin-4-yl, 4-methyl-piperazin-1-yl, 4-ethyl-piperazin-1-yl, 4-acetyl-piperazin-1-yl, morpholin-4-yl, 1,4-dioxan-2-yl and 4-methyl-1,4-diazepan-1-yl. Preferred examples of such unsubstituted or mono-substituted heterocyclyl groups are azetidin-1-yl, pyrrolidin-1-yl, (R)-3-fluoro-pyrrolidin-1-yl, (S)-3-fluoro-pyrrolidin-1-yl, 3,3-difluoro-pyrrolidin-1-yl, 2,5-dimethyl-pyrrolidin-1-yl, 2-methoxymethyl-pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, tetrahydrofuran-2-yl, imidazolidin-2-on-1-yl, piperidin-1-yl, piperidin-2-yl, piperidin-4-yl, 4-methyl-piperazin-1-yl, morpholin-4-yl, 1,4-dioxan-2-yl and 4-methyl-1,4-diazepan-1-yl.

In case **R**² represents "(C₁-C₆)alkyl, which is mono-substituted with optionally mono-substituted (C₁-C₄)alkoxy, wherein the substituent is heterocyclyl" the term "heterocyclyl" means the above-mentioned groups. Preferred heterocyclyl groups are azetidiny (notably azetidin-1-yl), pyrrolidiny (notably pyrrolidin-1-yl) and piperidiny (notably piperidin-1-yl). Most preferred is pyrrolidin-1-yl.

In case **R**² represents "(C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl" the term "heterocyclyl" means the above-mentioned groups. Preferred heterocyclyl groups are azetidiny (notably azetidin-1-yl), pyrrolidiny (notably pyrrolidin-1-yl and pyrrolidin-2-yl), pyrrolidinonyl (notably pyrrolidin-2-on-1-yl), tetrahydrofuranyl (notably tetrahydrofuran-2-yl), imidazolidinonyl (notably imidazolidin-2-on-1-yl), piperidiny (notably piperidin-1-yl, piperidin-3-yl and piperidin-4-yl), piperaziny (notably piperazin-1-yl), morpholinyl (notably morpholin-4-yl), dioxanyl (notably 1,4-dioxan-2-yl) and 1,4-diazepanyl (notably 1,4-diazepan-1-yl). More preferred heterocyclyl groups are azetidiny (notably azetidin-1-yl),

pyrrolidinyl (notably pyrrolidin-1-yl) and piperidinyl (notably piperidin-1-yl). Most preferred is pyrrolidin-1-yl. The above-mentioned heterocyclyl groups are unsubstituted (preferred) or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen (notably fluoro) and (C₁-C₄)alkyl (notably methyl).

- 5 The term "a ring of 5 to 7 members", as used in "**R**² and **R**³ form, together with the nitrogen that carries them, a ring of 5 to 7 members", refers to a heterocyclic ring selected from pyrrolidinyl (notably pyrrolidin-1-yl), piperidinyl (notably piperidin-1-yl) and azepanyl (notably azepan-1-yl). Preferred is piperidinyl (notably piperidin-1-yl). The ring with 5 to 7 members is substituted with amino-(C₁-C₄)alkyl.

- 10 For compounds of formula I_P the following definitions are preferred:

- The term "alkyl", used alone or in combination, refers to a straight or branched chain alkyl group containing one to six carbon atoms. The term "(C_x-C_y)alkyl" (x and y each being an integer), refers to an alkyl group as defined before containing x to y carbon atoms. For example a (C₁-C₆)alkyl group contains from one to six carbon atoms. Representative examples of alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. The alkyl group may be unsubstituted or substituted as explicitly defined.

- 15 In case a (C₁-C₄)alkyl group is a substituent to an aryl-, a heteroaryl- or a heterocyclyl-group, the term "(C₁-C₄)alkyl" means (C₁-C₄)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. Preferred are methyl, ethyl and *iso*-butyl, and most preferred is methyl.

- 20 In case a (C₁-C₆)alkyl group is a substituent to a heterocyclyl-group, the term "(C₁-C₆)alkyl" means (C₁-C₆)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are methyl, ethyl and 3-methyl-but-1-yl. Most preferred is 3-methyl-but-1-yl.

- 25 In case "**Y** together with **R**¹" represents "(C₄-C₆)alkyl" the term means (C₄-C₆)alkyl groups as defined above. Examples of said groups are *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are *n*-butyl, 3-methyl-butyl, 2-ethyl-butyl and *n*-pentyl. Most preferred is *n*-pentyl.

- 30 In case "**R**²" represents "(C₁-C₆)alkyl" the term means (C₁-C₆)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-

butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, the isomeric pentyls and the isomeric hexyls. Preferred are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, 2,2-dimethyl-prop-1-yl, 3-methyl-but-1-yl, 3,3-dimethyl-but-1-yl, pent-1-yl, pent-2-yl, 4-methyl-pent-2-yl and hex-1-yl. Most preferred are ethyl, *n*-propyl, *n*-butyl, *iso*-butyl, 2,2-dimethyl-prop-1-yl and pent-1-yl. The above-mentioned (C₁-C₆)alkyl groups are unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶ or -C(O)NR⁷R⁸. Preferably the substituent is selected from the group consisting of fluorine, trifluoromethyl, methoxy, ethoxy, ethylthio, hydroxy, cyano, -NR⁵R⁶ or -C(O)NH₂.

In case "**R**²" represents "(C₁-C₄)alkyl" the term means (C₁-C₄)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. Preferred are methyl, ethyl, *n*-propyl and *n*-butyl. Most preferred is *n*-butyl. The above-mentioned (C₁-C₄)alkyl groups are mono-substituted with (C₃-C₆)cycloalkyl; with heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl or *tert*-butoxycarbonyl; or with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. In a preferred embodiment the (C₁-C₄)alkyl groups are substituted with a heterocyclyl group, which is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl. In another preferred embodiment the (C₁-C₄)alkyl groups are substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, methyl, ethyl, -CH₂NH₂ and -SO₂NH₂.

In case "**R**³" represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

In case "**R**⁵" represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

In case "**R**⁶" represents "(C₁-C₃)alkyl" the term means (C₁-C₃)alkyl groups as defined above. Examples of said groups are methyl, ethyl, *n*-propyl and *iso*-propyl. Preferred are methyl, ethyl and *n*-propyl. Most preferred are methyl and ethyl.

- The term “(C₁-C₄)alkandiyl group” as used in **Y** refers to a carbon chain containing from one to four carbon atoms, which is attached to the residue **R**¹ and to the amide-nitrogen atom of the rest of the molecule as depicted in formula (I). The respective two residues may be attached to the same or to different carbon atoms of the alkandiyl group. Preferred examples of (C₁-C₄)alkandiyl groups are methandiyl, ethan-1,1-diyl, ethan-1,2-diyl, propan-1,3-diyl and butan-1,4-diyl. More preferred are methandiyl and ethan-1,2-diyl. Most preferred is methandiyl.

- The term “(C₃-C₆)cycloalkyl”, alone or in combination, means a cycloalkyl group with 3 to 6 carbon atoms. Examples of (C₃-C₆)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The (C₃-C₆)cycloalkyl group may be unsubstituted or substituted as explicitly defined.

In case “**R**²” represents “(C₃-C₆)cycloalkyl” the term means (C₃-C₆)cycloalkyl groups as defined above. Examples of said groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred are cyclopropyl, cyclopentyl and cyclohexyl. Most preferred are cyclopentyl and cyclohexyl. The above-mentioned (C₃-C₆)cycloalkyl groups are unsubstituted or mono-substituted with hydroxy (preferred) or -CONH₂.

In case “**R**²” represents “(C₁-C₄)alkyl, which is mono-substituted with (C₃-C₆)cycloalkyl” the term “(C₃-C₆)cycloalkyl” means the above-mentioned groups. A preferred (C₃-C₆)cycloalkyl group is cyclopropyl.

- The term “alkoxy”, used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term “(C_x-C_y)alkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C₁-C₄)alkoxy group contains from one to four carbon atoms. Representative examples of alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Preferred are methoxy and ethoxy. Most preferred is methoxy.

- The term “alkylthio”, used alone or in combination, refers to an alkyl-S- group wherein the alkyl group is as defined before. The term “(C_x-C_y)alkylthio” (x and y each being an integer) refers to an alkylthio group as defined before containing x to y carbon atoms. For example a (C₁-C₄)alkylthio group contains from one to four carbon atoms. Representative examples of alkylthio groups include methylthio,

ethylthio, *n*-propylthio, *iso*-propylthio, *n*-butylthio, *iso*-butylthio, *sec*-butylthio and *tert*-butylthio. Preferred are methylthio and ethylthio. Most preferred is ethylthio.

- 5 • The term “(C₁-C₂)alkyl-carbonyl”, used alone or in combination, refers to a (C₁-C₂)alkyl-C(O)- group wherein the (C₁-C₂)alkyl group is as defined before. Representative examples of (C₁-C₂)alkyl-carbonyl groups include methyl-carbonyl (acetyl) and ethyl-carbonyl (propionyl). Preferred is acetyl.
- 10 • The term “(C₁-C₄)alkoxy-carbonyl”, used alone or in combination, refers to a (C₁-C₄) alkoxy-C(O)- group wherein the (C₁-C₄)alkoxy group is as defined before. Representative examples of (C₁-C₄)alkoxy-carbonyl groups include methoxy-carbonyl, ethoxy-carbonyl, *n*-propoxy-carbonyl, *iso*-propoxy-carbonyl, *n*-butoxy-carbonyl, *iso*-butoxy-carbonyl, *sec*-butoxy-carbonyl and *tert*-butoxy-carbonyl. Preferred are methoxy-carbonyl and *tert*-butoxy-carbonyl. Most preferred is methoxy-carbonyl.
- 15 • The term “(C_x-C_y)fluoroalkyl” (x and y each being an integer) refers to an alkyl group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. For example a (C₁-C₂)fluoroalkyl group contains from one to two carbon atoms in which one to five hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, difluoromethyl and 2,2,2-trifluoroethyl.
- 20 Preferred are trifluoromethyl and 2,2,2-trifluoroethyl. Most preferred is trifluoromethyl.
- 25 • The term “(C_x-C_y)fluoroalkoxy” (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. For example a (C₁-C₂)fluoroalkoxy group contains from one to two carbon atoms in which one to five hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy and 2,2,2-trifluoroethoxy. Preferred are (C₁)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy. Most preferred is trifluoromethoxy.
- 30 • The term halogen means fluoro, chloro, bromo or iodo, preferably fluoro, chloro or bromo and most preferably chloro or bromo.

- The term "aryl", used alone or in any combination, means a phenyl or a naphthyl group. Preferred is a phenyl group. The aryl group may be unsubstituted or substituted as explicitly defined.

In case **R**¹ represents "aryl" the term means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted, mono- or di-substituted and most preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Preferably the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, trifluoromethyl and trifluoromethoxy (and most preferably from fluoro, bromo, methoxy and trifluoromethyl). Examples of such aryl groups are phenyl, 4-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-acetylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3-bromophenyl, 4-bromophenyl, 4-bromo-2-fluoro-phenyl and 4-iodophenyl (and preferably 4-methoxyphenyl, 4-trifluoromethylphenyl, 4-bromophenyl and 4-bromo-2-fluoro-phenyl).

In case **R**² represents "aryl" the term means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably mono- or di-substituted and most preferably di-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl (and preferably from halogen). Examples of such aryl groups are 4-bromophenyl and 2-chloro-3-fluorophenyl.

In case **R**² represents "(C₁-C₄)alkyl, which is mono-substituted with an aryl group" the term "aryl" means the above-mentioned groups (preferably phenyl), which groups are independently unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted or mono-substituted and most preferably mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. Preferably the substituents are independently selected from the group consisting of halogen, -CH₂NHR⁹ and -SO₂NH₂ (and most preferably from -CH₂NH₂ and -SO₂NH₂). Examples of such aryl groups are 4-fluorophenyl, 2-chlorophenyl, 3-aminomethyl-phenyl, 4-aminomethyl-phenyl, 3-(*tert*-butoxycarbonylamino-methyl)-phenyl, 4-(*tert*-butoxycarbonylamino-

methyl)-phenyl and 4-sulfamoyl-phenyl (and preferably 3-aminomethyl-phenyl, 4-aminomethyl-phenyl and 4-sulfamoyl-phenyl).

- The term "aryloxy", used alone or in combination, refers to an aryl-O- group wherein the aryl group is as defined before. A preferred example of an aryloxy group is phenoxy.

- The term "heteroaryl", used alone or in combination, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur. Examples of such heteroaryl groups are furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyridaziny, pyrazinyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzo[2,1,3]oxadiazolyl, benzo[2,1,3]thiadiazolyl, benzo[1,2,3]thiadiazolyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl and phthalazinyl. The heteroaryl group may be unsubstituted or substituted as explicitly defined.

In case R^1 represents "heteroaryl" the term means the above-mentioned groups. Preferred heteroaryl groups as used in R^1 are furanyl (notably furan-2-yl), oxazolyl (notably oxazol-5-yl), isoxazolyl (notably isoxazol-3-yl), thienyl (notably thiophen-2-yl and thiophen-3-yl), thiazolyl (notably thiazol-2-yl), thiadiazolyl (notably [1,2,4]thiadiazol-5-yl), imidazolyl (notably imidazol-1-yl and imidazol-2-yl), pyridyl (notably pyridin-2-yl and pyridin-3-yl), pyrimidyl (notably pyrimidin-5-yl), indolyl (notably indol-1-yl and indol-5-yl), benzimidazolyl (notably benzimidazol-2-yl), benzothiazolyl (notably benzothiazol-2-yl and benzothiazol-5-yl), benzoisothiazolyl (notably benzoisothiazol-5-yl) and benzo[2,1,3]oxadiazolyl (notably benzo[2,1,3]oxadiazol-4-yl). Most preferred heteroaryl groups are furanyl (notably furan-2-yl), thiazolyl (notably thiazol-2-yl), pyridyl (notably pyridin-2-yl and pyridin-3-yl) and benzothiazolyl (notably benzothiazol-5-yl). The above-mentioned heteroaryl groups as used in R^1 are unsubstituted, mono-, di- or tri-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoro-alkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Preferably the substituents are independently selected from the group

consisting of halogen, (C₁-C₄)alkyl, (C₁-C₂)alkyl-carbonyl, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen. Most preferably the substituents are independently selected from halogen, methyl and acetyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups as used in **R**¹ are furan-2-yl, 5-acetyl-furan-2-yl (preferred), 5-methyl-furan-2-yl, 2-acetyl-oxazol-5-yl, 5-*iso*-butyl-isoxazol-3-yl, 5-*tert*-butyl-isoxazol-3-yl, 5-acetyl-thiophen-2-yl, 5-bromo-thiophen-3-yl, 5-chloro-thiazol-2-yl, 5-bromo-thiazol-2-yl (preferred), 5-methyl-thiazol-2-yl, 4-*tert*-butyl-thiazol-2-yl, 4-acetyl-thiazol-2-yl, 5-nitro-thiazol-2-yl, 5-cyano-thiazol-2-yl, 4-(4-chloro-phenyl)-thiazol-2-yl, 3-phenyl-[1,2,4]thiadiazol-5-yl, imidazol-1-yl, 4,5-dimethyl-imidazol-2-yl (preferred), 5-bromo-pyridin-2-yl (preferred), 5-methyl-pyridin-2-yl (preferred), 6-chloro-pyridin-3-yl (preferred), 6-bromo-pyridin-3-yl (preferred), 2-chloro-pyrimidin-5-yl, indol-1-yl, 2-methyl-indol-1-yl, indol-5-yl, 1-methyl-benzimidazol-2-yl, benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, benzothiazol-5-yl (preferred), 2-methyl-benzothiazol-5-yl, 3-methyl-benzothiazol-5-yl and benzo[2,1,3]oxadiazol-4-yl.

In case **R**² represents "heteroaryl" the term means the above-mentioned groups. Preferred heteroaryl groups as used in **R**² are isoxazolyl (notably isoxazol-4-yl), pyrazolyl (notably pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl) and pyridyl (notably pyridin-3-yl). The above-mentioned heteroaryl groups as used in **R**² are unsubstituted, mono-, di- or tri-substituted (preferably mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl. Preferably the substituents are independently selected from the group consisting of methyl and phenyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups as used in **R**² are 5-phenyl-isoxazol-4-yl (preferred), 1,5-dimethyl-pyrazol-3-yl, 5-chloro-1,3-dimethyl-pyrazol-4-yl, 1-phenyl-pyrazol-5-yl (preferred) and 4-methyl-pyridin-3-yl.

In case **R**² represents "(C₁-C₄)alkyl, which is mono-substituted with a heteroaryl group" the term "heteroaryl" means the above-mentioned groups. Preferred heteroaryl groups are furanyl (notably furan-3-yl), isoxazolyl (notably isoxazol-4-yl), thiazolyl (notably thiazol-4-yl), imidazolyl (notably imidazol-1-yl and imidazol-2-yl), pyrazolyl (notably pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl), triazolyl (notably [1,2,4]triazol-1-yl), pyridyl (notably pyridin-2-yl and pyridin-3-yl), indolyl (notably indol-3-yl) and benzimidazolyl (notably benzimidazol-2-yl). The above-mentioned heteroaryl groups are unsubstituted, mono-, di- or tri-substituted

(preferably unsubstituted, mono- or disubstituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl. Preferably the substituents are independently selected from the group consisting of (C₁-C₄)alkyl and phenyl. Examples of such unsubstituted, mono-, di- or tri-substituted heteroaryl groups are furan-3-yl, 5-methyl-3-phenyl-isoxazol-4-yl, 2-methyl-thiazol-4-yl, 2,5-dimethyl-thiazol-4-yl, imidazol-1-yl (preferred), 4,5-dimethyl-imidazol-2-yl (preferred), pyrazol-1-yl (preferred), 3,5-dimethyl-pyrazol-1-yl (preferred), 1-ethyl-5-methyl-pyrazol-3-yl (preferred), 5-methyl-pyrazol-4-yl, 1-ethyl-3-methyl-pyrazol-5-yl, [1,2,4]triazol-1-yl (preferred), pyridin-2-yl, pyridin-3-yl, indol-3-yl, benzimidazol-2-yl (preferred) and 1-methyl-benzimidazol-2-yl.

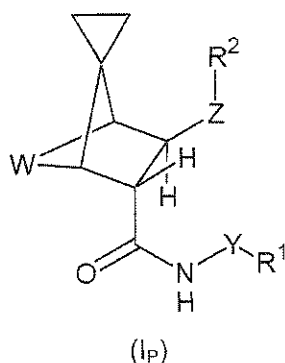
- The term "heterocyclyl", used alone or in combination, means a 4- to 6-membered saturated monocyclic ring containing 1 or 2 heteroatoms independently selected from the group consisting of sulfur, oxygen and nitrogen (preferably oxygen and nitrogen), wherein one or two methylene groups adjacent to a nitrogen atom are optionally replaced by carbonyl groups. Examples of such heterocyclyl groups are azetidiny, oxetanyl, pyrrolidinyl, pyrrolidonyl, tetrahydrofuranyl, tetrahydrothiophenyl, imidazolidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, thiazolidinonyl, piperidinyl, piperidonyl, piperazinyl, piperazinonyl, piperazine-dionyl, morpholinyl, morpholinonyl, thiomorpholinyl, thiomorpholinonyl and dioxanyl. Preferred examples are azetidiny, pyrrolidinyl, pyrrolidonyl, tetrahydrofuranyl, imidazolidinonyl, piperidinyl, piperidonyl, piperazinyl, morpholinyl and dioxanyl. The heterocyclyl group may be unsubstituted or substituted as explicitly defined.

In case **R**² represents "heterocyclyl" the term means the above-mentioned groups. Preferred heterocyclyl groups as used in **R**² are azetidiny (notably azetidin-3-yl), pyrrolidinyl (notably pyrrolidin-3-yl) and piperidinyl (notably piperidin-3-yl and piperidin-4-yl). The above-mentioned heterocyclyl groups are unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl. Examples of such unsubstituted or mono-substituted heterocyclyl groups are 1-*tert*-butoxycarbonyl-azetidin-3-yl, pyrrolidin-3-yl (preferred), 1-*tert*-butoxycarbonyl-pyrrolidin-3-yl, piperidin-3-yl (preferred), 1-*tert*-butoxycarbonyl-piperidin-3-yl, piperidin-4-yl (preferred), 1-methyl-piperidin-4-yl, 1-ethyl-piperidin-4-

yl, 1-(3-methyl-butyl)-piperidin-4-yl, 1-benzyl-piperidin-4-yl and 1-*tert*-butoxycarbonyl-piperidin-4-yl.

In case R^2 represents "(C₁-C₄)alkyl, which is mono-substituted with heterocyclyl" the term "heterocyclyl" means the above-mentioned groups. Preferred heterocyclyl groups are pyrrolidinyl (notably pyrrolidin-1-yl and pyrrolidin-2-yl), pyrrolidonyl (notably pyrrolidon-1-yl), tetrahydrofuranyl (notably tetrahydrofuran-2-yl), imidazolidinonyl (notably imidazolidin-2-on-1-yl), piperidinyl (notably piperidin-3-yl and piperidin-4-yl), piperazinyl (notably piperazin-1-yl), morpholinyl (notably morpholin-4-yl) and dioxanyl (notably 1,4-dioxan-2-yl). The above-mentioned heterocyclyl groups are unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl (preferred) or *tert*-butoxycarbonyl. Examples of such unsubstituted or mono-substituted heterocyclyl groups are pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, 1-ethyl-pyrrolidin-2-yl, 1-*tert*-butoxycarbonyl-pyrrolidin-2-yl, pyrrolidon-1-yl, tetrahydrofuran-2-yl, imidazolidin-2-on-1-yl, 1-*tert*-butoxycarbonyl-piperidin-3-yl, piperidin-4-yl, 1-*tert*-butoxycarbonyl-piperidin-4-yl, 4-methyl-piperazin-1-yl, morpholin-4-yl and 1,4-dioxan-2-yl. Preferred examples of such unsubstituted or mono-substituted heterocyclyl groups are pyrrolidin-1-yl, pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, tetrahydrofuran-2-yl, imidazolidin-2-on-1-yl, piperidin-4-yl, 4-methyl-piperazin-1-yl and 1,4-dioxan-2-yl.

2) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to embodiment 1) which are also compounds of formula (I_P)



wherein

W represents -CH₂CH₂- or -CH=CH-;

Y represents a bond or a (C₁-C₄)alkandiyl group and R^1 represents

an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen; or

aryloxy; or

cyclohexyl, which is unsubstituted or mono-substituted with methyl; or

(C₁-C₂)alkyl-carbonyl; or

(C₁-C₄)alkoxy-carbonyl;

10 or Y represents together with R¹ a (C₄-C₆)alkyl group;

Z represents -C(O)NR³-* or -CH₂NR⁴C(O)-*,

wherein the asterisks indicate the bond which is linked to R²;

R² represents

(C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or

15 -CONH₂; or

(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶ or -C(O)NR⁷R⁸; or

(C₁-C₄)alkyl, which is mono-substituted with (C₃-C₆)cycloalkyl; with heterocyclyl,

20 which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl or *tert*-butoxycarbonyl; or with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NHR⁹, -SO₂NH₂ and phenyl; or

25 heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl; or

an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl; or

30 a group selected from 1-carbamoyl-2-phenyl-ethyl, 1-methoxymethyl-2-phenyl-ethyl, 2-morpholino-2-phenyl-ethyl, 1-(1-piperidinecarbonyl)-ethyl, 2-phenyl-vinyl, 2,2-dichloro-1-methyl-cyclopropyl;

R³ represents hydrogen, (C₁-C₃)alkyl or 2-methoxy-ethyl;

R^4 represents hydrogen or methyl;

R^5 represents hydrogen, (C_1-C_3) alkyl or *tert*-butoxycarbonyl;

R^6 represents hydrogen or (C_1-C_3) alkyl;

R^7 and R^8 represent independently from each other hydrogen or methyl; and

5 R^9 represents hydrogen or *tert*-butoxycarbonyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

3) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to embodiment 1), wherein

W represents $-CH_2CH_2-$ or $-CH=CH-$;

10 **Y** represents a bond or a (C_1-C_4) alkandiyl group;

R^1 represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_2) alkyl-carbonyl, (C_1-C_2) fluoroalkyl, (C_1-C_2) fluoroalkoxy, nitro, cyano and phenyl, wherein the
15 phenyl is unsubstituted or mono-substituted with halogen;

Z represents $-C(O)NR^3-^*$ or $-CH_2NR^4C(O)-^*$,
wherein the asterisks indicate the bond which is linked to R^2 ;

R^2 represents

- 20 • (C_3-C_6) cycloalkyl, which is unsubstituted or mono-substituted with hydroxy, pyrrolidin-1-yl-methyl or $-CONH_2$; or
- (C_1-C_6) alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C_1-C_4) alkylthio, (C_1-C_4) alkoxy-carbonyl, hydroxy, cyano, $-NR^5R^6$, $-C(O)NR^7R^8$ or optionally mono-substituted (C_1-C_4) alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or
- 25 • (C_1-C_5) alkyl, which is mono-substituted
 - ◊ with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with (C_1-C_4) alkyl, or mono- or di-substituted at one or

two of the carbon atoms with substituents independently selected from halogen, (C₁-C₄)alkyl and (C₁-C₂)alkoxy-(C₁-C₂)alkyl; or

◇ with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and -SO₂NH₂; or

- (C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted (preferred) or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen and (C₁-C₄)alkyl; or

- heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl; or

- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl;

R³ represents hydrogen, (C₁-C₃)alkyl or 2-methoxy-ethyl; or

R² and **R**³ form, together with the nitrogen that carries them, a piperidine ring, which ring is substituted with amino-(C₁-C₄)alkyl (preferably amino-methyl);

R⁴ represents hydrogen or methyl;

R⁵ represents hydrogen, (C₁-C₃)alkyl or *tert*-butoxycarbonyl;

R⁶ represents hydrogen or (C₁-C₃)alkyl;

R⁷ and **R**⁸ represent independently from each other hydrogen or methyl; or

R⁷ and **R**⁸ form, together with the nitrogen that carries them, a pyrrolidine ring;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

4) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 3), wherein

W represents -CH₂CH₂- or -CH=CH-;

Y represents a bond or a (C₁-C₄)alkandiyl group;

R¹ represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the
5 phenyl is unsubstituted or mono-substituted with halogen;

Z represents -C(O)NR³-* or -CH₂NR⁴C(O)-*,
wherein the asterisks indicate the bond which is linked to R²;

R² represents

(C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or
10 -CONH₂; or
(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶ or -C(O)NR⁷R⁸; or
(C₁-C₄)alkyl, which is mono-substituted with heterocyclyl, which is unsubstituted or
15 mono-substituted at a nitrogen atom with (C₁-C₄)alkyl; or
(C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and -SO₂NH₂; or
20 heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl; or
an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl;

25 **R**³ represents hydrogen, (C₁-C₃)alkyl or 2-methoxy-ethyl;

R⁴ represents hydrogen or methyl;

R⁵ represents hydrogen, (C₁-C₃)alkyl or *tert*-butoxycarbonyl;

R⁶ represents hydrogen or (C₁-C₃)alkyl; and

R⁷ and **R**⁸ represent independently from each other hydrogen or methyl;

30 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) or 3), wherein

W represents -CH₂CH₂- or -CH=CH-;

Y represents a bond;

5 **R**¹ represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen (preferably bromo), (C₁-C₄)alkyl (preferably methyl), (C₁-C₄)alkoxy (preferably methoxy), (C₁-C₂)alkyl-carbonyl (preferably acetyl), and (C₁-C₂)fluoroalkyl (preferably trifluoromethyl);

10 **Z** represents -C(O)NR³-,
wherein the asterisk indicates the bond which is linked to R²;

R² represents

- (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or pyrrolidin-1-yl-methyl; or
- 15 • (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio (preferably ethylthio), hydroxy, cyano, -NR⁵R⁶, -C(O)NH₂ or optionally mono-substituted (C₁-C₄)alkoxy (preferably methoxy or ethoxy), wherein the substituent is selected from hydroxy and heterocyclyl; or
- (C₁-C₅)alkyl, which is mono-substituted
 - 20 ◇ with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl (preferably methyl), or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from fluorine, methyl and methoxy-methyl; or
 - ◇ with an aryl- or heteroaryl-group, which groups are independently
 - 25 unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and -CH₂NH₂; or
- (C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl (preferably pyrrolidin-1-yl); or
- 30 • heterocyclyl, which is unsubstituted or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl;

R^3 represents hydrogen, (C₁-C₃)alkyl (preferably methyl or ethyl) or 2-methoxy-ethyl;

R^5 represents hydrogen, (C₁-C₃)alkyl (preferably methyl or ethyl) or *tert*-butoxycarbonyl;
and

R^6 represents hydrogen or (C₁-C₃)alkyl (preferably methyl or ethyl);

5 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

6) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 5), wherein

W represents -CH₂CH₂- or -CH=CH-;

10 **Y** represents a bond;

R^1 represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted or mono-substituted, wherein the substituent is selected from the group consisting of halogen (preferably bromo), (C₁-C₄)alkyl (preferably methyl), (C₁-C₄)alkoxy (preferably methoxy), (C₁-C₂)alkyl-carbonyl (preferably acetyl) and (C₁-C₂)fluoroalkyl
15 (preferably trifluoromethyl);

Z represents -C(O)NR³*,

wherein the asterisk indicates the bond which is linked to R²;

R^2 represents

- 20 (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy; or
(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy (preferably methoxy or ethoxy), (C₁-C₄)alkylthio (preferably ethylthio), hydroxy, cyano, -NR⁵R⁶ or -C(O)NH₂; or
(C₁-C₄)alkyl, which is mono-substituted with heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with methyl; or
25 (C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and -CH₂NH₂; or heterocyclyl;

R³ represents hydrogen, (C₁-C₃)alkyl (preferably methyl or ethyl) or 2-methoxy-ethyl;

R⁵ represents hydrogen, (C₁-C₃)alkyl (preferably methyl or ethyl) or *tert*-butoxycarbonyl;
and

R⁶ represents hydrogen or (C₁-C₃)alkyl (preferably methyl or ethyl);

5 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

7) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 6), wherein

W represents -CH₂CH₂-;

10 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

8) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 6), wherein

W represents -CH=CH-;

15 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

9) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 8), wherein

Y represents a bond;

20 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4) or 7) to 8), wherein

Y represents a (C₁-C₄)alkandiyl group (preferably methandiyl);

25 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

11) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4) or 7) to 10), wherein

30 **R**¹ represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl, (C₁-C₂)fluoroalkyl, (C₁-C₂)fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

12) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 11), wherein

5 **R¹** represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted or mono-substituted, wherein the substituent is selected from the group consisting of halogen (preferably bromo), (C₁-C₄)alkyl (preferably methyl), (C₁-C₄)alkoxy (preferably methoxy), (C₁-C₂)alkyl-carbonyl (preferably acetyl) and (C₁-C₂)fluoroalkyl (preferably trifluoromethyl);

10 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

13) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 2) or 7) to 10), wherein

15 **R¹** represents aryloxy (preferably phenoxy), cyclohexyl, 4-methyl-cyclohexyl, (C₁-C₂)alkyl-carbonyl (preferably acetyl) or (C₁-C₄)alkoxy-carbonyl (preferably methoxy-carbonyl);
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

14) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 7) or 8), wherein

20 **Y** represents together with **R¹** a (C₄-C₆)alkyl group or a amino-(C₄-C₆)alkyl group;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 2), 7) or 8), wherein

25 **Y** represents together with **R¹** a (C₄-C₆)alkyl group;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

16) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 7) or 8), wherein

30 **Y** represents together with **R¹** a amino-(C₄-C₆)alkyl group;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

17) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 7) or 8), wherein

35 **Y** represents a (C₁-C₂)alkandiyl group (preferably ethan-1,2-diyl) and **R¹** represents

- an aryl-group, which group is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen (preferably fluoro, chloro and bromo), (C₁-C₄)alkyl (preferably methyl) and (C₁-C₄)alkoxy (preferably methoxy); or
- 5 • benzo[d][1,3]dioxolyl;
- and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

18) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 17), wherein

- 10 **Z** represents -C(O)NR³-, wherein the asterisk indicates the bond which is linked to R²; and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

19) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4) or 7) to 17), wherein

- 15 **Z** represents -CH₂NR⁴C(O)-*, wherein the asterisk indicates the bond which is linked to R²; and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

20) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3) or 7) to 19), wherein

- 20 **R**² represents
- (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy, pyrrolidin-1-yl-methyl or -CONH₂; or
- (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶, -C(O)NR⁷R⁸ or optionally
- 25 mono-substituted (C₁-C₄)alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or
- (C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl, or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected
- 30 from halogen, (C₁-C₄)alkyl and (C₁-C₂)alkoxy-(C₁-C₂)alkyl; or
- (C₁-C₅)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and -SO₂NH₂; or
- 35 (C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl; or

heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl; or

- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-,
5 di-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl and phenyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 21) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives
10 according to any one of embodiments 1) to 4) or 7) to 19), wherein

R² represents

- (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or -CONH₂; or
(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl,
(C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkoxy-carbonyl, hydroxy, cyano, -NR⁵R⁶ or
15 -C(O)NR⁷R⁸; or

(C₁-C₄)alkyl, which is mono-substituted with heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl; or

- (C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are
independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are
20 independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and
-SO₂NH₂; or

heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl, benzyl or *tert*-butoxycarbonyl; or

- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono- or di-
25 substituted, wherein the substituents are independently selected from the group consisting
of halogen, (C₁-C₄)alkyl and phenyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

- 22) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives
30 according to any one of embodiments 1), 3) or 7) to 19), wherein

R² represents

- (C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or pyrrolidin-1-yl-methyl; or
(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-
35 C₄)alkylthio (preferably ethylthio), hydroxy, cyano, -NR⁵R⁶, -C(O)NH₂ or optionally mono-

substituted (C₁-C₄)alkoxy (preferably methoxy or ethoxy), wherein the substituent is selected from hydroxy and heterocyclyl; or

(C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl (preferably methyl), or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from fluorine, methyl and methoxy-methyl; or

(C₁-C₅)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and

-CH₂NH₂; or

(C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl (preferably pyrrolidin-1-yl); or

heterocyclyl, which is unsubstituted or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

23) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents

(C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy; or

(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy (preferably methoxy or ethoxy), (C₁-C₄)alkylthio (preferably ethylthio), hydroxy, cyano, -NR⁵R⁶ or -C(O)NH₂; or

(C₁-C₄)alkyl, which is mono-substituted with heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with methyl; or

(C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and -CH₂NH₂; or

heterocyclyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

24) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3), 5) or 7) to 19), wherein

R^2 represents (C₃-C₆)cycloalkyl (preferably cyclopentyl or cyclohexyl), which is unsubstituted or mono-substituted with hydroxy, hydroxy-methyl, amino-methyl, pyrrolidin-1-yl-methyl or -CONH₂ (and preferably unsubstituted or mono-substituted with hydroxy or pyrrolidin-1-yl-methyl);

5 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

10 R^2 represents (C₃-C₆)cycloalkyl (preferably cyclopentyl or cyclohexyl), which is unsubstituted or mono-substituted with hydroxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

26) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3) or 7) to 19), wherein

15 R^2 represents (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, hydroxy, cyano, -NR⁵R⁶, -C(O)NR⁷R⁸ or optionally mono-substituted (C₁-C₄)alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

20

27) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R^2 represents (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, hydroxy, cyano, -NR⁵R⁶ or -C(O)NH₂ (preferably fluorine, trifluoromethyl, methoxy, ethoxy, hydroxy, cyano, -NR⁵R⁶ or -C(O)NH₂);

25

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

28) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3), 5) or 7) to 19), wherein

30 R^2 represents (C₂-C₅)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, hydroxy, -NR⁵R⁶, -C(O)NR⁷R⁸, methoxy, ethoxy or 2-(pyrrolidin-1-yl)-ethoxy;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

35

29) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3) or 7) to 19), wherein

R² represents

(C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is
5 unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₄)alkyl (preferably methyl or ethyl), or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen, (C₁-C₄)alkyl and (C₁-C₂)alkoxy-(C₁-C₂)alkyl (preferably from fluorine, methyl and methoxy-methyl); or

(C₁-C₅)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are
10 independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and -SO₂NH₂ (and preferably from methyl and -CH₂NH₂);

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15 30) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents (C₁-C₄)alkyl, which is mono-substituted with heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with methyl; or

(C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are
20 independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and -CH₂NH₂;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 31) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3), 5) or 7) to 19), wherein

R² represents (C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl (preferably methyl), or mono- or di-substituted at one or two of the carbon atoms with substituents
30 independently selected from fluorine, methyl and methoxy-methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

32) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents (C₁-C₄)alkyl (preferably methyl or *n*-butyl and most preferably *n*-butyl), which is mono-substituted with heterocyclyl, which is unsubstituted (preferred) or mono-substituted at a nitrogen atom with methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5

33) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 29) to 32), wherein

the heterocyclyl is selected from the group consisting of azetidiny (preferably azetidin-1-yl), pyrrolidiny (preferably pyrrolidin-1-yl and pyrrolidin-2-yl), tetrahydrofurany (preferably tetrahydrofuran-2-yl), imidazolidinony (preferably imidazolidin-2-on-1-yl), piperidiny (preferably piperidin-1-yl, piperidin-2-yl and piperidin-4-yl), piperaziny (preferably piperazin-1-yl), morpholiny (preferably morpholin-4-yl) and 1,4-diazepany (preferably 1,4-diazepan-1-yl);

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15

34) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents (C₁-C₅)alkyl (preferably (C₁-C₃)alkyl), which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of halogen, (C₁-C₄)alkyl, -CH₂NH₂ and -SO₂NH₂ (and preferably from methyl and -CH₂NH₂);

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25

35) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents (C₁-C₄)alkyl (preferably methyl, ethyl or *n*-propyl), which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted (preferably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl (preferably methyl) and -CH₂NH₂;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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36) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 19), wherein

R² represents (C₁-C₅)alkyl (preferably (C₁-C₃)alkyl), which is mono-substituted with a heteroaryl-group, which is unsubstituted, mono- or di-substituted (preferably unsubstituted or di-substituted) with (C₁-C₄)alkyl (preferably methyl);

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

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37) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3), 5) or 7) to 19), wherein

R² represents (C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl (preferably pyrrolidin-1-yl);

10 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

38) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to embodiment 37), wherein

(C₃-C₅)fluoroalkyl means 3-fluorobutyl (preferred) or 3,3-difluorobutyl;

15 and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

39) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3) or 7) to 19), wherein

20 **R²** represents heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

40) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4) or 6 to 19), wherein

25 **R²** represents heterocyclyl, which is unsubstituted (preferred) or mono-substituted at a nitrogen atom with (C₁-C₆)alkyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

41) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 18) or 20) to 40), wherein

30 **R³** represents hydrogen (preferred), methyl, ethyl or 2-methoxy-ethyl;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

42) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 3) or 7) to 19), wherein

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R^2 and R^3 form, together with the nitrogen that carries them, a piperidine ring, which ring is substituted with amino-(C₁-C₄)alkyl (preferably amino-methyl);
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5 43) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4), 7) to 17) or 19) to 40), wherein R^4 represents hydrogen;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

10 44) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 23), 26) to 28), 41) or 43), wherein R^5 represents hydrogen, methyl or ethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

15 45) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 23), 26) to 28), 41), 43) or 44), wherein R^6 represents hydrogen, methyl or ethyl;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

20 46) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 4), 7) to 21), 26), 28), 41) or 43), wherein R^7 and R^8 represent hydrogen;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

25 47) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1), 2), 7) to 19), 41) or 43), wherein R^9 represents hydrogen;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds..

30 48) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 47), wherein the absolute configuration of the stereogenic centers is as depicted in formula I_{ST1} above;
and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

49) A further embodiment of the invention relates to bridged spiro[2.4]heptane derivatives according to any one of embodiments 1) to 47), wherein the absolute configuration of the stereogenic centers is as depicted in formula I₈₂ above;

and to the salts (in particular pharmaceutically acceptable salts) of such compounds.

5 50) Preferred compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-iso-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-*N,N*-dimethyl-amino-ethyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-((3-aminomethyl-phenyl)-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-piperidiny-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-(*N,N*-diethyl-amino)-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-hydroxy-propyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-ethyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N-tert*-butoxycarbonyl-pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-ethoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidinyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2,2-trifluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-fluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-methyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-tetrahydrofuranyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-ethylsulfanyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(*N,N*-diethyl-amino)-pent-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-*tert*-butoxycarbonyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-hydroxy-prop-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-imidazolidin-2-on-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-hydroxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyano-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-pyrazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-aminomethyl-phenyl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-ethyl-*N*⁶-(2-diethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-imidazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[1,4]-dioxan-2-yl-methyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-*tert*-butoxycarbonyl-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methyl-*tert*-butoxycarbonyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidin-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-1*H*-[1,2,4]-triazol-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(furan-3-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-dimethyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1-ethyl-pyrrolidin-2-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-[1,2,4]-triazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(*N*-*tert*-butoxycarbonyl-amino)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-1-hydroxy-4-methyl-pent-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methoxy-carbonyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-5-methyl-1*H*-pyrazol-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-diethyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-(3-methyl-butyl)-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyridin-2-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-*N*-*tert*-butoxycarbonyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-phenyl-1*H*-pyrazol-5-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(hexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-phenyl-2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-diethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-pyrrolidin-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-piperidin-1-yl-propan-1-on-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-benzyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-hexyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3,3-dimethyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-methyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-morpholino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(5-methyl-1*H*-pyrazol-4-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-*tert*-butoxycarbonyl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(3-*N*-*tert*-butoxycarbonyl-aminomethyl)-phenyl]-methyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-propyl-*N*⁶-(cyclopropylmethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl)-methyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-2-phenyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-*N*-*tert*-butoxycarbonyl-aminomethyl)-phenyl]-methyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-azetidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-2-methoxy-1-benzyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-ethyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(tetrahydrofuran-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2-imidazolidin-2-on-1-yl)-ethyl]-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-hydroxy-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(1*H*-imidazol-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(dimethyl-amino)-pentyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromopyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Methoxyphenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(Benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-Pentyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(4-Methyl-phenyl)-methyl]-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(2-Methoxycarbonyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Cyclohexyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Methyl-cyclohex-1-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(5-Oxo-hexyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Nitro-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(5-Chloro-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Cyano-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(1-(4-Bromophenyl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Trifluoromethoxyphenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-Phenoxy-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Methyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-Butyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Methyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Methyl-benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2-Phenyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Oxo-pentyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(3-(1*H*-Imidazol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-pyrimidin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(Benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-*tert*-Butyl-isoxazol-3-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(3-Methyl-benzo[*d*]isothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(1*H*-Indol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(6-Fluoro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(2-Ethyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-(4-Chlorophenyl)-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(Benzo[2,1,3]oxadiazol-4-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-*tert*-Butyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(3-Phenyl-[1,2,4]thiadiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(6-Chloro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-(2-Methyl-1*H*-indol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2-(1-Methyl-1*H*-benzimidazol-2-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(1*H*-Indol-1-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(2-(2-Methoxy-phenyl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(3,5-dimethyl-pyrazol-1-yl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(5-phenyl-isoxazole-4-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-(2-oxo-pyrrolidin-1-yl)-butyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-chloro-phenyl)-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-methoxy-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(*N,N*-dimethyl-aminocarbonyl)-propionyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2,2-dichloro-1-methyl-cyclopropylcarbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-methoxycarbonyl-butanoyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-(pentanoylamino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;

- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2,5-dimethyl-thiazol-4-yl)-acetylamino)-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(1-phenyl-1*H*-pyrazole-5-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-aminocarbonyl-propionyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-methyl-pyridine-3-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(isobutyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-
10 spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(*N*-ethyl-piperidine-4-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-pyridin-3-yl-propionylamino)-methyl]-(4*S**,7*R**)-
[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(*N*-(3-methoxy-propionyl)-*N*-methyl-amino)-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-chloro-3-fluoro-phenyl-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-pyrrolidin-1-yl-butanoylamino)-methyl]-(4*S**,7*R**)-
20 [4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-amino]-
methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(cyclopentyl-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-
ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-methyl-thiazol-4-yl)-acetylamino)-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(*N,N*-dimethyl-amino)-acetylamino)-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(*N*-(2-(2-chloro-phenyl)-acetyl)-*N*-methyl-amino)-
30 methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(*N*-(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-*N*-methyl-
amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-cyclopropyl-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-
ethenylene-spiro[2.4]heptane]-5-carboxamide;

- (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[(3-(1-methyl-1H-benzimidazol-2-yl)-propionylamino)-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[(3-1H-indol-3-yl-propionylamino)-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 5 (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[(butanoylamino)-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[(3-(4-fluoro-phenyl)-propionylamino)-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[(3-phenyl-acryloylamino)-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 10 (5R*)-N⁵-(4-Bromo-phenyl)-(6R*)-6-[[5-chloro-1,3-dimethyl-1H-pyrazole-4-carbonyl]-amino]-methyl]-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5R*)-N⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5R*)-N⁵-(4-Acetyl-phenyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(5-Methyl-thiazol-2-yl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(5-Acetyl-thiophen-2-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5R*)-N⁵-(5-Acetyl-furan-2-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(5-Acetyl-furan-2-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5R*)-N⁵-(4-Trifluoromethyl-phenyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(2-Acetyl-oxazol-5-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(2-(4,5-Dimethyl-1H-imidazol-2-yl)-ethyl)-(6R*)-N⁶-(4-bromophenyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5R*)-N⁵-(4-Iodophenyl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5R*)-N⁵-(5-(iso-Butyl)-isoxazol-3-yl-methyl)-(6R*)-N⁶-(4-pyrrolidin-1-yl-butyl)-(4S*,7R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(2-Bromo-thiophen-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide; and

(5*R**)-*N*⁵-(2-Fluoro-4-bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

5 or salts (in particular pharmaceutically acceptable salts) of such compounds;

it is to be understood for any of the above listed compounds, that a stereogenic center, which is not specifically assigned, may be in absolute (*R*)- or absolute (*S*)-configuration and that a double bond, which is not specifically assigned, may be in (*E*)- or (*Z*)-configuration. Especially, for a compound mentioned in the above list to have the relative (4*S**,5*R**,6*R**,7*R**)-configuration it is to be understood that also the respective enantiomer with the absolute (4*R*,5*S*,6*S*,7*S*)-configuration and/or the respective enantiomer with the absolute (4*S*,5*R*,6*R*,7*R*)-configuration is encompassed.

51) Further preferred compounds of formula (I) as defined in embodiment 1) are selected from the group consisting of:

15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethylamino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-4-oxobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-2-oxoethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-ethyl-piperazin-1-yl)-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

25 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-piperidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(azetidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-morpholino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

30 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-1,4-diazepan-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-4-oxobutyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-(2-(pyrrolidin-1-yl)ethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-((3*R*,6*S*)-6-(pyrrolidin-1-ylmethyl)tetrahydro-2*H*-pyran-3-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-acetyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*R*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*S*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(5-pyrrolidino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(3-methylamino-3-oxopropyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*^{*})-*N*⁵-(2-Acetyl-thiazol-5-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*^{*})-*N*⁵-(2,6-Difluoro-4-methoxy-phenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(2,3-Difluoro-4-methoxy-phenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(3-Fluoro-4-methoxy-phenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*^{*})-*N*⁵-(3,5-Difluoro-4-methoxy-phenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Chloro-phenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Fluoro-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Trifluoromethoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Isopropoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromo-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Acetyl-oxazol-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromo-pyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Acetyl-oxazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(2-Methoxy-pyrid-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromo-pyrazin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Trifluoromethyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2-Methyl-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Benzo[*d*]oxazol-6-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(5-Methyl-isoxazol-3-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Methyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Trifluoromethyl-1,3,4-thiadiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(2-Bromo-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2-fluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-ethoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-pyrrolidino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-dimethylamino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-fluoroethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(3-dimethylamino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(5-Bromopyrid-2-yl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloropyrid-5-yl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromothiazol-5-yl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-hydroxyl-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-methylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(4-Bromo-3-chlorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2-methylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(5-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-methylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-(aminomethyl)phenyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromo-thiazol-5-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromo-2,5-difluorophenyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromo-2,6-difluorophenyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶,*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(isobutyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-*tert*-butoxycarbonyl-amino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Aminobutyl)-(6*R*^{*})-*N*⁶-(4-bromophenyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*^{*})-*N*⁵-(5-Aminopentyl)-(6*R*^{*})-*N*⁶-(4-bromophenyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(2-(Cyclohexen-1-yl)ethyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-*tert*-Butyl-cyclohexyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*^{*})-*N*⁵-(2-(Pyridin-2-yl)ethyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*^{*})-*N*⁵-(4-Trifluoromethyl-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(2,4,6-Trifluorophenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(2,4-Dimethylphenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*^{*})-*N*⁵-[(2-Acetyl-thiazol-4-yl)methyl]-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(3-Chloro-2-fluorophenyl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Methyl-oxazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(5-Acetyl-thiazol-2-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(3-Acetylphenyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2,3,5-Trifluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(2-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(3-Difluoromethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(2-Methoxypyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(3-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(2-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-[(2,6-Dichloropyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4,5-Dimethyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Methoxy-5-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-3,6-difluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2-Isopropoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-6-fluoro-3-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(3-Chloro-4-methoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(2-(3,4-Dimethoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(4-Methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(2-(4-Bromophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(3,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(4-Methylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(2-(4-Fluorophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-(3-Bromo-4-methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(2,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Ethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-dimethylamino-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(pyridin-2-yl)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(2-(2,4-Dichlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(*N*-isopentyl-piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3-trifluoromethylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-[(4-Acetyl-thiazol-2-yl)methyl]-(6*R**)-*N*⁶-(2-methylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2,5-dimethylpyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(pyrrolidin-1-yl)pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3-fluoro-4-(pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2-(methoxymethyl)pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(3,3-difluoropyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-hydroxyethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-hydroxypropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxybutyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-methyl-3-hydroxyprop-2-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(2-hydroxyethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(1-hydroxy-cyclohexyl)methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*trans*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*cis*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(pyrrolidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(*N*-methylamino)-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-(*N*-methylamino)-propyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(pyrrolidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-3-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(azetidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;

5 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide; and

10 (5*R*^{*})-*N*⁵-(2-Trifluoromethyl-pyridin-5-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

or salts (in particular pharmaceutically acceptable salts) of such compounds;

it is to be understood for any of the above listed compounds, that a stereogenic center, which is not specifically assigned, may be in absolute (*R*)- or absolute (*S*)-configuration and that a double bond, which is not specifically assigned, may be in (*E*)- or (*Z*)-
15 configuration. Especially, for a compound mentioned in the above list to have the relative (4*S*^{*},5*R*^{*},6*R*^{*},7*R*^{*})-configuration it is to be understood that also the respective enantiomer with the absolute (4*R*,5*S*,6*S*,7*S*)-configuration and/or the respective enantiomer with the absolute (4*S*,5*R*,6*R*,7*R*)-configuration is encompassed.

The present invention also includes isotopically labelled, especially ²H (deuterium)
20 labelled compounds of formula (I), which compounds are identical to the compounds of formula (I) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ²H (deuterium) labelled compounds of formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen
25 with the heavier isotope ²H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula (I) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the
30 compounds of formula (I) are not isotopically labelled at all. Isotopically labelled compounds of formula (I) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts, Lit. e.g. "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

The compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for use as medicaments. In particular, compounds of formula (I) modulate the ALX receptor and/or FPRL2, i.e. they act as ALX receptor agonists and/or as FPRL2 agonists, and are useful for the prevention or treatment of diseases which respond to the activation of the ALX receptor and/or FPRL2 such as inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer's disease); in addition they are useful for the modulation of immune responses (especially those elicited by vaccination). Especially, compounds of formula (I) are useful for the prevention or treatment of diseases such as inflammatory diseases, obstructive airway diseases, allergic conditions, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders (especially Alzheimer's disease).

In particular, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from inflammatory diseases, obstructive airway diseases and allergic conditions.

Inflammatory diseases, obstructive airway diseases and allergic conditions include, but are not limited to, one, several or all of the following groups of diseases and disorders:

1) Acute lung injury (ALI); adult/acute respiratory distress syndrome (ARDS); chronic obstructive pulmonary, airway or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith; emphysema; as well as exacerbation of airway hyper reactivity consequent to other drug therapy, in particular other inhaled drug therapy. Especially, inflammatory diseases, obstructive airway diseases and allergic conditions include COPD, COAD and COLD.

2) Further inflammatory diseases, obstructive airway diseases and allergic conditions include bronchitis of whatever type or genesis.

3) Further inflammatory diseases, obstructive airway diseases and allergic conditions include bronchiectasis, and pneumoconiosis of whatever type or genesis.

4) Further inflammatory diseases, obstructive airway diseases and allergic conditions include asthma of whatever type or genesis, including intrinsic (non-allergic) asthma and
5 extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and induced asthma following bacterial infection.

5) In a further embodiment the compounds of formula (I) according to any one of
embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are particularly
10 suitable for the prevention or treatment of inflammatory diseases. Inflammatory diseases include one, several or all of the following groups of diseases and disorders:

5a) In particular, inflammatory diseases refer to neutrophil related disorders, especially neutrophil related disorders of the airway including hyper-neutrophilia as it affects the airway and/or lungs. Further neutrophil related disorders also include
15 periodontitis, glomerulonephritis, and cystic fibrosis.

5b) Further inflammatory diseases include skin diseases such as psoriasis, contact dermatitis, atopic dermatitis, dermatitis herpetiformis, scleroderma, hypersensitivity
angiitis, urticaria, lupus erythematosus, and epidermolysis.

5c) Further inflammatory diseases also relate to diseases or conditions having an
20 inflammatory component. Diseases or conditions having an inflammatory component include, but are not limited to, diseases and conditions affecting the eye such as uveitis (anterior, intermediate and posterior), Behçet syndrome uveitis, conjunctivitis, keratoconjunctivitis sicca, Sjögren syndrome keratoconjunctivitis sicca, and vernal conjunctivitis (and especially conjunctivitis, keratoconjunctivitis
25 sicca, and vernal conjunctivitis); diseases affecting the nose including rhinitis and allergic rhinitis (and especially allergic rhinitis); and inflammatory diseases in which autoimmune reactions are implicated or which have an autoimmune component or aetiology, such as systemic lupus erythematosus, ankylosing spondylitis, Behçet syndrome, Sjögren syndrome, polychondritis, scleroderma, Wegener
30 granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmopathy, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and
35 glomerulonephritis (and especially systemic lupus erythematosus, polychondritis,

scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis).

5d) Further inflammatory diseases in which autoimmune reactions are implicated or which have an autoimmune component or aetiology include rheumatoid arthritis, Hashimoto's thyroid and diabetes type I or II.

- 10 Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of organ or tissue transplant rejection, for example for the treatment of the recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, and the prevention of graft-versus-host disease, such as sometimes occurs following bone marrow transplantation, particularly in the treatment of acute or chronic allo- and xenograft rejection or in the transplantation of insulin producing cells, e.g. pancreatic islet cells.

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of HIV-mediated retroviral infections.

- 20 HIV-mediated retroviral infections include, but are not limited to, one, several or all of the groups of diseases and disorders caused by HIV-1 and HIV-2 strains such as GUN-4v, GUN-7wt, AG204, AG206, AG208, HCM305, HCM308, HCM342, mSTD104, and HCM309.

- Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of cardiovascular disorders.

- Cardiovascular disorders refer to one or more disease states of the cardiovascular tree (including the heart) and to diseases of dependent organs. Disease states of the cardiovascular tree and diseases of dependent organs include, but are not limited to, disorders of the heart muscle (cardiomyopathy or myocarditis) such as idiopathic cardiomyopathy, metabolic cardiomyopathy which includes diabetic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy; atheromatous disorders of the major blood vessels

(macrovascular disease) such as the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries; toxic, drug-induced, and metabolic (including hypertensive and/or diabetic) disorders of small blood vessels (microvascular disease) such as the retinal arterioles, the glomerular arterioles, the vasa nervorum, cardiac arterioles, and associated capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems; and, plaque rupture of atheromatous lesions of major blood vessels such as the aorta, the coronary arteries, the carotid arteries, the cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries and the popliteal arteries.

- 5 Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of neuroinflammation. Neuroinflammation refers to cell signalling molecule production, activation of glia or glial activation pathways and responses, proinflammatory cytokines or chemokines, activation of astrocytes or astrocyte activation pathways and responses, activation of microglia or microglial activation pathways and responses, oxidative stress-related responses such as nitric oxide synthase production and nitric oxide accumulation, acute phase proteins, loss of synaptophysin and Post Synaptic Density-95 Protein (PSD-95), components of the complement cascade, loss or reduction of synaptic function, protein kinase activity (e.g., death associated protein kinase activity), behavioral deficits, cell damage (e.g., neuronal cell damage), cell death (e.g., neuronal cell death), and/or amyloid β deposition of amyloid plaques.

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of neurological disorders.

- 25 In particular, neurological disorders include, but are not limited to, epilepsy, stroke, cerebral ischemia, cerebral palsy, relapsing remitting multiple sclerosis, progressive multiple sclerosis, neuromyelitis optica, clinically isolated syndrome, Alpers' disease, amyotrophic lateral sclerosis (ALS), senile dementia, dementia with Lewy bodies, Rett syndrome, spinal cord trauma, traumatic brain injury, trigeminal neuralgia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed vertebral disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, mild cognitive decline, cognitive decline,

Alzheimer's disease, Parkinson's disease, and Huntington's chorea (and especially epilepsy, stroke, cerebral ischemia, cerebral palsy, relapsing remitting multiple sclerosis, progressive multiple sclerosis, Alpers' disease, amyotrophic lateral sclerosis (ALS), senile dementia, dementia with Lewy bodies, Rett syndrome, spinal cord trauma, traumatic brain injury, trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed vertebral disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies, mild cognitive decline, cognitive decline, Alzheimer's disease, Parkinson's disease, and Huntington's chorea).

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of pain. Pain includes, but is not limited to, neuropathic pain exemplified by conditions such as diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, painful diabetic polyneuropathy, post-stroke pain, post-amputation pain, myelopathic or radiculopathic pain, atypical facial pain and causalgia-like syndromes.

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of prion-mediated diseases. Prion-mediated diseases, also known as transmissible spongiform encephalopathies (TSEs), include, but are not limited to, kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and Creutzfeldt-Jakob Disease (CJD).

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the treatment of amyloid-mediated disorders. Amyloid-mediated disorders are defined as diseases and disorders, that are caused by or associated with amyloid or amyloid-like proteins. Diseases and disorders caused by or associated with amyloid or amyloid-like proteins include, but are not limited to, Alzheimer's Disease (AD), including diseases or conditions characterized by a loss of cognitive memory capacity such as, for example, mild cognitive impairment (MCI); dementia with Lewy bodies; Down's syndrome; cerebral hemorrhage with amyloidosis. In another embodiment, diseases and disorders caused by or associated with amyloid or amyloid-like proteins include progressive supranuclear palsy, amyloid light chain amyloidosis, familial amyloid neuropathies, multiple sclerosis, Creutzfeldt Jakob

disease, Parkinson's disease, HIV-related dementia, Amyotrophic Lateral Sclerosis (ALS), inclusion-body myositis (IBM), Adult Onset Diabetes, and senile cardiac amyloidosis (and especially progressive supranuclear palsy, multiple sclerosis, Creutzfeldt Jakob disease, Parkinson's disease, HIV-related dementia, Amyotrophic Lateral Sclerosis (ALS),
5 inclusion-body myositis (IBM), Adult Onset Diabetes, and senile cardiac amyloidosis).

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the modulation of immune responses.

The modulation of immune responses includes, but is not limited to, methods based on
10 the administration to a subject a composition of at least one antigen and at least one compound of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof. In some cases, the antigen-containing composition is administrated first, followed by administration of a composition of at least one compounds of formula (I) according to any one of embodiments 1) to 51), or
15 pharmaceutically acceptable salts thereof. In other cases, the antigen-containing composition is administrated last. The different compositions may be administrated simultaneously, closely in sequence, or separated in time. Those methods and compositions are provided for therapeutic and prophylactic immunisation (i.e., the deliberate provocation, enhancement, intensification or modulation of an adaptative and/or
20 innate immune response). Particular advantages may include one or more of the following:

- 1) An accelerated immune response following administration of at least one compound of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, and the antigen, as compared to sole administration of the antigen;
- 25 2) A greater sensitivity to small amounts of antigen (e.g., toxin or pathogen) or antigens that do not habitually induce strong immune responses; and
- 3) More effective anti-tumor therapies.

Further, the compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of
30 cystic fibrosis, pulmonary fibrosis, pulmonary hypertension, wound healing, diabetic nephropathy, reduction of inflammation in transplanted tissue, inflammatory diseases caused by pathogenic organisms.

Especially, compounds of formula (I) according to any one of embodiments 1) to 51), or pharmaceutically acceptable salts thereof, are suitable for the prevention or treatment of diseases selected from one, several or all of the following groups of diseases and disorders:

- 5 1) Inflammatory diseases, obstructive airway diseases and allergic conditions such as acute lung injury (ALI); adult/acute respiratory distress syndrome (ARDS); chronic obstructive pulmonary, airway or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith; and asthma of whatever type or genesis, including intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma,
10 moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and induced asthma following bacterial infection (and especially acute lung injury (ALI); adult/acute respiratory distress syndrome (ARDS); and asthma of whatever type or genesis, including intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-
15 induced asthma, occupational asthma and induced asthma following bacterial infection);
- 2) Inflammatory diseases such as neutrophil related disorders, especially neutrophil related disorders of the airway including hyper-neutrophilia as it affects the airway and/or lungs; periodontitis; glomerulonephritis; cystic fibrosis; and skin diseases such as psoriasis, contact dermatitis, atopic dermatitis, dermatitis herpetiformis, scleroderma,
20 hypersensitivity angitis, urticaria, lupus erythematosus, and epidermolysis;
- 3) Diseases having an inflammatory component such as diseases and conditions affecting the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis; inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or aetiology; and autoimmune inflammatory bowel disease (e.g.
25 ulcerative colitis and Crohn's disease);
- 4) HIV-mediated retroviral infections such as diseases and disorders caused by HIV-1 and HIV-2 strains such as GUN-4v, GUN-7wt, AG204, AG206, AG208, HCM305, HCM308, HCM342, mSTD104, and HCM309;
- 5) Neuroinflammation which refers to cell signalling molecule production, activation of glia
30 or glial activation pathways and responses, proinflammatory cytokines or chemokines, activation of astrocytes or astrocyte activation pathways and responses, activation of

microglia or microglial activation pathways and responses, oxidative stress-related responses such as amyloid β deposition of amyloid plaques;

6) Neurological disorders such as stroke, cerebral ischemia, Alzheimer's disease, and Parkinson's disease;

5 7) Prion-mediated diseases, also known as transmissible spongiform encephalopathies (TSEs), such as kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI) and Creutzfeldt- Jakob Disease (CJD);

8) Amyloid-mediated disorders;

9) Cystic fibrosis, wound healing and inflammatory diseases caused by pathogenic
10 organisms.

The invention also relates to the use of a compound of formula (I) according to any one of embodiments 1) to 51) for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of the above-mentioned diseases.

The present invention also relates to pharmaceutically acceptable salts and to
15 pharmaceutical compositions and formulations of compounds of formula (I) according to any one of embodiments 1) to 51).

A pharmaceutical composition according to the present invention contains at least one compound of formula (I) according to any one of embodiments 1) to 51) (or a pharmaceutically acceptable salt thereof) as the active agent and optionally carriers
20 and/or diluents and/or adjuvants.

The compounds of formula (I) according to any one of embodiments 1) to 51) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

The production of the pharmaceutical compositions can be effected in a manner which will
25 be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with
30 suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a

disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I) according to any one of embodiments 1) to 51), or a pharmaceutically acceptable salt thereof.

Any reference to a compound of formula I, I_P, I_{ST1} or I_{ST2} in this text is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient. The preferences indicated for the compounds of formula I of course apply *mutatis mutandis* to the compounds of formula I_P, to the compounds of formula I_{ST1} and the compounds of formula I_{ST2} as well as to the salts and pharmaceutically acceptable salts of the compounds of formula I, of formula I_P, of formula I_{ST1} or of formula I_{ST2}. The same applies to these compounds as medicaments, to pharmaceutical compositions containing these compounds as active principles or to the uses of these compounds for the manufacture of a medicament for the treatment of the diseases according to this invention.

Unless used regarding temperatures, the term "about" (or alternatively "around") placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" (or alternatively "around") placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C. Besides, the term "room temperature" (rt) as used herein refers to a temperature of about 25°C.

The compounds of Formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

If not indicated otherwise, the generic groups **R¹**, **R²**, **R³**, **R⁴**, **R⁵**, **R⁶**, **R⁷**, **R⁸**, **R⁹**, **W**, **Y** and **Z** are as defined for formula (I). Other abbreviations used are defined in the experimental section.

Reactions of alcohols with methanesulfonyl chloride may result in the formation of the respective chloride or the respective mesylate derivative depending on the reaction conditions used; it is well known in the art that already small changes in such reaction conditions may have an influence on the outcome of said reactions; it should be

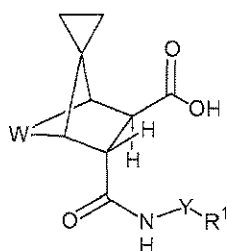
understood that normally both reagents, the chloride and the mesylate, might be useful as electrophiles in reactions discussed below.

In some instances the generic groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , W , Y and Z might be incompatible with the assembly illustrated in the schemes below and will therefore require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups are as necessary in place.

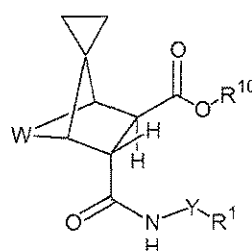
10 A. Synthesis of final products

Sections A.a) to A.g) hereafter describe general methods for preparing compounds of formula (I).

A.a) The compounds of formula (I) wherein Z represents $-C(O)NR^3$ can be prepared from carboxylic acids of structure 1 by reaction with an appropriate amine R^2R^3NH using standard amide coupling conditions such as EDC / HOBt / DMAP, or DCC / HOAt, or PyBOP, or HATU / DMAP in the presence of a base such as DIPEA at a temperature about rt in a suitable solvent such as CH_2Cl_2 . Alternatively, the compounds of formula (I) can be prepared by coupling carboxylic acids of structure 1 with an appropriate amine R^2R^3NH using $POCl_3$ in a suitable solvent such as DCE/pyridine (1:1). Alternatively, the compounds of formula (I) can be prepared by coupling carboxylic acids of structure 1 via formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene). Alternatively, the compounds of formula (I) can be prepared from esters of structure 2 wherein R^{10} represents (C_1-C_2) alkyl with an appropriate amine R^2R^3NH using $AlMe_3$ in a suitable solvent such as CH_2Cl_2 .

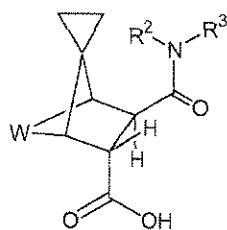


Structure 1



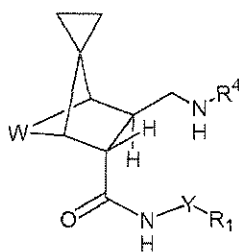
Structure 2

- A.b) Alternatively, the compounds of formula (I) wherein **Z** represents $-\text{C}(\text{O})\text{NR}^3-$ may be prepared from carboxylic acids of structure 3 with an appropriate amine $\text{R}^1-\text{Y}-\text{NH}_2$ using standard amide coupling conditions such as EDC / HOBt / DMAP or DCC / HOAt in the presence of a base such as DIPEA at a temperature about rt in a suitable solvent such as CH_2Cl_2 . Alternatively, the compounds of formula (I) can be prepared by coupling carboxylic acids of structure 3 with an appropriate amine $\text{R}^1-\text{Y}-\text{NH}_2$ using POCl_3 in a suitable solvent such as DCE/pyridine (1:1).



Structure 3

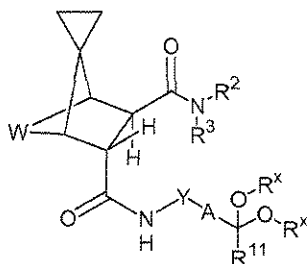
- A.c) Alternatively, the compounds of formula (I) wherein **Z** represents $-\text{CH}_2-\text{NR}^4\text{C}(\text{O})-$ can be prepared from amines of structure 4 with an appropriate carboxylic acid R^2COOH using standard amide coupling conditions such as EDC / HOBt / DMAP or DCC / HOAt in the presence of a base such as DIPEA at a temperature about rt in a suitable solvent such as CH_2Cl_2 .



Structure 4

- A.d) Alternatively, the compounds of formula (I) wherein **R**¹ represents or contains a (C_1-C_2) alkyl-carbonyl group may be prepared by deprotection of a ketal of structure 5, wherein **A** represents a bond (in case **Y** represents a (C_1-C_4) alkandiyl group) or an aryl- or a heteroaryl-group, using an acid such as diluted aqueous HCl in a solvent such as THF at a temperature about rt.

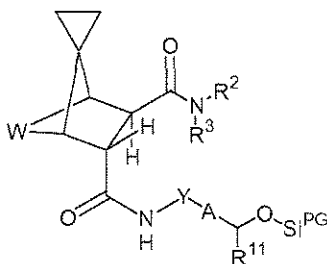
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Structure 5

R^{11} represents (C₁-C₂)alkyl and R^x represents (C₁-C₂)alkyl or both R^x together form an ethane-1,2-diyl bridge

- 5 A.e) Alternatively, the compounds of formula (I) wherein R^1 represents or contains a (C₁-C₂)alkyl-carbonyl group may be prepared by deprotection of a silyl-protected alcohol of structure 6, wherein **A** represents a bond (in case **Y** represents a (C₁-C₄)alkandiyl group) or an aryl- or a heteroaryl-group, using for example TBAF in a suitable solvent such as THF, followed by oxidation using for example MnO₂ in a suitable solvent such as AcCN.



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Structure 6

R^{11} represents (C₁-C₂)alkyl and Si^{PG} represents an appropriate silyl protecting group such as TMS, TIPS, TBDMS or TBDPS (preferably TBDMS)

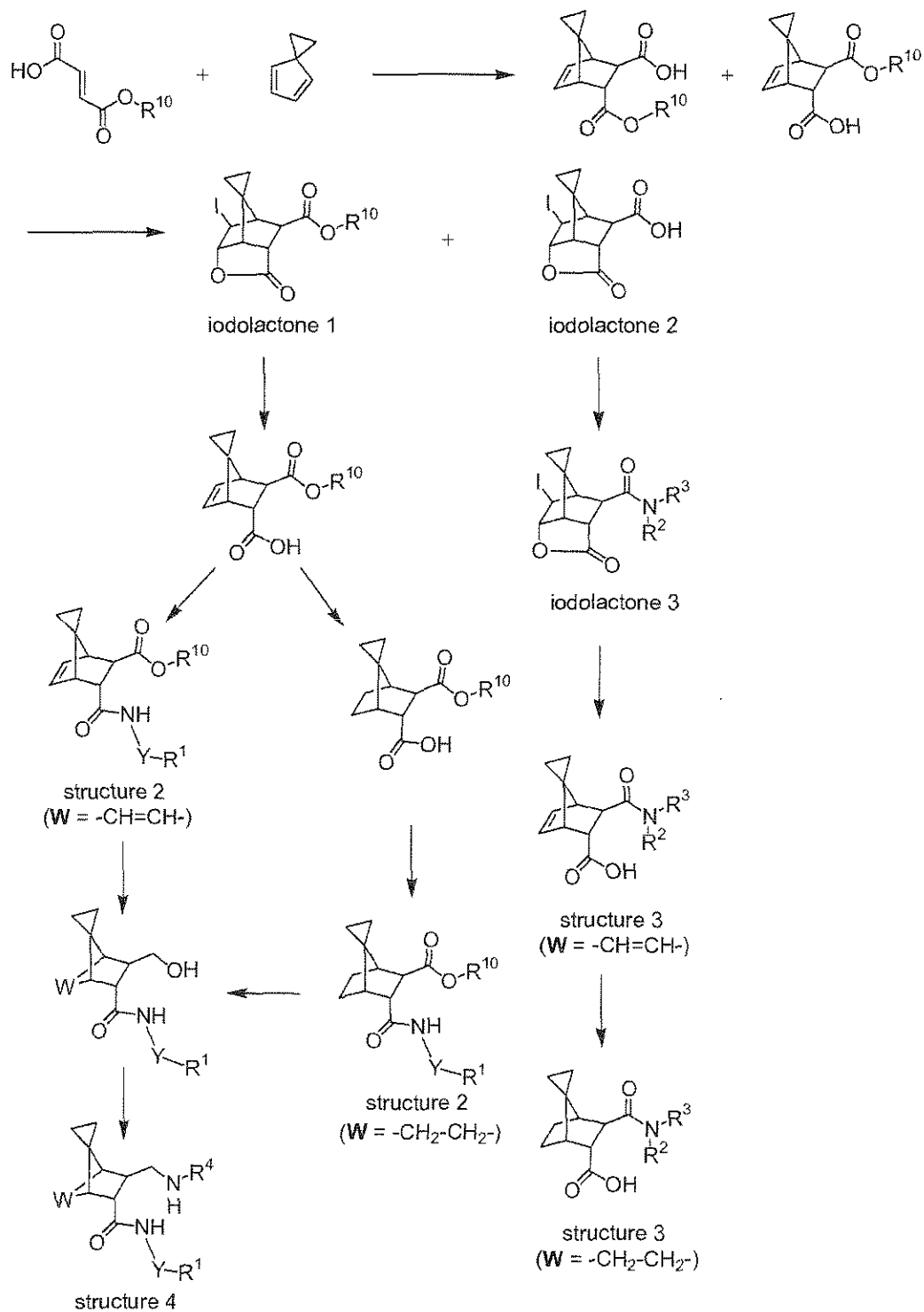
- 15 A.f) Alternatively, the compounds of formula (I) wherein R^2 contains a primary or secondary amino group may be prepared by deprotection of the corresponding protected amine such as *N-tert*-butoxycarbonyl protected amine using an acid such as HCl in a solvent mixture such as dioxane and CH₂Cl₂ at a temperature about rt.

- 20 A.g) Alternatively, the compounds of formula (I) wherein R^2 contains an amide group (-C(O)NR⁷R⁸) may be prepared by saponification of the corresponding ester followed by activation of the resulting carboxylic acid *via* a mixed anhydride for example using ethyl chloroformate and a base such as Et₃N in a suitable solvent such as THF at a

temperature ranging from 0 °C to rt, and subsequent reaction with an appropriate amine R^7R^6NH .

B. Synthesis of intermediates

B1. Synthesis of spiro compounds



Scheme 1

R¹⁰ represents (C₁-C₂)alkyl

Compounds of structure 1 can be obtained by saponification of the ester moiety of compounds of structure 2 using a base such as LiOH or NaOH in a solvent such as a mixture of water and an organic solvent such as THF or EtOH.

Compounds of structure 2 wherein **W** represents -CH=CH- can be prepared by the following sequence (see scheme 1): a) Diels-Alder reaction between spiro[2.4]hepta-4,6-diene (prepared according to J. W. Coe et al. *Org. Letters* **2004**, 6, 1589) and commercially available (*E*)-but-2-enedioic acid monoethyl ester in a suitable solvent such as MeOH to obtain a mixture of *endo* and *exo* products; b) iodolactonization using KI and I₂ in the presence of a base such as NaHCO₃ in a solvent such as CH₂Cl₂ at a temperature about rt to enable separation of the isomers (iodolactone 1 (ester) and iodolactone 2 (carboxylic acid)); c) retro-iodolactonization of the resulting iodolactone 1 using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C; and d) amide coupling of the resulting carboxylic acid with an appropriate amine R¹-Y-NH₂ via formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or CH₂Cl₂) in the presence of a base such as DIPEA, Et₃N or pyridine and in a suitable solvent such as CH₂Cl₂, THF or acetone or via activation of the carboxylic acid using standard amide coupling conditions such as EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂. It is to be understood that, in case the substituent **R**¹ represents or contains a (C₁-C₂)alkylcarbonyl group, the respective keto-function may be protected in the amines used in step d) as a ketal or as a silylated alcohol; the obtained intermediates may then be transferred to compounds of structure 5 or 6 respectively (see below).

Compounds of structure 2 wherein **W** represents -CH₂-CH₂- can be prepared by the following sequence (see scheme 1): a) Diels-Alder reaction between spiro[2.4]hepta-4,6-diene and commercially available (*E*)-but-2-enedioic acid monoethyl ester in a suitable solvent such as MeOH to obtain a mixture of *endo* and *exo* products; b) iodolactonization using KI and I₂ in the presence of a base such as NaHCO₃ in a solvent such as CH₂Cl₂ at a temperature about rt to enable separation of the isomers (iodolactone 1 (ester) and iodolactone 2 (carboxylic acid)); c) retro-iodolactonization of the resulting iodolactone 1 using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C; d) reduction of the double bond using cyclohexene in the presence of Pd/C in a suitable solvent such as THF; and e) amide coupling of the resulting carboxylic acid with an appropriate amine R¹-Y-NH₂ via formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or

CH₂Cl₂) in the presence of a base such as DIPEA, Et₃N or pyridine and in a suitable solvent such as CH₂Cl₂, THF or acetone or *via* activation of the carboxylic acid using standard amide coupling conditions such as EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂. In case the substituent **R**¹ represents or contains a (C₁-C₂)alkylcarbonyl group, the respective keto-function may be protected as described above (compounds of structure 2 wherein **W** represents -CH=CH-).

Compounds of structure 3 wherein **W** represents -CH=CH- can be prepared by the following sequence (see scheme 1): a) amide coupling of iodolactone 2 with an appropriate amine R²R³NH, wherein **R**², if containing a primary or secondary amine function, might require protection for example as a *N*-*tert*-butoxycarbonyl protected amine, *via* formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene) in the presence of a base such as DIPEA and in a suitable solvent such as CH₂Cl₂ or *via* activation of the carboxylic acid using standard amide coupling conditions such as EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂; and b) retro-iodolactonization of the resulting iodolactone 3 using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C.

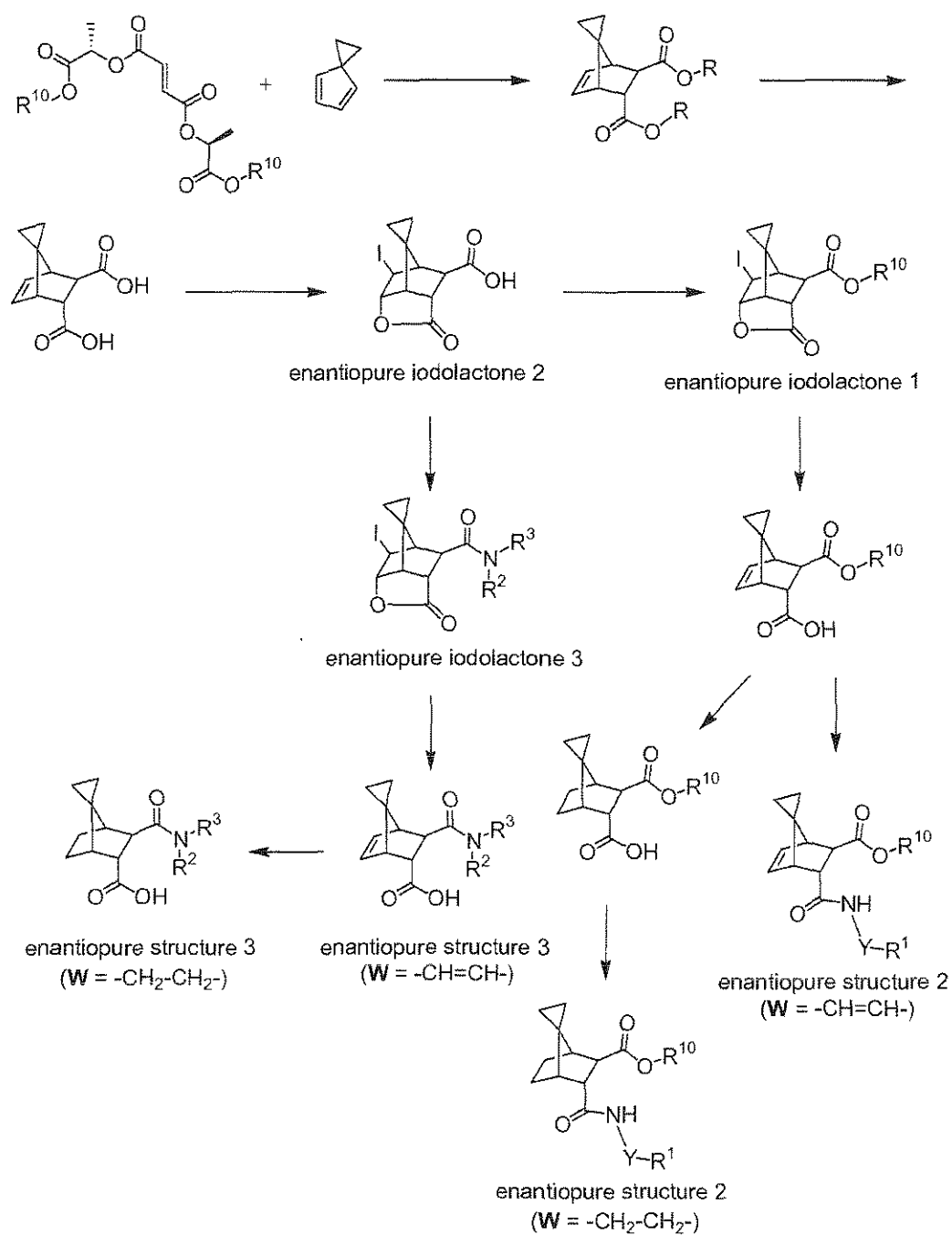
Compounds of structure 3 wherein **W** represents -CH₂-CH₂- can be prepared by reduction of the double bond of compounds of structure 3 wherein **W** represents -CH=CH- using for example hydrogen in the presence of Pd/C in a suitable solvent such as EtOH or cyclohexene in the presence of Pd/C in a suitable solvent such as THF (see scheme 1).

Compounds of structure 4 can be prepared by reduction of the ester of compounds of structure 2 using a reducing agent such as LiBH₄ in a suitable solvent such as THF at a temperature about 65 °C followed by formation of the corresponding sulfonate (e.g. triflate) by reaction of the alcohol with a sulfonyl chloride or anhydride derivative (e.g. trifluoromethane sulfonic anhydride) in a suitable solvent such as CH₂Cl₂ in the presence of a base such as DIPEA at a temperature ranging from -78 °C to 0 °C and subsequent reaction with R⁴NH₂ in a suitable solvent such as CH₂Cl₂ at a temperature ranging from -78 °C to rt. Alternatively the intermediate sulfonate can be converted into the corresponding azide using sodium azide in a suitable solvent such as DMF at a temperature about 80 °C and subsequent reduction of the azide to the amine using Ph₃P in a suitable solvent such as THF/H₂O.

Compounds of structures 5 and 6 can be prepared from carboxylic esters of structure 2 wherein R^1 represents or contains a masked (C_1-C_2)alkyl-carbonyl group (for example a silylated alcohol or an acetal protected ketone) by saponification of the ester moiety using
5 a base such as LiOH or NaOH in a solvent such as a mixture of water and an organic solvent such as THF or EtOH, followed by reaction of the obtained carboxylic acid with an appropriate amine R^2R^3NH using standard amide coupling conditions such as EDC / HOBt / DMAP or DCC / HOAt in the presence of a base such as DIPEA at a temperature about rt in a suitable solvent such as CH_2Cl_2 . Alternatively, compounds of structures 5 and
10 6 can be prepared from esters of structure 2 wherein R^1 represents or contains a masked (C_1-C_2)alkyl-carbonyl group with an appropriate amine R^2R^3NH using $AlMe_3$ in a suitable solvent such as CH_2Cl_2 . Compounds of structure 2 wherein R^1 represents or contains a masked (C_1-C_2)alkyl-carbonyl group can be prepared according to scheme 1 using an appropriate amine R^1-Y-NH_2 , wherein R^1 represents or contains a masked (C_1-C_2)alkyl-
15 carbonyl group (see above).

Alternatively, compounds of structures 5 and 6 can be prepared from compounds of structure 3 by reaction with an appropriate amine R^1-Y-NH_2 wherein R^1 represents or contains a masked (C_1-C_2)alkyl-carbonyl group as defined above using standard amide coupling conditions such as EDC / HOBt / DMAP or DCC / HOAt in the presence of a
20 base such as DIPEA at a temperature about rt in a suitable solvent such as CH_2Cl_2 .

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Scheme 2

R^{10} represents (C_1-C_2) alkyl and R represents (S) -CH(Me)COOR¹⁰

Enantiopure compounds of structure 1 can be obtained by saponification of the ester moiety of enantiopure compounds of structure 2 using a base such as LiOH or NaOH in a solvent such as a mixture of water and an organic solvent such as THF or EtOH.

Enantiopure compounds of structure 2 wherein **W** represents -CH=CH- can be prepared
5 by the following sequence (see scheme 2): a) Diels-Alder reaction between spiro[2.4]hepta-4,6-diene and commercially available (*E*)-1,2-bis-(((1*S*)-1-ethoxycarbonyl-ethoxy)-carbonyl)-ethene in a suitable solvent such as hexane; the assignment of the stereogenic centers of the obtained intermediates was made based on a literature reference (G. Helmchen et al., *Angew. Chem. Int. Ed.* **1987**, 26, 1143), describing the
10 Diels-Alder reaction between cyclopentadiene and (*E*)-1,2-bis-(((1*S*)-1-ethoxycarbonyl-ethoxy)-carbonyl)-ethene; b) saponification of the ester moieties using a base such as LiOH in a suitable solvent such as a mixture of THF and water; c) iodolactonization using KI and I₂ in the presence of a base such as NaHCO₃ in a solvent such as CH₂Cl₂ at a temperature about rt to give enantiopure iodolactone 2; d) esterification of the resulting
15 carboxylic acid using standard conditions such as TMSCH₂N₂ in a suitable solvent such as MeOH or *via* formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or CH₂Cl₂) and subsequent reaction with MeOH; e) retro-iodolactonization of the resulting iodolactone ester using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C;
20 and f) amide coupling of the resulting carboxylic acid with an appropriate amine R¹-Y-NH₂ *via* formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or CH₂Cl₂) in the presence of a base such as DIPEA, Et₃N or pyridine and in a suitable solvent such as CH₂Cl₂, THF or acetone or *via* activation of the carboxylic acid using standard amide coupling conditions such as
25 EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂. It is to be understood that, in case the substituent R¹ represents or contains a (C₁-C₂)alkylcarbonyl group, the respective keto-function may be protected in the amines used in step f) as a ketal or as a silylated alcohol.

Enantiopure compounds of structure 2 wherein **W** represents -CH₂-CH₂- can be prepared
30 by the following sequence (see scheme 2): a) esterification of enantiopure iodolactone 2 using standard conditions such as TMSCH₂N₂ in a suitable solvent such as MeOH or *via* formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or CH₂Cl₂) and subsequent reaction with MeOH to give enantiopure iodolactone 1; b) retro-iodolactonization of the resulting

iodolactone ester using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C; c) reduction of the double bond using cyclohexene in the presence of Pd/C in a suitable solvent such as THF; and d) amide coupling of the resulting carboxylic acid with an appropriate amine R^1 -Y-NH₂ via formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene or CH₂Cl₂) in the presence of a base such as DIPEA, Et₃N or pyridine and in a suitable solvent such as CH₂Cl₂, THF or acetone or via activation of the carboxylic acid using standard amide coupling conditions such as EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂. It is to be understood that, in case the substituent R^1 represents or contains a (C₁-C₂)alkylcarbonyl group, the respective keto-function may be protected in the amines used in step d) as a ketal or as a silylated alcohol.

Enantiopure compounds of structure 3 wherein **W** represents -CH=CH- can be prepared by the following sequence (see scheme 2): a) amide coupling of enantiopure iodolactone 2 with an appropriate amine R^2R^3 NH, wherein R^2 , if containing a primary or secondary amine function, might require protection for example as a *N-tert*-butoxycarbonyl protected amine, via formation of the acyl chloride (using standard conditions such as oxalyl chloride and a catalytic amount of DMF in a solvent such as toluene) in the presence of a base such as DIPEA and in a suitable solvent such as CH₂Cl₂ or via activation of the carboxylic acid using standard amide coupling conditions such as EDC / HOBt / DMAP in the presence of a base such as DIPEA in a suitable solvent such as CH₂Cl₂; and b) retro-iodolactonization of the resulting enantiopure iodolactone 3 using an excess of zinc in a solvent such as AcOH at a temperature about 65 °C.

Enantiopure compounds of structure 3 wherein **W** represents -CH₂-CH₂- can be prepared by reduction of the double bond of enantiopure compounds of structure 3 wherein **W** represents -CH=CH- with, for instance, hydrogen in the presence of Pd/C in a suitable solvent such as EtOH or cyclohexene in the presence of Pd/C in a suitable solvent such as THF (see scheme 2).

Enantiopure compounds of structure 4 wherein **W** represents -CH=CH- or -CH₂-CH₂- can be prepared from enantiopure compounds of structure 2 by analogy to the synthesis described in scheme 1.

Enantiopure compounds of structures 5 and 6 wherein **W** represents -CH=CH- or -CH₂-CH₂- can be prepared by analogy to scheme 1.

In a general way, enantiopure compounds of structure 1 can be obtained either in analogy to the synthesis of racemic compounds of structure 1 starting from enantiopure iodolactone 1 or 2 or by chiral HPLC purification of a mixture of enantiomers.

5 B2. Synthesis of amines $R^1\text{-Y-NH}_2$

Amines of formula $R^1\text{-Y-NH}_2$, if not commercially available, may be prepared for instance by the following sequence: a) conversion of alcohol $R^1\text{-Y-OH}$ into the corresponding mesylate or chloride using for example MsCl in the presence of a base such as Et_3N and DMAP in a suitable solvent such as CH_2Cl_2 ; b) conversion of the mesylate or chloride into
10 the corresponding azide using for example NaN_3 in a solvent such as DMF at a temperature about 80°C ; c) reduction of the azide moiety either using Ph_3P and water in a solvent such as THF at a temperature about 60°C , or by hydrogenation using a metal catalyst such as Pd/C in a suitable solvent such as MeOH. The paragraphs below describe the synthesis of some of these amines.

- 15 1-(5-Aminomethyl-furan-2-yl)-ethanone may be prepared using the following sequence: a) protection of commercially available 5-hydroxymethyl-2-furaldehyde using 3,4-dihydro-2H-pyran in the presence of pyridinium toluene-4-sulfonate in a solvent such as CH_2Cl_2 ; b) methylation of the aldehyde using for example methylmagnesium chloride in a solvent such as THF at a temperature about 0°C ; c) oxidation of the resulting secondary alcohol
20 using an oxidizing agent such as MnO_2 in a solvent such as CH_2Cl_2 at a temperature about 45°C ; d) removal of the protecting group using an acid such as Amberlyst 15 in a suitable solvent such as MeOH at a temperature about 35°C ; e) chlorination of the alcohol using for example Ms-Cl in the presence of a base such as Et_3N and DMAP in a solvent such as CH_2Cl_2 at a temperature ranging from 0°C to rt; f) formation of the
25 corresponding azide using NaN_3 in a solvent such as DMF at a temperature about 80°C ; and g) reduction of the azide moiety using Ph_3P and water in a solvent such as THF at a temperature about 60°C .

- 30 3-(2-Methyl-[1,3]dioxolan-2-yl)-propylamine may be prepared using the following sequence: a) condensation of commercially available methyl vinyl ketone and nitromethane in the presence of a catalyst such as activated $\text{KF/Al}_2\text{O}_3$; b) protection of the resulting ketone with ethylene glycol and a catalyst such as *p*-TsOH in a solvent such as

toluene at a temperature about 120 °C; and c) reduction of the nitro group using a metal catalyst such as Pd/C in a solvent such as MeOH under an H₂ atmosphere.

4-(2-Methyl-[1,3]dioxolan-2-yl)-butylamine may be prepared using the following sequence: a) condensation of commercially available ethyl acetoacetate and acrylonitrile in the presence of a base such as sodium ethylate; b) decarboxylation using a base such as Na₂CO₃ in a solvent such as water at a temperature about 100 °C; c) protection of the resulting ketone with ethylene glycol and a catalyst such as *p*-TsOH in a solvent such as toluene at a temperature about 120 °C; and d) reduction of the nitrile using a reducing agent such as LiAlH₄ in a solvent such as Et₂O at a temperature about 35 °C.

10 [4-(2-Methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methylamine may be prepared using the following sequence: a) reaction of commercially available 2,4-dibromo-thiazole with an organolithium reagent such as *n*-butyl lithium in a solvent such as ether at a temperature about -78 °C and subsequent formylation with *N,N*-dimethylformamide at a temperature ranging from -78 °C to rt; b) reduction with a reducing agent such as NaBH₄ in a solvent
15 such as MeOH at a temperature about rt; c) protection of the alcohol with a protecting group such as *tert*-butyldimethylsilyl chloride in the presence of a base such as imidazole in a solvent such as dichloromethane; d) reaction of the protected alcohol with an organolithium reagent such as *n*-butyl lithium in a solvent such as ether at a temperature about -78 °C and subsequent acetylation with *N,N*-dimethylacetamide at a temperature
20 ranging from -78 °C to rt; e) ketal formation in the presence of trimethylorthoformate and a catalyst such as LiBF₄ in a solvent such as ethylene glycol at a temperature about 95 °C; f) deprotection of the silyl protecting group under standard conditions such as TBAF in a solvent such as THF at a temperature about rt or 0 °C; g) mesylation using a reagent such as methanesulfonyl chloride in a solvent such as CH₂Cl₂ in the presence of a base such
25 as Et₃N and DMAP at a temperature about 0 °C; h) formation of the corresponding azide using NaN₃ in a solvent such as DMF at a temperature about 80 °C; and i) reduction of the azide moiety using Ph₃P and water in a solvent such as THF at a temperature about 60 °C.

30 [5-(2-Methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-methylamine may be prepared using the following sequence: a) lithiation of commercially available 2-methyl-2-thiophen-2-yl-[1,3]dioxolane with an organolithium reagent such as *n*-butyl lithium in the presence of *N,N,N',N'*-tetramethyl-ethylenediamine in a solvent such as THF at a temperature about -78 °C and subsequent addition of DMF; b) reduction with a reducing agent such as NaBH₄

in a solvent such as MeOH at a temperature about 0 °C; c) chlorination of the alcohol using for example Ms-Cl in presence of a base such as Et₃N and DMAP in a solvent such as CH₂Cl₂ at a temperature about 0 °C; d) formation of the corresponding azide using NaN₃ in a solvent such as DMF at a temperature about 80 °C; and e) reduction of the azide moiety using Ph₃P and water in a solvent such as THF at a temperature about 60 °C.

2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methylamine may be prepared using the following sequence: a) reaction of commercially available 1,3-oxazole with an organomagnesium reagent such as *iso*-propylmagnesium chloride in a solvent such as THF at a temperature about -10 °C and subsequent acetylation with *N*-methoxy-*N*-methyl-acetamide at a temperature ranging from -10 °C to rt; b) reduction of the ketone with a reducing agent such as NaBH₄ in a solvent such as MeOH at a temperature ranging from 0 °C to rt; c) protection of the alcohol with a protecting group such as *tert*-butyldimethylsilyl chloride in the presence of a base such as imidazole in a solvent such as THF; d) reaction of the protected alcohol with an organolithium reagent such as *tert*-butyllithium in a solvent such as THF at a temperature ranging from -78 °C to -40 °C and subsequent formylation with *N,N*-dimethylformamide at a temperature ranging from -78 °C to rt; e) reduction of the aldehyde with a reducing agent such as NaBH₄ in a solvent such as MeOH at a temperature ranging from 0 °C to rt; f) chlorination using a reagent such as methanesulfonyl chloride in a solvent such as CH₂Cl₂ in the presence of a base such as Et₃N and DMAP at a temperature about 0 °C; g) formation of the corresponding azide using NaN₃ in a solvent such as DMF at a temperature about 80 °C; and h) reduction of the azide moiety using Ph₃P and water in a solvent such as THF at a temperature about 60 °C.

4-Bromo-2,3-difluorobenzylamine can be prepared using the following sequence: a) reaction of commercially available 1,2-difluorobenzene and trimethylsilyl chloride in the presence of a base such as lithium diisopropylamide in a suitable solvent such as THF at a temperature about -78 °C; b) conversion of the resulting (2,3-difluoro-1,4-phenylene)-bis(trimethylsilane) to the corresponding 1,4-dibromo-2,3-difluorobenzene using a source of bromine such as bromine at a temperature ranging from 0 °C to 58 °C; c) reaction with an organolithium reagent such as *n*-butyllithium in a solvent such as THF at a temperature ranging about -78 °C and subsequent carboxylation with solid carbon dioxide for example at a temperature ranging from -78 °C to rt; d) reduction of the resulting carboxylic acid to the corresponding benzyl alcohol using a suitable reducing agent such as borane in a

suitable solvent such as THF at a temperature ranging from 0 °C to 50 °C; e) mesylation using a reagent such as methanesulfonyl chloride in a solvent such as CH₂Cl₂ in the presence of a base such as Et₃N and DMAP at a temperature about 0 °C; f) formation of the corresponding azide using NaN₃ in a solvent such as DMF at a temperature about 80 °C; and g) reduction of the azide moiety using Ph₃P and water in a solvent such as THF at a temperature about 60 °C.

B3. Synthesis of amines R²-NH₂

Amines of formula R²-NH₂, if not commercially available, may be prepared for instance by the following sequence: a) conversion of alcohol R²-OH into the corresponding mesylate or chloride using for example MsCl in the presence of a base such as Et₃N and DMAP in a suitable solvent such as CH₂Cl₂ or conversion of alcohol R²-OH into the corresponding iodide using for example iodine and Ph₃P in the presence of a base such as imidazole in a suitable solvent such as CH₂Cl₂; b) conversion of the mesylate, chloride or iodide into the corresponding azide using for example NaN₃ in a solvent such as DMF at a temperature about 80 °C; c) reduction of the azide moiety either using Ph₃P and water in a solvent such as THF at a temperature about 60 °C, or by hydrogenation using a metal catalyst such as Pd/C in a suitable solvent such as MeOH.

Alternatively, if not commercially available, amines of formula R²-NH₂, which are also amines of formula R^{2a}CH₂-NH₂, may be prepared by reduction of nitriles R^{2a}-CN either using a reducing agent such as LiAlH₄ in a suitable solvent such as THF at a temperature ranging from 0 °C to rt, or by hydrogenation using a metal catalyst such as Pd/C in a suitable solvent such as MeOH.

Whenever the compounds of formula (I) are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Regis Whelk-O1(R,R) (10 μm) column, a Daicel ChiralCel OD-H (5-10 μm) column, or a Daicel ChiralPak IA (10 μm) or AD-H (5-10 μm) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH, in presence or absence of an amine such as Et₃N or diethylamine) and eluent B (hexane), at a flow rate of 0.8 to 150 mL/min.

For instance, enantiopure compounds of structure 2 may be obtained by chiral HPLC separation of a mixture of enantiomers; for example, (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-ethoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide may be obtained by chiral HPLC separation of (5*R*^{*})-*N*⁵-(4-bromo-phenyl)-(6*R*^{*})-6-ethoxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide. Preferably such separations are performed using a Daicel ChiralPak AD-H column with a mixture of EtOH and hexane (15/85) as eluent.

Experimental Part

10 **Abbreviations** (as used herein and in the description above)

	Ac	acetyl
	AcCN	acetonitrile
	AcOH	acetic acid
	AlMe ₃	trimethyl aluminium
15	aq.	aqueous
	atm	atmosphere
	Boc	<i>tert</i> -butoxycarbonyl
	bp	boiling point
	(<i>n</i> -)Bu	butyl
20	BuLi	<i>n</i> -butyllithium
	<i>ca.</i>	About
	Cbz	benzyloxycarbonyl
	COAD	chronic obstructive airway disease
	COLD	chronic obstructive lung disease
25	COPD	chronic obstructive pulmonary disease
	DAD	diode array detector
	DC	dendritic cells
	DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
	PL-DCC	polymer supported <i>N,N'</i> -dicyclohexylcarbodiimide
30	DCE	1,2-dichloroethane
	DIPEA	diisopropylethylamine
	DMAP	4- <i>N,N</i> -dimethylaminopyridine
	DMEM	dulbecco's modified eagle's medium

	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	EA	ethyl acetate
	EC ₅₀	half maximal effective concentration
5	EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethyl-carbodiimide
	ELSD	evaporative light-scattering detection
	eq.	equivalent(s)
	ES+	electro-spray, positive ionization
	Et	ethyl
10	Ether or Et ₂ O	diethylether
	Et ₃ N	triethylamine
	EtOH	ethanol
	FA	formic acid
	FAD	familial autosomic dominant
15	FC	flash column chromatography on silica gel
	FLIPR	fluorescence imaging plate reader
	FPRL1	formyl-peptide receptor like-1
	FPRL2	formyl-peptide receptor like-2
	h	hour(s)
20	HATU	2-(7-aza-1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	HBSS	hanks' balanced salt solution
	HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	hept	heptane
25	HIV	human immunodeficiency virus
	HOBt	hydroxybenzotriazole
	HOAt	7-aza-1-hydroxybenzotriazole
	HPLC	high performance liquid chromatography
	LC-MS	liquid chromatography – mass spectrometry
30	lem	emission wavelength
	lex	excitation wavelength
	LPS	lipopolysaccharide
	Me	methyl
	MeOH	methanol
35	min	minute(s)

	mM	millimolar
	μ M	micromolar
	mRNA	messenger ribonucleic acid
	MPLC	medium pressure liquid chromatography
5	MS	mass spectrometry
	Ms	methanesulfonyl
	nm	nanometer
	nM	nanomolar
	NMR	nuclear magnetic resonance
10	OAc	acetate
	org.	organic
	<i>p</i>	<i>para</i>
	<i>p</i> -TsOH	<i>para</i> -toluene sulfonic acid
	PG	protecting group
15	PyBOP	benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium-hexafluoro-phosphate
	rf	retention factor
	rpm	rotation per minute
	rt	room temperature
20	sat.	saturated
	SCX	strong cation exchanger
	TBA	<i>tetra-n</i> -butylammonium
	TBAF	<i>tetra-n</i> -butylammonium fluoride
	TBME	<i>tert</i> -butyl methyl ester
25	TBDMS	<i>tert</i> -butyl-dimethyl-silyl
	TBDPS	<i>tert</i> -butyl-diphenyl-silyl
	<i>t</i> -Bu	<i>tert</i> -butyl
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
30	TIPS	tri-isopropyl-silyl
	TLC	thin layer chromatography
	TMS	trimethyl-silyl
	t_R	retention time
	UV	ultra violet
35	Vis	visible

I Chemistry

General. All temperatures are stated in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at rt.

As SCX material SiliaBond® SCX from Silicycle was used.

- 5 As polymer supported DCC, PL-DCC from Polymer Laboratories was used.

As polymer supported SO₂Cl, PL-SO₂Cl from Polymer Laboratories was used.

- Analytical thin layer chromatography (TLC) was performed with 0.2 mm plates: Merck, Silica gel 60 F₂₅₄. Preparative thin layer chromatography (TLC) was performed with 0.2 or 0.5 mm plates: Merck, Silica gel 60 F₂₅₄. Detection was done with UV or with a solution of
10 KMnO₄ (3 g), K₂CO₃ (20 g), NaOH 5% (3 mL) and H₂O (300 mL) with subsequent heating.

Flash column chromatography (FC) and filtration were performed using *silica gel 60 Merck* (0.063-0.200mm) or *Macherey-Nagel silica gel* (0.063-0.200mm): elution with EA, Et₂O, hept, hexane, CH₂Cl₂, CHCl₃, MeOH, NH₄OH or mixtures thereof.

- MPLC were performed using isolute® SPE Flash SI II columns from international sorbent
15 technology, elution with EA, Et₂O, hept, hexane, CH₂Cl₂, CHCl₃, MeOH, NH₄OH or mixtures thereof.

- LC-MS-conditions 01 (if not indicated otherwise): Analytical: Thermo Finnigan MSQ Surveyor MS with Agilent 1100 Binary Pump and DAD. Column: Zorbax SB-AQ 5 µm, 4.6x50 mm ID from Agilent Technologies. Eluents: A: H₂O + 0.04% TFA; B: AcCN; Gradient: 5% B → 95% B over 1 min. Flow: 4.50 mL/min. Detection: UV/Vis and/or ELSD,
20 and MS, t_R is given in min.

- LC-MS-conditions 01b (if not indicated otherwise): Analytical: Thermo Finnigan MSQ Surveyor MS with Agilent 1100 Binary Pump and DAD. Column: Xbridge C18 5 µm, 4.6x50 mm ID from Waters. Eluents: A: H₂O + 0.04% TFA; B: AcCN; Gradient: 5% B →
25 95% B over 1 min. Flow: 4.50 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

LC-MS-conditions 02 (if not indicated otherwise): Analytical: Thermo Finnigan MSQ Plus MS with Agilent 1100 Binary Pump and DAD. Column: Zorbax SB-AQ 5 µm, 4.6x50 mm

ID from Agilent Technologies. Eluents: A: H₂O + 0.04% TFA; B: AcCN; Gradient: 5% B → 95% B over 1 min. Flow: 4.50 mL/min. Detection: UV/Vis and/or ELSD, and MS, *t_R* is given in min.

5 LC-MS-conditions 05 (if not indicated otherwise): Analytical: Dionex GHP 3200 Binary Pump, MS: Thermo MSQ Plus, DAD: Dionex PDA 3000, ELSD: Sedere Sedex 85, column: Xbridge C18 5 μM, 4.6x50 mm ID from Waters, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 5% B → 95% B over 1 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, *t_R* is given in min.

10 LC-MS-conditions 05b (if not indicated otherwise): Analytical: Dionex GHP 3200 Binary Pump, MS: Thermo MSQ Plus, DAD: Dionex PDA 3000, ELSD: Sedere Sedex 85. Column: Zorbax Extend C18 1.8 μM, 4.6x20 mm from Agilent Technologies, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 2% B → 95% B over 1.20 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or
15 ELSD, and MS, *t_R* is given in min.

LC-MS-conditions 05c (if not indicated otherwise): Analytical: Dionex GHP 3200 Binary Pump, MS: Thermo MSQ Plus, DAD: Dionex PDA 3000, ELSD: Sedere Sedex 85. Column: Zorbax SB-AQ 1.8 μm, 4.6x20 mm ID from Agilent Technologies, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method:
20 Gradient: 5% B → 95% B over 1 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, *t_R* is given in min.

LC-MS-conditions 06 (if not indicated otherwise): Analytical: Dionex HPG-3000 Binary Pump, MS: Thermo MSQ MS, DAD: Dionex PDA 3000, ELSD: PolymerLab ELS 2100. Column: Ascentis C18 2.7 μm, 3x30 mm ID from Sigma-Aldrich, thermostated in the
25 Dionex TCC-3000 compartment. Eluents: A: H₂O + 0.05% FA; B: AcCN. Method: Gradient: 5% B → 95% B over 1.40 min. Flow: 3.0 mL/min. Detection: UV/Vis and/or ELSD, and MS, *t_R* is given in min.

LC-MS-conditions 07 (if not indicated otherwise): Analytical. Pump: Dionex HPG-3200RS, MS: Thermo MSQ Plus, DAD: Dionex DAD-3000RS, ELSD: Sedere Sedex 85. Column:
30 Xbridge C18 2.5 μM, 4.6x30 mm ID from Waters, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 5% B → 95% B

over 1.00 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

LC-MS-conditions 07b (if not indicated otherwise): Analytical. Pump: Dionex HPG-3200RS, MS: Thermo MSQ Plus, DAD: Dionex DAD-3000RS, ELSD: Sedere Sedex 85.

- 5 Column: Zorbax SB-Aq 3.5 μ M, 4.6x50 mm ID from Agilent Technologies, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 5% B → 95% B over 1.00 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

LC-MS-conditions 07c (if not indicated otherwise): Analytical. Pump: Dionex HPG-

- 10 3200RS, MS: Thermo MSQ Plus, DAD: Dionex DAD-3000RS, ELSD: Sedere Sedex 85. Column: Atlantis T3 5 μ M, 4.6x30 mm ID from Waters, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 5% B → 95% B over 1.00 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

15 LC-MS-conditions 07d (if not indicated otherwise): Analytical. Pump: Dionex HPG-3200RS, MS: Thermo MSQ Plus, DAD: Dionex DAD-3000RS, ELSD: Sedere Sedex 85. Column: Ascentis Express C18 2.7 μ m, 4.6x30 mm ID from Sigma-Aldrich, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O + 0.04% TFA; B: AcCN. Method: Gradient: 2% B → 95% B over 1.20 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or

- 20 ELSD, and MS, t_R is given in min.

LC-MS-conditions 04 (if not indicated otherwise): Analytical. Pump: Dionex HPG-3200RS, MS: Thermo MSQ Plus, DAD: Dionex DAD-3000RS, ELSD: Sedere Sedex 85. Column: Xbridge C18 5 μ M, 4.6x50 mm ID from Waters, thermostated in the Dionex TCC-3200 compartment. Eluents: A: H₂O/NH₃ (c(NH₃) = 13 mmol/L); B: AcCN. Method: Gradient: 2%

- 25 B → 95% B over 1.20 min. Flow: 4.5 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

LC-MS-conditions FA (if not indicated otherwise): Analytical. Pump: Waters Acquity Binary Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column: Acquity UPLC BEH C18 1.7 μ m 2.1x50 mm ID from

- 30 Waters, thermostated in the Acquity UPLC Column Manager. Eluents: A: H₂O + 0.05%

FA; B: AcCN + 0.05% FA. Method: Gradient: 2% B → 98% B over 2.00 min. Flow: 1.2 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

- LC-MS-conditions TFA (if not indicated otherwise): Analytical. Pump: Waters Acquity Binary Solvent Manager, MS: Waters SQ Detector, DAD: Acquity UPLC PDA Detector,
5 ELSD: Acquity UPLC ELSD. Column: Acquity UPLC BEH C18 1.7 μ m 2.1x50 mm ID from Waters, thermostated in the Acquity UPLC Column Manager. Eluents: A: H₂O + 0.05% TFA; B: AcCN + 0.05% TFA. Method: Gradient: 2% B → 98% B over 2.00 min. Flow: 1.2 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

- 10 HPLC preparative: X-Bridge C18 5 μ m, 50x19 mm ID from Waters. Eluents: A: H₂O + 0.5% NH₄OH; B: AcCN; Gradient: 10% B → 90% B over 5 min. Flow: 40.0 mL/min. Detection: UV/Vis and/or ELSD, and MS, t_R is given in min.

- HPLC chiral, analytical: a) Regis Whelk column, 4.6 x 250 mm, 10 μ m. Eluent A: EtOH + 0.05% Et₃N. Eluent B: hexane. Flow: 1 mL/min. b) ChiralPak AD, 4.6 x 250 mm, 5 μ m.
15 Eluent A: EtOH + 0.05% Et₃N. Eluent B: hexane. Flow: 1 mL/min. c) ChiralCel OD, 4.6 x 250 mm, 10 μ m. Eluent A: EtOH + 0.1% Et₃N. Eluent B: hexane. Flow: 0.8 mL/min. Detection: UV/Vis, t_R is given in min.

- HPLC chiral, preparative: a) Regis Whelk 01 column, 50 x 250 mm. Flow: 100 mL/min. b) ChiralPak AD, 20 x 250 mm. Flow: 10 mL/min. c) ChiralCel OD, 20 μ m, 50 mm x 250 mm.
20 Flow: 100 mL/min. Detection: UV/Vis, t_R is given in min.

- GC-MS-conditions 01: Thermo Trace GC Ultra, Thermo DSQ II MS detector, Thermo TriPlus Autosampler, Column: Zebron ZB-5 MS, 15 m x 0.25 mm ID, 0.25 μ m film, Column flow: 2.0 mL/min, Carrier gas: Helium, Split ratio: 20, SSL Inlet Temperature: 200 °C, Temperature gradient: 60 °C to 300 °C from 0.0 min to 4.0 min, 300 °C isotherm from
25 4.0 min to 5.0 min, Ionization: chemical ionization with CH₄ as reagent gas.

NMR: *Bruker Avance 400* (400 MHz); *Varian Mercury 300* (300 MHz); chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet, q

= quadruplet, p = pentuplet, hex = hextet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz.

As continuous-flow hydrogenation reactor H-Cube® from ThalesNano was used.

- 5 The following examples illustrate the invention but do not at all limit the scope thereof.

General procedures

General procedure A: Amide coupling (1):

In a glass vial, under inert atmosphere (N₂), to an amine (3.0 eq.) in CH₂Cl₂ (0.3 M) were added DMAP (0.25 eq.), EDC.HCl (2.0 eq.) and DIPEA (1.0-3.0 eq., when necessary). A
10 solution of the carboxylic acid (1.0 eq.) in CH₂Cl₂ (0.1 M) was then added and the reaction mixture stirred at rt overnight. The reaction mixture was poured on a syringe containing diatomaceous earth (Isolute® HM-N from Separtis) treated with 1M HCl (1.0 mL per g of Isolute®). The product was eluted with CH₂Cl₂ (3 × 1 mL) and the solvent was removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired
15 compound.

General procedure B: Amide coupling (2):

In a glass vial, under inert atmosphere (N₂), a mixture of the carboxylic acid (1.0 eq.), an amine (3.0 eq.) and HOAt or HOBt (1.0 eq.) in CH₂Cl₂ (10 mL per 0.5 mmol of HOAt) was added to PL-DCC Resin (4.0 eq.) in CH₂Cl₂ (0.2 M) in the presence of PS-DIPEA when
20 needed. The reaction mixture was stirred at rt for 2 days. The reaction mixture was filtered over an Isolute® Phase Separator syringe washed with CH₂Cl₂ (3 × 1 mL) and the solvent was removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure C: Amide coupling (3):

In a glass vial, under inert atmosphere (N₂), a mixture of the carboxylic acid (1.0 eq.) and an amine (1.0 eq.) in DCE/pyridine (1:1, 0.2 M) was cooled to -10 °C. POCl₃ (2.5 eq.) in DCE/pyridine (1:1, 1.2 M) was added and the reaction mixture was stirred at -10 °C for 1 h. The reaction mixture was poured on a syringe containing diatomaceous earth (Isolute® HM-N from Separtis) treated with 1 M NaOH (1.0 mL per g of Isolute®). The product was
25 eluted with CH₂Cl₂ (3 × 2 mL) and the solvent was removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.
30

General procedure D: Amide coupling (4):

In a glass vial, under inert atmosphere (N_2), to a mixture of the amine (1.0 eq.) and a carboxylic acid (1.2 eq.) in CH_2Cl_2 (10 mL per mmol of acid) was added a solution of HOBt (1.25 eq.), DMAP (0.25 eq.), EDC·HCl (1.5-2.0 eq.) and DIPEA (4.0-5.0 eq.) in CH_2Cl_2 (6 mL per mmol of HOBt). The reaction mixture was stirred at rt overnight. The reaction mixture was poured on a syringe containing diatomaceous earth (Isolute[®] HM-N from Separtis) treated with 1M HCl (1.0 mL per g of Isolute[®]). The product was eluted with CH_2Cl_2 (3 × 1 mL) and the solvent was removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure E: Amide coupling (5):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of the carboxylic acid (1.0 eq.) in CH_2Cl_2 (0.2 M) were added an amine (1.0-2.0 eq.), EDC·HCl (2.0-3.0 eq.), DIPEA (3.0-6.0 eq., when necessary) and DMAP (0.25 eq.). The reaction mixture was stirred at rt until completion of the reaction. Water was then added, the layers separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure F: Weinreb Amidation:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of an amine (2.0 eq.) in CH_2Cl_2 (0.4 M) was added $AlMe_3$ (1.0 M in heptane, 6.0 eq.). The reaction mixture was stirred at rt for 1 h and was then cooled to 0 °C. A solution of the ester (1.0 eq.) in CH_2Cl_2 (0.2 M) was added and the reaction mixture stirred at rt until completion of the reaction. Aq. sat. $NaHCO_3$ was carefully added, the layers separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure G: Dioxolane deprotection:

In a glass vial, under inert atmosphere (N_2), a 0.06 M solution of the dioxolane (1.0 eq.) in THF was treated with 1N HCl (2.7 eq.) and the reaction mixture was stirred at rt until completion. Aq. 1N NaOH was added and the product extracted with EA (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure H: Boc deprotection:

In a glass vial, under inert atmosphere (N_2), a 0.06 M solution of the Boc-protected amine (1.0 eq.) in CH_2Cl_2 (+ 1 drop of MeOH) was treated with 4N HCl in dioxane (15 mL/mmol amine) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then concentrated under reduced pressure and the residue purified by FC or HPLC to give the desired compound.

General procedure I: Amide coupling (6):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of the carboxylic acid (1.0 eq.) in CH_2Cl_2 (0.2 M) were added HOBt (1.2 eq.), DMAP (0.25 eq.), EDC-HCl (2.5 eq.) and DIPEA (4.0 eq.). The reaction mixture was stirred at rt for 30 min. A solution of an amine (1.0 eq.) in CH_2Cl_2 (0.2 M) was then added and the reaction mixture stirred at rt overnight. Water was added, the layers separated, and the org. layer dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure J: Amide coupling (7):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of the carboxylic acid (1.0 eq.) in CH_2Cl_2 (0.1 M) were added oxalyl chloride (1.1 eq.) and a few drops of DMF. The reaction mixture was stirred at rt until completion. A solution of an amine (2.2 eq.) in CH_2Cl_2 (0.4 M) was then added and the reaction mixture stirred at rt until completion of the reaction. Water and CH_2Cl_2 were then added, the layers separated and the aq. layer extracted with CH_2Cl_2 (2x). The combined org. extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure K: Amide coupling (8):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a mixture of the carboxylic acid (1.0 eq.), an amine (1.0 eq.) and HOBt (1.2 eq.) in CH_2Cl_2 (1 mL per 0.3 mmol of HOBt) was added to PL-DCC Resin (2.0 eq.) in CH_2Cl_2 (0.2 M). The reaction mixture was stirred at rt for 1 day. The reaction mixture was filtered and the solvent was removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure L: Amide coupling (9):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a mixture of the carboxylic acid (1.0 eq.), an amine (1.1 eq.) and

HATU (1.2 eq.) in THF/DMF 4:1 (1 mL per 0.2 mmol of HATU) was added DIPEA (3.0 eq.). The reaction mixture was stirred at rt for 1 day. Water was then added and the mixture extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification of the residue
5 by FC or HPLC gave the desired compound.

General procedure M: Carboxamide formation:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), the ester (1.0 eq.) was dissolved in THF (0.2 M) and treated with aq. 1N NaOH (2.0 eq.) at rt until completion of the reaction. The reaction mixture was poured into
10 aq. 1N HCl and extracted with EA (3x). The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. To a solution of the crude carboxylic acid (1.0 eq.) and Et_3N (1.0 eq.) in dry THF (0.1 M) was added ethyl chloroformate (1.0 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and an amine (aq. NH_3 (excess) or MeNH_2 (1.0 eq.)) was then added. The reaction mixture was
15 stirred at 0 °C until completion of the reaction then concentrated under reduced pressure. The residue was partitioned between water and CH_2Cl_2 , the layers separated and the aq. layer extracted with CH_2Cl_2 (2x). The combined org. extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

General procedure N: Amide coupling (10):

In a glass vial, under inert atmosphere (N_2), to a solution of the carboxylic acid (1.0 eq.) in CH_2Cl_2 (0.25 M) were added HOBt (1.20 eq.), DMAP (0.25 eq.), EDC·HCl (2.5 eq.) and DIPEA (4.0 eq.). The reaction mixture was stirred at rt for 30 min. An amine (2.0 eq.) was then added and the reaction mixture stirred at rt until completion of the reaction. DMF (0.3
25 vol. CH_2Cl_2) and $\text{PL-SO}_2\text{Cl}_2$ (1.0 eq.) were added and after stirring at rt for 1h the mixture was filtered (CH_2Cl_2) and concentrated under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

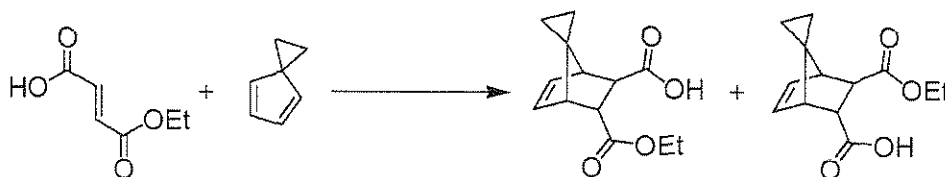
Synthesis of Intermediates

30 Spiro[2.4]hepta-4,6-diene:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a mixture of benzyltriethylammonium chloride (18.0 g, 78 mmol) in 50%

aqueous NaOH solution (1.2 L) was heated to 45 °C. A chilled solution of cyclopentadiene (formed by cracking of cyclopentadiene dimer at 180 °C, 140 mL, 1.70 mol) in 1,2-dichloroethane (122 mL, 1.55 mol) was added to the stirred NaOH solution while keeping the internal temperature below 55 °C. After completion of the addition (ca. 1.75 h), the reaction mixture was stirred at 50 °C for 2 h and allowed to cool down to rt. The layers were separated, the organic layer washed with 1M NaOH, dried (Na₂SO₄) and filtered. The crude brown liquid was distilled under reduced pressure (85-95 mbar) and the title compound was obtained as a colorless liquid (bp = 45-50 °C at 80 mbar). ¹H NMR (400 MHz, CDCl₃) δ 6.58 (m, 2H), 6.19 (m, 2H), 1.71 (s, 4H).

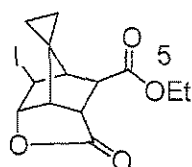
Diels Alder reaction – formation of (5*R)-5-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(6*R**)-6-carboxylic acid and (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid:**



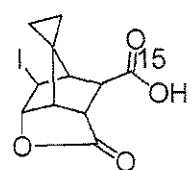
In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of (*E*)-but-2-enedioic acid monoethyl ester (63.8 g, 0.44 mol) in MeOH (425 mL) was treated with spiro[2.4]hepta-4,6-diene (57.6 mL, 0.57 mol) at rt. The reaction mixture was stirred at this temperature for 11 days. The mixture was concentrated under reduced pressure and the crude residue recrystallized from EA and pentane. (6*R**)-6-Ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (*exo* product) was obtained as a white solid. The mother liquor was then concentrated under reduced pressure, the residue purified by FC (heptane/acetone, 2-5% of acetone) and the product obtained as a mixture of *endo/exo* products (yellow solid). TLC: rf (7:3 hept-*acetone*) = 0.29. LC-MS-conditions 02: *t_R* = 0.89 min; [M+H]⁺ = 373.99. ¹H NMR (400 MHz, CDCl₃) δ 6.42 (m, 1H), 6.24 (dd, *J* = 5.8, 2.5 Hz, 1H), 4.20 (qd, *J* = 7.3, 1.3 Hz, 2H), 3.74 (t, *J* = 4.0 Hz, 1H), 2.82 (d, *J* = 4.5 Hz, 1H), 2.74 (br s, 1H), 2.69 (br s, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.50 (m, 4H) for pure isomer. ¹H NMR (400 MHz, CDCl₃) δ 6.40 (m, 1Ha + 1Hb), 6.23 (dd, *J* = 5.8, 2.8 Hz, 1Ha), 6.16 (dd, *J* = 5.8, 2.8 Hz, 1Hb), 4.18 (qd, *J* = 7.0, 1.3 Hz, 2Ha), 4.12 (qd, *J* = 7.3, 2.0 Hz, 2Hb), 3.73 (t, *J* = 4.3 Hz, 1Ha), 3.62 (t, *J* = 4.3 Hz, 1Hb), 2.92 (d, *J* = 4.5 Hz, 1Hb), 2.81 (d, *J* = 4.5 Hz, 1Ha), 2.75 (br s, 1Hb),

2.72 (br s, 1Ha), 2.67 (br s, 1Ha + 1Hb), 1.28 (t, $J = 7.3$ Hz, 3Ha), 1.25 (t, $J = 7.0$ Hz, 3Hb), 0.50 (m, 4Ha + 4Hb) for mixture of stereoisomers.

Iodolactonization – formation of ($\pm$)-iodolactones 1 ($R^{10} = Et$) and 2:



To a solution of 6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylenespiro[2.4]heptane]-5-carboxylic acid (15.00 g, 63.5 mmol, mixture of isomers as obtained above) in CH_2Cl_2 (95 mL) were added $NaHCO_3$ (5.87 g, 69.8 mmol), water (286 mL), KI (39.00 g, 234.9 mmol) and I_2 (3.55 g, 11.0 mmol). The reaction mixture was stirred at rt overnight. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$. The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were successively washed with aq. sat. $NaHCO_3$ and brine, then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give ($\pm$)-iodolactone 1 ($R^{10} = Et$) (ethyl ester) as a pale yellow oil. TLC: rf (4:1 hept–acetone) = 0.25. LC-MS-conditions 02: $t_R = 1.02$ min; $[M+H]^+ = 363.53$.



The aq. layer was then acidified (pH = 1) and extracted with EA. The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude solid was purified by FC to give ($\pm$)-iodolactone 2 (carboxylic acid) as a white solid. TLC: rf (70:30:1.1 hept–acetone–MeOH) = 0.15. LC-MS-conditions 02: $t_R = 0.86$ min; $[M+AcCN+H]^+ = 376.49$.

Retro-iodolactonization – formation of (6*R)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylenespiro[2.4]heptane]-(5*R**)-5-carboxylic acid:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of ($\pm$)-iodolactone 1 ($R^{10} = Et$) (5.00 g, 13.8 mmol) in acetic acid (50 mL) was added zinc powder (13.54 g, 207.1 mmol). The reaction mixture was stirred at 65 °C for 2 h, cooled down to rt, filtered and partitioned between water and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept–EA, 1:0 $\rightarrow$ 1:1) and the title compound was obtained as a white solid. TLC: rf (7:3 hept–EA) = 0.18. LC-MS-conditions 02: $t_R = 0.89$ min; $[M+H]^+ = 237.30$.

Amide coupling (with 4-bromo-aniline) – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (17.9 g, 75.6 mmol) in dry toluene (350 mL) were added a few drops of DMF and oxalyl chloride (10.1 mL, 113.5 mmol). The reaction mixture was stirred at reflux for 40 minutes, cooled down to rt, concentrated under reduced pressure and the residue dried under high vacuum.

To a solution of this acyl chloride in dry CH₂Cl₂ (350 mL) were added 4-bromoaniline (26.8 g, 151.3 mmol) and DIPEA (38.8 mL, 151.3 mmol). The reaction mixture was stirred at rt for 2 h. 1N HCl was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was triturated with MeOH and the title compound obtained as a pale brown solid. TLC: rf (7:3 hept-EA) = 0.46. LC-MS-conditions 02: t_R = 1.09 min; [M+H]⁺ = 390.30.

Saponification – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (2.70 g, 6.92 mmol) in EtOH (69 mL) and 1N NaOH (69 mL) was stirred at 80 °C for 1 h. The reaction mixture was then cooled down to rt and EtOH was removed under reduced pressure. The residue was partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow solid. LC-MS-conditions 02: t_R = 0.98 min; [M+H]⁺ = 362.20.

Amide coupling (with beta-alanine methyl ester hydrochloride) – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (200 mg, 0.55 mmol) in dry toluene (1.7 mL) were added a few drops of DMF and oxalyl chloride (1.1 eq.). The reaction mixture was stirred at rt for 90 min, concentrated under reduced pressure and the

residue co-evaporated with toluene (2x). The residue was then redissolved in CH₂Cl₂ (0.7 mL) and added to a mixture of beta-alanine methyl ester hydrochloride (85 mg, 0.61 mmol) and DIPEA (0.28 mL, 3.0 eq.) at rt. The reaction mixture was stirred at rt for 20 minutes, diluted with CH₂Cl₂ and washed with aq. 1N HCl. The layers were separated, and the aq. layer back-extracted with CH₂Cl₂ (2x). The combined org. extracts were washed with aq. sat. NaHCO₃, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA) and the title compound obtained as a white solid. TLC: rf (6:4 hept-EA) = 0.35. LC-MS-conditions 02: t_R = 0.98 min; [M+H]⁺ = 446.90.

10 **(5*R*^{*})-5-Hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-bromo-phenyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (±)-iodolactone 2 (1.00 g, 2.99 mmol) in dry toluene (17 mL) were added a few drops of DMF and oxalyl chloride (0.38 mL, 4.49 mmol). The reaction mixture was stirred at reflux for 20 minutes, cooled down to rt, concentrated under reduced pressure and the residue dried under high vacuum.

To a solution of this acyl chloride in dry CH₂Cl₂ (5 mL) were added 4-bromoaniline (730 mg, 4.24 mmol) and DIPEA (1.5 mL, 8.98 mmol). The reaction mixture was stirred at rt for 20 min. 1N HCl was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 7:3) and the pure amide was obtained as a pale orange foam. TLC: rf (7:3 hept-EA) = 0.21. LC-MS-conditions 02: t_R = 1.08 min. In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of the above iodolactone (1.29 g, 2.64 mmol) in acetic acid (10 mL) was added zinc powder (2.59 g, 39.64 mmol). The reaction mixture was stirred at 65 °C for 2 h, cooled down to rt, filtered and partitioned between water and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 4:6) and the title compound was obtained as a white foam. TLC: rf (4:6 hept-EA) = 0.43. LC-MS-conditions 02: t_R = 0.98 min; [M+H]⁺ = 362.31.

Double bond reduction – formation of (6*R)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a deoxygenated suspension of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (2.00 g, 8.46 mmol), Pd/C 10% (339 mg) and cyclohexene (1.72 mL, 7.93 mmol) in dry THF (31 mL) was stirred at reflux for 4 h. The reaction mixture was filtered through celite and the filter cake washed with EtOH. The filtrate was concentrated under reduced pressure and the title compound obtained as a white solid. TLC: rf (7:3 hept-EA) = 0.26. LC-MS-conditions 02: t_R = 0.93 min; [M+H]⁺ = 239.34.

Amide coupling (with 4-bromo-aniline) – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (2.00 g, 8.46 mmol) in dry toluene (40 mL) were added a few drops of DMF and oxalyl chloride (1.13 mL, 12.70 mmol). The reaction mixture was stirred at reflux for 40 minutes, cooled down to rt, concentrated under reduced pressure and the residue dried under high vacuum.

To a solution of this acyl chloride in dry CH₂Cl₂ (40 mL) were added 4-bromoaniline (3.00 g, 16.93 mmol) and DIPEA (4.35 mL, 25.40 mmol). The reaction mixture was stirred at rt for 1 h. 1N HCl was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 7:3) and the title compound obtained as a pale brown solid. TLC: rf (7:3 hept-EA) = 0.46. LC-MS-conditions 02: t_R = 1.13 min; [M+H]⁺ = 392.30.

Saponification – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (2.78 g, 7.09 mmol) in EtOH (71 mL) and 1N NaOH (71 mL) was stirred at 80 °C for 1 h. The reaction mixture was then cooled down to rt and EtOH was removed under reduced pressure. The residue was partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and

concentrated under reduced pressure to give the title compound as an orange powder. TLC: rf (7:3 hept-EA) = 0.18. LC-MS-conditions 02: t_R = 1.01 min; $[M+H]^+$ = 364.30.

Amide coupling (with 4-pyrrolidin-1-yl-butylamine) – formation of (±)-iodolactone 3 (R^2 = 4-pyrrolidin-1-yl-butyl and R^3 = H):

5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (±)-iodolactone 2 (6.92 g, 20.71 mmol) in dry CH_2Cl_2 (42 mL) were added a few drops of DMF and oxalyl chloride (1.96 mL, 22.78 mmol). The reaction mixture was stirred at rt for 30 min, after which 4-(1-pyrrolidino)-butylamine (3.00 g, 20.71 mmol) and DIPEA (3.55 mL, 20.71 mmol) were added. The reaction mixture was
10 stirred at rt for 15 minutes, diluted with CH_2Cl_2 and washed with sat. aq. NH_4Cl . The layers were separated, and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (CH_2Cl_2 /MeOH, 95:5) and the title compound obtained as a white solid. TLC: rf (95:5 CH_2Cl_2 /MeOH) = 0.12. LC-MS-
15 conditions 02: t_R = 0.74 min; $[M+H]^+$ = 459.30.

Retro-iodolactonization – formation of (5*R)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (±)-iodolactone 3 (R^2 = 4-pyrrolidin-1-yl-butyl and R^3 = H) (7.11 g, 15.51 mmol) in acetic acid (100 mL) was added zinc powder (15.21 g, 232.70 mmol). The reaction mixture was stirred at 65 °C for 2 h, cooled down to rt, filtered,
20 washed with CH_2Cl_2 and the filtrate concentrated under reduced pressure. The crude residue was purified by FC (C-18 reverse phase silica, H_2O /MeOH, 1:0 then 0:1) and the title compound was obtained as a white solid. LC-MS-conditions 02: t_R = 0.64 min; $[M+H]^+$ = 333.34.
25

Ester reduction – formation of (5*R)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-(hydroxymethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (10.00 g, 25.62 mmol) in dry
30 THF (120 mL) was added $LiBH_4$ (2.55 g, 64.06 mmol). The reaction mixture was stirred at 65 °C for 2.5 h and cooled down to rt. Sat. aq. NH_4Cl and EA were added, the layers separated and the aq. layer extracted with EA (3x). The combined org. extracts were

washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 7:3) and the title compound was obtained as a white solid. TLC: r_f (7:3 hept-EA) = 0.25. LC-MS-conditions 02: t_R = 0.99 min; $[\text{M}+\text{H}]^+$ = 348.30.

5 **Amine formation via triflate – formation of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-(hydroxymethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (1.00 g, 2.87 mmol) in dry
10 CH_2Cl_2 (20 mL) was added DIPEA (1.23 mL, 7.18 mmol). The reaction mixture was cooled to -78 °C and trifluoromethane sulfonic anhydride (0.55 mL, 3.33 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. NH_3 in dioxane (0.5 M, 15 mL, 7.50 mmol) was then added and the reaction mixture allowed to warm up to rt and stirred at this temperature overnight. Water was added, the layers separated and the org.
15 layer successively washed with sat. aq. NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The title compound was obtained as an orange solid. TLC: r_f (9:1:0.1 CH_2Cl_2 -MeOH- NH_4OH) = 0.28. LC-MS-conditions 02: t_R = 0.82 min; $[\text{M}+\text{H}]^+$ = 347.24.

20 **Amine formation via triflate – formation of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-[(methyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-(hydroxymethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (120 mg, 0.35 mmol) in dry
25 CH_2Cl_2 (2.4 mL) was added DIPEA (0.15 mL, 0.86 mmol). The reaction mixture was cooled to -78 °C and trifluoromethane sulfonic anhydride (0.09 mL, 0.57 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. Methylamine (2 M in THF, 1.73 mL, 3.46 mmol) was then added and the reaction mixture allowed to warm up to rt and stirred at this temperature for 1h30. Water and EA were added, the layers separated
30 and the org. layer successively washed with sat. aq. NaHCO_3 and brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The title compound was obtained as an orange solid. LC-MS-conditions 02: t_R = 0.82 min; $[\text{M}+\text{H}]^+$ = 361.29.

1-(5-Hydroxymethyl-furan-2-yl)-ethanone:

In a flame dried round-bottomed flask under inert atmosphere (N_2), to a mixture of 5-hydroxymethyl-2-furaldehyde (100 g, 0.79 mol) and pyridinium toluene-4-sulfonate (10 g, 0.04 mol) in CH_2Cl_2 (1 L) was added 3,4-dihydro-2H-pyran (150 mL, 1.62 mol) while
5 keeping the internal temperature below 28 °C (water bath). The reaction mixture was stirred at rt for 5 h. Water (1 L) was added, the layers separated and the org. layer washed with water (500 mL) and evaporated to dryness to give crude 5-(tetrahydro-pyran-2-yloxymethyl)-furan-2-carbaldehyde as a yellow oil.

Crude 5-(tetrahydro-pyran-2-yloxymethyl)-furan-2-carbaldehyde (171 g) was dissolved in
10 THF (1 L) and cooled to 1 °C. Methylmagnesium chloride (3 M in THF, 325 mL, 0.97 mol) was then added while keeping the internal temperature below 5 °C. After the addition, the reaction mixture was stirred at rt for 1 h. Water (1 L), TBME (1 L) and 40% aq. citric acid (200 mL) were added, the layers separated and the org. layer washed with water (500 mL) and evaporated to dryness to give crude 1-[5-(tetrahydro-pyran-2-yloxymethyl)-furan-
15 2-yl]-ethanol. Part of the crude material (96 g, 0.43 mol) was dissolved in CH_2Cl_2 (1 L) and treated with MnO_2 (371 g, 4.26 mol) at rt. The reaction mixture was heated to 45 °C and stirred at this temperature for 24 h. The mixture was then filtered over celite and the filter cake washed with CH_2Cl_2 . The filtrate was evaporated to dryness to give crude 1-[5-(tetrahydro-pyran-2-yloxymethyl)-furan-2-yl]-ethanone as a yellow oil.

20 Crude 1-[5-(tetrahydro-pyran-2-yloxymethyl)-furan-2-yl]-ethanone (89 g, 0.40 mol) was dissolved in MeOH (500 mL) and treated with Amberlyst 15 (15 g) at rt. The reaction mixture was stirred at 35 °C for 1 h, cooled to rt and filtered over celite. Et_3N (1 mL) was added and the mixture was evaporated to dryness. The residue was stripped with methylcyclohexane and 1-(5-hydroxymethyl-furan-2-yl)-ethanone was obtained as a
25 yellow oil that solidified on standing.

1-(5-Aminomethyl-furan-2-yl)-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 1-(5-hydroxymethyl-furan-2-yl)-ethanone (2.00 g, 14.27 mmol) in dry CH_2Cl_2 (29 mL) was treated at 0 °C with Et_3N (2.58 mL, 18.55 mmol)
30 followed by DMAP (178 mg, 1.43 mmol) and Ms-Cl (1.33 mL, 17.13 mmol). After stirring at rt for 3 h, the reaction was quenched with water. The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The org. layer was dried over $MgSO_4$, filtered, and the

solvents were removed under reduced pressure to give crude 1-(5-chloromethyl-furan-2-yl)-ethanone as a brown oil. Part of this crude material (2.33 g, 14.72 mmol) was dissolved in dry DMF (50 mL) and treated with NaN_3 (2.90 g, 44.16 mmol) at 80 °C for 24 h. The reaction mixture was then cooled down to rt and partitioned between EA and water.

5 The layers were separated and the aq. layer extracted with EA (1x). The combined org. extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude 1-(5-azidomethyl-furan-2-yl)-ethanone as a brown oil. LC-MS-conditions 02: $t_R = 0.81$ min; $[\text{M}+\text{AcCN}+\text{H}]^+ = 207.50$.

To a solution of the crude azide (500 mg, 3.03 mmol) in THF (15 mL) were added Ph_3P (polymer-supported, 3.0 mmol/g, 1.5 eq.) and water (5 mL). The reaction mixture was stirred at 60 °C until reaction completion, cooled down to rt and filtered. Sat. aq. NaHCO_3 and EA were then added, the layers separated and the aq. layer extracted with EA (1x). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) and the title
10 compound was obtained as an orange oil. LC-MS-conditions 02: $t_R = 0.27$ min; $[\text{M}+\text{AcCN}+\text{H}]^+ = 181.61$.

5-Nitro-pentan-2-one:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of methyl vinyl ketone (2.32 mL, 28.53 mmol) in nitromethane (29.6 mL) was added activated $\text{KF}/\text{Al}_2\text{O}_3$ (323 mg, prepared by mixing KF and basic Al_2O_3 in water followed by concentrating and drying) at 0 °C. The reaction mixture was then allowed to warm up to rt and stirred at this temperature for 18 h. The mixture was filtered through neutral Al_2O_3 and washed with CH_2Cl_2 . The filtrate was
20 concentrated under reduced pressure to give the title compound as a colorless oil.

2-Methyl-2-(3-nitro-propyl)-[1,3]dioxolane:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and a Dean-Stark apparatus and under inert atmosphere (N_2), crude 5-nitro-pentan-2-one (28.53 mmol) was dissolved in dry toluene (28 mL). Ethylene glycol (10.2 mL, 183.02 mmol) and *p*-TsOH (696 mg, 3.66 mmol) were added and the reaction mixture stirred at 120 °C for 5 h. The
30 reaction mixture was then cooled down to rt and sat. aq. NaHCO_3 was added. The layers were separated and the org. layer washed with brine (2x), dried over Na_2SO_4 , filtered, and

concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 4:1) to give the title compound as a pale brown oil. TLC: r_f (4:1 hept-EA) = 0.21.

3-(2-Methyl-[1,3]dioxolan-2-yl)-propylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar, a mixture of 2-methyl-2-(3-nitro-propyl)-[1,3]dioxolane (1.80 g, 10.27 mmol) and Pd/C 10% (176 mg) in dry MeOH (35 mL) was stirred at rt under atmospheric H_2 for 11 h. The reaction mixture was then filtered and concentrated under reduced pressure to give the title compound as a colorless oil. LC-MS-conditions 02: t_R = 0.25 min; $[M+H]^+$ = 146.41.

2-Acetyl-4-cyano-butyric acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to sodium ethylate (prepared from 62 mg sodium in 8 mL of EtOH) was added ethyl acetoacetate (9.7 mL, 76.1 mmol). Acrylonitrile (5 mL, 76.1 mmol) was then added dropwise at 40-45 °C and the reaction mixture was stirred at this temperature overnight. Ethanol was removed and the residue washed with 65 mL of water containing 3.5 mL of acetic acid, diluted with CH_2Cl_2 and dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was distilled (bp = 95-105 °C at 1 atm) to give the title compound. TLC: r_f (7:3 hept-EA) = 0.29.

5-Oxo-hexanenitrile:

A mixture of 2-acetyl-4-cyano-butyric acid ethyl ester (5.70 g, 31.1 mmol) and Na_2CO_3 (5.52 g, 52.1 mmol) in water (55 mL) was stirred at reflux for 4 h. After cooling, K_2CO_3 (1.9 g) was added and the reaction mixture extracted with Et_2O (3x) then with CH_2Cl_2 (4x). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 65:35) to give the title compound as a colorless oil. TLC: r_f (65:35 hept-EA) = 0.21.

4-(2-Methyl-[1,3]dioxolan-2-yl)-butyronitrile:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and a Dean-Stark apparatus and under inert atmosphere (N_2), 5-oxo-hexanenitrile (1.69 g, 15.2 mmol) was dissolved in dry toluene (10 mL). Ethylene glycol (4.24 mL, 76.0 mmol) and *p*-TsOH (289 mg, 1.5 mmol) were added and the reaction mixture stirred at 120 °C for 5 h. The reaction mixture was then cooled down to rt and sat. aq. $NaHCO_3$ was added. The layers were separated and the aq. layer extracted with CH_2Cl_2 (2x). The combined organic extracts

were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow oil. LC-MS-conditions 02: t_R = 0.94 min.

4-(2-Methyl-[1,3]dioxolan-2-yl)-butylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-(2-methyl-[1,3]dioxolan-2-yl)-butyronitrile (2.23 g, 14.4 mmol) in dry Et₂O (2.5 mL) was added to a suspension of LiAlH₄ (1.36 g, 35.9 mmol) in dry Et₂O (50 mL). The reaction mixture was stirred at reflux for 3 h, cooled down to rt and treated with water (2 mL), 15% aq. NaOH (2 mL) and water (4 mL). The precipitate was filtered off and washed with Et₂O. The filtrate was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as a light brown oil. LC-MS-conditions 02: t_R = 0.32 min; [M+H]⁺ = 160.29.

4-Bromo-thiazole-2-carbaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of commercially available 2,4-dibromo-thiazole (3.50 g, 14.41 mmol) in dry Et₂O (120 mL) was treated with *n*-BuLi (5.9 mL of a 2.5 M solution in hexanes, 14.72 mmol) at -78 °C. The reaction mixture was stirred at this temperature for 30 min. *N,N*-Dimethylformamide (1.35 mL, 14.47 mmol) was then added and the mixture allowed to warm to rt over a period of 1 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (50 mL). The layers were separated and the aq. layer extracted with Et₂O (3 × 50 mL). The combined org. extracts dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (10:1 → 3:1 hept-EA) gave the title compound as a pale yellow solid. TLC: rf (1:1 hept-EA) = 0.21. LC-MS-conditions 02: t_R = 0.81 min.

(4-Bromo-thiazol-2-yl)-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), 4-bromo-thiazole-2-carbaldehyde (1.68 g, 8.75 mmol) was dissolved in MeOH (10 mL). NaBH₄ (428 mg, 10.86 mmol) was added portionwise at 0 °C and the reaction mixture stirred at rt for 1 h. Water (10 mL) was added and the mixture extracted with EA (3 × 20 mL). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (6:1 → 2:1 hept-EA) gave the title compound as a pale yellow solid. TLC: rf (1:1 hept-EA) = 0.31. LC-MS-conditions 02: t_R = 0.62 min [M+H]⁺ = 194.31.

4-Bromo-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), (4-bromo-thiazol-2-yl)-methanol (1.37 g, 7.06 mmol) was dissolved in dry CH_2Cl_2 (21 mL). *tert*-Butyldimethylsilyl chloride (1.17 g, 7.77 mmol) was added at 0 °C
5 followed by imidazole (985 mg, 14.47 mmol). The reaction mixture was stirred at rt for 2 h. 10% Aq. K_2CO_3 (10 mL) was added, the layers separated and the aq. layer extracted with CH_2Cl_2 (2 x 20 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the title compound as a colorless oil. TLC: rf (1:1 hept-EA) = 0.80.

1-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-thiazol-4-yl]-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 4-bromo-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazole (1.94 g, 6.29 mmol) in dry Et_2O (50 mL) was added *n*-BuLi (2.76 mL of a 2.5 M solution in hexanes, 6.92 mmol) at -78 °C. The reaction mixture was then stirred for 30 min at -78
15 °C before *N,N*-dimethylacetamide (1.17 mL, 12.58 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt over a period of 1 h and stirred at this temperature for 20 min. Sat. aq. NH_4Cl (20 mL) was added, the layers separated and the aq. layer extracted with Et_2O (3 x 30 mL). The combined org. extracts were dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Purification of the
20 residue by FC (20:1 -> 5:1 hept-EA) gave the title compound as a yellow solid. TLC: rf (1:1 hept-EA) = 0.51. LC-MS-conditions 02: t_R = 1.11 min; $[M+H]^+$ = 272.39.

2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-(2-methyl-[1,3]dioxolan-2-yl)-thiazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 1-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazol-4-yl]-
25 ethanone (1.77 g, 6.52 mmol) in ethylene glycol (7 mL) was treated with trimethylorthoformate (1.46 mL, 13.29 mmol) followed by $LiBF_4$ (125 mg, 1.30 mmol). The reaction mixture was heated at 95 °C for 4 h. Sat. aq. Na_2CO_3 (5 mL) was added and the mixture was extracted with Et_2O (2 x 20 mL). The org. extracts were dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Purification of the residue
30 by FC (20:1 -> 3:1 hept-EA) gave the title compound as a brown oil. TLC: rf (1:1 hept-EA) = 0.56. LC-MS-conditions 02: t_R = 1.11 min; $[M+H]^+$ = 316.36.

[4-(2-Methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-(2-methyl-[1,3]dioxolan-2-yl)-thiazole (1.30 g, 4.12 mmol) in dry THF (10 mL) was treated at 0 °C with TBAF (6.2 mL of a 1M solution in THF, 6.20 mmol). The reaction mixture was stirred at 0 °C for 5 min and at rt for 1h30. The mixture was then diluted with EA (10 mL), washed with brine (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by FC (5:1 -> 1:3 hept-EA) gave the title compound as a yellow oil. TLC: rf (1:2 hept-EA) = 0.20. LC-MS-conditions 02: t_R = 0.59 min; $[M+H]^+$ = 202.48.

[4-(2-Methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of [4-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methanol (745 mg, 3.70 mmol) in dry CH_2Cl_2 (5 mL) was treated at 0 °C with Et_3N (0.67 mL, 4.79 mmol) followed by DMAP (46 mg, 0.37 mmol) and Ms-Cl (0.37 mL, 4.67 mmol). After stirring at 0 °C for 1h30, the reaction was quenched with water (5 mL). The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give crude methanesulfonic acid 4-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-ylmethyl ester as a yellow oil. Part of this crude material (200 mg, 0.72 mmol) was dissolved in dry DMF (2.5 mL) and treated with NaN_3 (50 mg, 0.76 mmol) at 80 °C for 24 h. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 2-azidomethyl-4-(2-methyl-[1,3]dioxolan-2-yl)-thiazole as a yellow oil. LC-MS-conditions 02: t_R = 0.82 min; $[M+H]^+$ = 227.46.

To a solution of the crude azide (160 mg, 0.71 mmol) in THF (4.5 mL) were added Ph_3P (371 mg, 1.41 mmol) and water (1 mL). The reaction mixture was stirred at 60 °C for 4 h and cooled down to rt. Sat. aq. $NaHCO_3$ and EA were then added, the layers separated and the aq. layer extracted with EA (1x). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by FC (1:0 -> 9:1 CH_2Cl_2 -MeOH) to give the title compound as a yellow oil. LC-MS-conditions 02: t_R = 0.37 min; $[M+H]^+$ = 201.54.

[5-(2-Methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of commercially available 2-methyl-2-thiophen-2-yl-[1,3]dioxolane (5.00 g, 28.49 mmol) in THF (145.0 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise
5 N,N,N',N' -tetramethyl-ethylenediamine (4.41 mL, 29.06 mmol) followed by n -BuLi (18.14 mL of a 1.6 M solution in hexanes, 29.06 mmol), maintaining the temperature at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was then stirred for 2 h at $-78\text{ }^{\circ}\text{C}$ before DMF (6.74 mL, 87.22 mmol) was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 16 h. The reaction mixture was poured in sat. aq. NaH_4Cl (200 mL) and extracted with
10 EA (2×200 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give crude 5-(2-methyl-[1,3]dioxolan-2-yl)-thiophene-2-carbaldehyde as a yellow oil. LC-MS-conditions 02: $t_R = 0.87$ min; $[M+AcCN+H]^+ = 240.32$. The crude material was dissolved, under inert atmosphere (N_2) in MeOH (51.2 mL) and treated at $0\text{ }^{\circ}\text{C}$, portionwise, over 20 min, with $NaBH_4$ (1.35 g, 34.19
15 mmol in five equal portions). The reaction mixture was stirred at rt for 45 min. The reaction mixture was poured in water (90 mL) and the aq. layer was extracted with EA (2×225 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (50:50 hept-EA) gave the title compound. TLC: rf (50:50 hept-EA) = 0.40. LC-MS-conditions 02: $t_R = 0.72$ min;
20 $[M+H]^+ = 201.46$.

[5-(2-Methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-methylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of [5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-methanol (5.00 g, 25.0 mmol) in dry CH_2Cl_2 (46 mL) was treated at $0\text{ }^{\circ}\text{C}$ with Et_3N (4.5 mL, 32.5
25 mmol) followed by DMAP (305 mg, 2.5 mmol) and $Ms-Cl$ (2.3 mL, 30.0 mmol). After stirring at rt for 2 h, the reaction was quenched with water (50 mL). The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give crude 2-(5-chloromethyl-thiophen-2-yl)-2-methyl-[1,3]dioxolane as a yellow oil. Part of this crude material (953 mg, 4.36 mmol) was dissolved in dry DMF (15 mL) and treated
30 with NaN_3 (859 mg, 13.08 mmol) at $80\text{ }^{\circ}\text{C}$ for 24 h. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give crude 2-azidomethyl-5-(2-methyl-[1,3]dioxolan-2-yl)-thiophene as a yellow oil. LC-MS-conditions 02: $t_R = 0.97$ min; $[M+H]^+ = 226.50$.

To a solution of the crude azide (150 mg, 0.67 mmol) in THF (6 mL) were added Ph_3P (polymer-supported, 1.6 mmol/g, 2.0 eq.) and water (2 mL). The reaction mixture was stirred at 60 °C until reaction completion, cooled down to rt and filtered. Sat. aq. NaHCO_3 and EA were then added, the layers separated and the aq. layer extracted with EA (1x).
5 The combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The title compound was obtained as a yellow oil. LC-MS-conditions 01: $t_R = 0.50$ min; $[\text{M}+\text{H}]^+ = 199.99$.

1-Oxazol-2-yl-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of commercially available 1,3-oxazole (3.25 mL, 48.49 mmol)
10 in dry THF (34.00 mL) was treated with isopropylmagnesium chloride (24.00 mL of a 2.0 M solution in THF, 48.00 mmol) at -15 °C (while the internal temperature was kept below -10 °C). The reaction mixture was stirred at this temperature for 40 min. A solution of *N*-methoxy-*N*-methylacetamide (4.12 mL, 38.79 mmol) in dry THF (10 mL) was then added
15 dropwise while keeping the internal temperature below -14 °C. The reaction mixture was allowed to warm to rt and stirred at this temperature overnight. The reaction was quenched by the addition of 20% aq. NH_4Cl (150 mL). The layers were separated and the aq. layer extracted with Et_2O (3 × 100 mL). The combined org. extracts dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the
20 residue by FC (6:4 hexane- Et_2O) gave the title compound as an orange oil. TLC: r_f (6:4 hexane- Et_2O) = 0.27. LC-MS-conditions 02: $t_R = 0.47$ min.

1-Oxazol-2-yl-ethanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), 1-oxazol-2-yl-ethanone (1.76 g, 15.84 mmol) was dissolved in MeOH
25 (30 mL). NaBH_4 (811 mg, 20.59 mmol) was added portionwise at 0 °C and the reaction mixture stirred at rt for 1h30. Water (30 mL) was added and the MeOH removed under reduced pressure. The mixture was then extracted with EA (7 × 50 mL). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The title compound was obtained as a pale yellow oil. LC-MS-
30 conditions 02: $t_R = 0.33$ min.

2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-oxazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), 1-oxazol-2-yl-ethanol (1.21 g, 10.71 mmol) was dissolved in dry THF (50 mL). *tert*-Butyldimethylsilyl chloride (3.23 g, 21.43 mmol) was added at rt followed by imidazole (1.46 g, 21.43 mmol). The reaction mixture was stirred at rt for 16 h. Sat. aq. NH₄Cl (100 mL) and EA (100 mL) were added, the layers separated and the aq. layer extracted with EA (1 x 100 mL). The combined org. extracts were dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Purification of the residue by FC (4:1 hexane–Et₂O) gave the title compound as a colorless oil. TLC: rf (4:1 hexane–Et₂O) = 0.39. LC-MS-conditions 02: t_R = 1.08 min; [M+H]⁺ = 228.56.

2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-oxazole-5-carbaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazole (733 mg, 3.22 mmol) in dry THF (16 mL) was added *tert*-BuLi (2.62 mL of a 1.6 M solution in pentane, 4.19 mmol) at -78 °C. The reaction mixture was then stirred for 1 h at -40 °C and cooled to -78 °C before *N,N*-dimethylformamide (0.49 mL, 6.44 mmol) was added dropwise. The reaction mixture was allowed to warm up to rt over a period of 1 h and stirred at this temperature for 2 h. Water (30 mL) and sat. aq. NH₄Cl (20 mL) were added, the layers separated and the aq. layer extracted with EA (2 x 30 mL). The combined org. extracts were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. Purification of the residue by FC (4:1 hept–EA) gave the title compound as a colorless oil. TLC: rf (4:1 hept–EA) = 0.33. LC-MS-conditions 02: t_R = 1.08 min; [M+H]⁺ = 256.37.

2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazole-5-carbaldehyde (457 mg, 1.79 mmol) was dissolved in MeOH (8 mL). NaBH₄ (92 mg, 2.33 mmol) was added portionwise at 0 °C and the reaction mixture stirred at rt for 20 min. Water (16 mL) was added and the MeOH removed under reduced pressure. The mixture was then extracted with EA (2 x 20 mL). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The title compound was obtained as a colorless oil. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 258.37.

2-[1-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methylamine:

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methanol (760 mg, 2.95 mmol) in dry CH_2Cl_2 (15 mL) was treated at 0 °C with Et_3N (0.53 mL, 3.82 mmol) followed by DMAP (36 mg, 0.30 mmol) and $Ms-Cl$ (0.30 mL, 3.73 mmol). After stirring at 0 °C until reaction completion, the reaction was quenched with water (50 mL). The org. layer was dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure to give crude 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-5-chloromethyl-oxazole as a yellow oil. The crude material (2.95 mmol) was dissolved in dry DMF (15 mL) and treated with NaN_3 (205 mg, 3.01 mmol) at 80 °C for 40 h. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 5-azidomethyl-2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazole as a yellow oil. LC-MS-conditions 02: $t_R = 1.12$ min; $[M+H]^+ = 283.55$.
- To a solution of the crude azide (700 mg, 2.48 mmol) in THF (12 mL) were added Ph_3P (polymer-supported, 1.6 mmol/g, 3.0 eq.) and water (4 mL). The reaction mixture was stirred at 60 °C until reaction completion, cooled down to rt and filtered. Sat. aq. $NaHCO_3$ and EA were then added, the layers separated and the aq. layer extracted with EA (1x). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by FC (1:0 $\rightarrow$ 9:1 CH_2Cl_2 -MeOH + 2% Et_3N) to give the title compound as a yellow oil. LC-MS-conditions 01: $t_R = 0.75$ min; $[M+H]^+ = 257.08$.

(2-Bromo-thiazol-5-yl)-methanol:

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), 2-bromo-thiazole-5-carbaldehyde (10.66 g, 55.51 mmol) was dissolved in MeOH (150 mL). $NaBH_4$ (2.71 g, 68.91 mmol) was added portionwise at 0 °C and the reaction mixture stirred at 0 °C for 1 h. Water (10 mL) was added and the mixture extracted with EA (3 x 70 mL). The combined org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure to give crude (2-bromo-thiazol-5-yl)-methanol as an orange oil. TLC: rf (1:1 hept-EA) = 0.25. LC-MS-conditions 01: $t_R = 0.56$ min $[M+H]^+ = 193.81$.

2-Bromo-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), (2-bromo-thiazol-5-yl)-methanol (10.65 g, 54.88 mmol) was dissolved in dry CH₂Cl₂ (150 mL). *tert*-Butyldimethylsilyl chloride (9.58 g, 60.37 mmol) was added at 0 °C followed by imidazole (7.66 g, 112.51 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water (100 mL) was added, the layers separated and the org. layer dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Purification of the residue by FC (1:0 to 30:1 hept-EA) gave the title compound as a yellow oil. TLC: rf (9:1 hept-EA) = 0.46. LC-MS-conditions 01: t_R = 1.13 min [M+H]⁺ = 309.90.

1-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-thiazol-2-yl]-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of *n*-BuLi (4.3 mL of a 2.5 M solution in hexanes, 10.75 mmol) in dry Et₂O (15 mL) was added a solution of 2-bromo-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazole (3.03 g, 9.83 mmol) in dry Et₂O (10 mL) at -78 °C. The reaction mixture was then stirred for 30 min at -78 °C before *N,N*-dimethylacetamide (1.9 mL, 20.43 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. Sat. aq. NH₄Cl (20 mL) was added, the layers separated and the aq. layer extracted with Et₂O (2 × 30 mL). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to give the title compound as an orange oil. TLC: rf (2:1 hept-EA) = 0.60. LC-MS-conditions 02: t_R = 1.14 min; [M+H]⁺ = 272.32.

(2-(2-Methyl-[1,3]dioxolan-2-yl)thiazol-5-yl)methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 1-[5-(*tert*-butyl-dimethyl-silanyloxymethyl)-thiazol-2-yl]-ethanone (1.00 g, 3.68 mmol) in ethylene glycol (4 mL) was treated with trimethylorthoformate (0.82 mL, 7.51 mmol) followed by LiBF₄ (70 mg, 0.74 mmol). The reaction mixture was heated at 95 °C for 2 days. Sat. aq. Na₂CO₃ (5 mL) was added and the mixture was extracted with Et₂O (3 × 20 mL). The org. extracts were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The crude residue (mixture of silylated/desilylated products) in dry THF (10 mL) was treated at rt with TBAF (1.1 mL of a 1M solution in THF, 1.10 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then diluted with EA, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the

residue by FC (4:1 -> 1:2 hept-EA) gave the title compound as a pale yellow solid. TLC: rf (EA) = 0.47. LC-MS-conditions 02: t_R = 0.60 min; $[M+H]^+$ = 202.46.

(2-(2-Methyl-[1,3]dioxolan-2-yl)thiazol-5-yl)methanamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of (2-(2-methyl-[1,3]dioxolan-2-yl)thiazol-5-yl)methanol (389 mg, 1.93 mmol) in dry CH_2Cl_2 (10 mL) was treated at 0 °C with Et_3N (0.35 mL, 2.50 mmol) followed by DMAP (24 mg, 0.19 mmol) and Ms-Cl (0.19 mL, 2.40 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (1:1 -> 1:2 hept-EA +1% Et_3N) gave pure (2-(2-methyl-[1,3]dioxolan-2-yl)thiazol-5-yl)methyl methanesulfonate as a pale yellow oil. Part of this material (140 mg, 0.50 mmol) was dissolved in dry DMF (1 mL) and treated with NaN_3 (35 mg, 0.53 mmol) at 80 °C for 1h30. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 5-(azidomethyl)-2-(2-methyl-[1,3]dioxolan-2-yl)thiazole as a brown oil. LC-MS-conditions 01: t_R = 0.80 min; $[M+H]^+$ = 226.96.

To a solution of the crude azide (113 mg, 0.50 mmol) in THF (6 mL) were added polymer supported Ph_3P (262 mg, 1.00 mmol) and water (2 mL). The reaction mixture was stirred at 60 °C for 1 h, cooled down to rt, filtered and concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 /MeOH 9:1, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound as an orange oil. LC-MS-conditions 02: t_R = 0.48 min.

1-(2-Bromo-thiazol-5-yl)-ethanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of commercially available 2-bromo-thiazole-5-carbaldehyde (1.96 g, 10.00 mmol) in CH_2Cl_2 (20 mL) was treated at 0 °C with trimethylaluminum (15 mL of a 2M solution in toluene, 30.00 mmol). The reaction mixture was then stirred at 0 °C for 45 min. CH_2Cl_2 (100 mL) was then added followed by sat. aq. NH_4Cl (100 mL). The mixture was then treated with 1N HCl (50 mL) and the aq. layer was extracted with CH_2Cl_2 (150 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give the title compound as an orange oil. TLC: rf (1:1 hept-EA) = 0.38. LC-MS-conditions 02: t_R = 0.70 min; $[M+H]^+$ = 208.38.

1-(2-Bromo-thiazol-5-yl)-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 1-(2-bromo-thiazol-5-yl)-ethanol (14.85 g, 71.37 mmol) in CH_3CN (160 mL) was treated at rt with MnO_2 (34.47 g, 356.84 mmol) and the reaction mixture was stirred for 20 h at rt before being filtered through Celite. The solvent was removed under reduced pressure to give the title compound as a yellow solid. TLC: rf (1:1 hept-EA) = 0.54. LC-MS-conditions 02: t_R = 0.79 min.

2-Bromo-5-(2-methyl-[1,3]dioxolan-2-yl)-thiazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and a condenser under inert atmosphere (N_2), a solution of 1-(2-bromo-thiazol-5-yl)-ethanone (16.22 g, 78.71 mmol) in ethylene glycol (85 mL) was treated with trimethylorthoformate (18 mL, 164.19 mmol) followed by $LiBF_4$ (1.51 g, 15.74 mmol). The reaction mixture was heated at 95 °C for 2 days. Sat. aq. $NaHCO_3$ was added and the mixture was extracted with Et_2O (3x). The org. extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification of the residue by FC (20:1 to 3:1 hept-EA) gave the title compound as a yellow solid. TLC: rf (1:1 hept-EA) = 0.63. LC-MS-conditions 02: t_R = 0.89 min; $[M+H]^+$ = 250.24.

5-(2-Methyl-[1,3]dioxolan-2-yl)-thiazole-2-carbaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-bromo-5-(2-methyl-[1,3]dioxolan-2-yl)-thiazole (5.00 g, 20.00 mmol) in dry Et_2O (40 mL) was added to a $n-BuLi$ (8.40 mL of a 2.5M solution in hexanes, 21.00 mmol) at -78 °C. The reaction mixture was then stirred for 30 min at -78 °C before DMF (2.5 mL, 32.29 mmol) was added dropwise. The reaction mixture was stirred at -60 °C for 1 h. Sat. aq. NH_4Cl (100 mL) was added, followed by aq. 1N HCl (50 mL). The layers separated and the aq. layer extracted with Et_2O (5x). The combined org. extracts were dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure to give the title compound as an orange oil. TLC: rf (1:1 hept-EA) = 0.50. LC-MS-conditions 01: t_R = 0.78 min; $[M+H]^+$ = 199.93.

[5-(2-Methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), 5-(2-methyl-[1,3]dioxolan-2-yl)-thiazole-2-carbaldehyde (5.12 g, 25.70 mmol) was dissolved in MeOH (60 mL). $NaBH_4$ (1.26 g, 31.89 mmol) was added portionwise at 0 °C and the reaction mixture stirred at 0 °C for 1 h. Water was added and

the mixture extracted with EA (3x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure to give the title compound as an orange oil. TLC: rf (1:1 hept-EA) = 0.31. LC-MS-conditions 02: t_R = 0.64 min; [M+H]⁺ = 202.52.

5 **(5-(2-Methyl-[1,3]dioxolan-2-yl)thiazol-2-yl)methanamine:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of [5-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methanol (500 mg, 2.48 mmol) in dry CH₂Cl₂ (15 mL) was treated at 0 °C with Et₃N (0.45 mL, 3.21 mmol) followed by DMAP (31 mg, 0.25 mmol) and Ms-Cl (0.25 mL, 3.14 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (5-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl)methyl methanesulfonate as a brown oil. This material was dissolved in dry DMF (10 mL) and treated with NaN₃ (175 mg, 2.66 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 2-(azidomethyl)-5-(2-methyl-[1,3]dioxolan-2-yl)-thiazole as a yellow oil. LC-MS-conditions 02: t_R = 0.86 min; [M+H]⁺ = 227.47.

To a solution of the crude azide (565 mg, 2.50 mmol) in THF (12 mL) were added polymer-supported Ph₃P (2.0 eq.) and water (4 mL). The reaction mixture was stirred at 60 °C until completion of the reaction, cooled down to rt, filtered and partitioned between EA and sat. aq. NaHCO₃. The layers were separated and the aq. layer extracted with EA. The combined org. extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a brown oil after purification by FC (CH₂Cl₂-MeOH 1:0 to 9:1). LC-MS-conditions 01: t_R = 0.38 min; [M+H]⁺ = 200.96.

(4-Bromothiazol-2-yl)methanamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of (4-bromo-thiazol-2-yl)-methanol (695 mg, 3.58 mmol) in dry CH₂Cl₂ (10 mL) was treated at 0 °C with Et₃N (0.67 mL, 4.74 mmol) followed by DMAP (44 mg, 0.36 mmol) and Ms-Cl (0.36 mL, 4.65 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-bromothiazol-2-yl)methyl methanesulfonate as a brown oil. The crude material was dissolved in dry DMF (6 mL)

and treated with NaN₃ (257 mg, 3.91 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 2-(azidomethyl)-4-bromothiazole as a yellow oil.

5 LC-MS-conditions 01: $t_R = 0.83$ min.

To a solution of the crude azide in THF (12 mL) were added polymer supported Ph₃P (5.16 mmol) and water (4 mL). The reaction mixture was stirred at 60 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃, the layers separated and the aq. layer extracted with EA. The combined
10 org. extracts were dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as an orange oil. LC-MS-conditions 02: $t_R = 0.24$ min; $[M+H]^+ = 192.85$.

(E)-2-Methyl-3-phenylacrylamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of alpha-methylcinnamic acid (19.0 g, 116 mmol) and Et₃N (17.1 mL, 122 mmol) in dry THF (500 mL) was treated with ethyl chloroformate (11.4 mL, 117 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min then aq. NH₃ (250 mL) in THF (150 mL) was added. The reaction mixture was vigorously stirred at 0 °C for 30 min and at rt for 1h30. The layers were then separated, the aq. layer extracted with
20 CH₂Cl₂ (2x) and the combined organic extracts were concentrated under reduced pressure. The residue was partitioned between water and CH₂Cl₂, the layers separated and the aq. layer extracted with CH₂Cl₂ (2x). The combined org. extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to give the title compound as a white solid. LC-MS-conditions 01: $t_R = 0.75$ min; $[M+H]^+ = 162.07$.

25 **(E)-2-(1-Phenylprop-1-en-2-yl)oxazole-4-carboxylic acid ethyl ester:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a suspension of (E)-2-methyl-3-phenylacrylamide (29.4 g, 0.18 mol) and NaHCO₃ (68.7 g, 0.82 mol) in THF (500 mL) was treated with 3-bromo-2-oxo-propionic acid ethyl ester (35.6 mL, 0.24 mol) and the reaction mixture was heated at reflux for 20 h.
30 3-Bromo-2-oxo-propionic acid ethyl ester (10.0 mL, 0.68 mol) was added again and the reaction mixture was stirred at reflux for 10 h. The reaction mixture was then filtered over celite and the solvents were evaporated under reduced pressure. The residue was dissolved in THF (500 mL) and treated at 0 °C, dropwise, with trifluoroacetic anhydride

(78.0 mL, 0.55 mol). The reaction mixture was then stirred at rt overnight. Sat. aq. Na_2CO_3 was added and the mixture was extracted with EA (4x), dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. Purification of the residue by FC (0:1 - > 1:9 EA-Hept) gave the title compound as a brown oil. TLC: rf (1:9 EA-Hept) = 0.13. LC-MS-conditions 01: t_R = 1.02 min; $[\text{M}+\text{H}]^+$ = 257.97.

2-Acetyl-oxazole-4-carboxylic acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of NaIO_4 (23 g, 108 mmol) in water (150 mL) was slowly added to a vigorously stirred suspension of silica gel (110 g) in acetone (500 mL). The mixture was then concentrated under reduced pressure and the lumpy solid slurried in CH_2Cl_2 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (500 mL) was added and the reaction mixture was treated at rt with (E)-2-(1-phenylprop-1-en-2-yl)oxazole-4-carboxylic acid ethyl ester (8.3 g, 32 mmol) and RuCl_3 hydrate (1.1 g, 2 mmol). The reaction mixture was stirred at rt in the dark for 60 min, filtered and concentrated under reduced pressure. Purification of the residue by FC (1:0 to 1:5 petroleum ether- Et_2O) gave the title compound as a pale yellow solid. TLC: rf (1:1 EA-Hept) = 0.52. LC-MS-conditions 01: t_R = 0.70 min; $[\text{M}+\text{H}]^+$ = 183.99.

2-(2-Methyl-[1,3]dioxolan-2-yl)-oxazole-4-carboxylic acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-acetyl-oxazole-4-carboxylic acid ethyl ester (7.0 g, 38.0 mmol) in ethylene glycol (42.7 mL) was treated with trimethylorthoformate (10.5 mL, 96.0 mmol) followed by LiBF_4 (0.73 g, 8.0 mmol). The reaction mixture was heated at 95 °C until completion of the reaction. Aq. 0.5 M Na_2CO_3 was added and the mixture was extracted with Et_2O . The org. layer was washed with aq. 0.5 M Na_2CO_3 (2x), dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 01: t_R = 0.76 min; $[\text{M}+\text{H}]^+$ = 227.99.

(2-(2-Methyl-[1,3]dioxolan-2-yl)oxazol-4-yl)methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to an ice-cold solution of 2-(2-methyl-[1,3]dioxolan-2-yl)-oxazole-4-carboxylic acid ethyl ester (5.05 g, 22.2 mmol) in dry THF (80 mL) was added an ice-cold solution of LiAlH_4 (1.0 M in THF, 24.7 mL, 24.7 mmol). The reaction mixture was stirred at 0 °C until completion of the reaction. Water (2.0 mL) was carefully added at 0 °C followed by aq. 1 M NaOH (2.0 mL) and water (2.0 mL). The resulting suspension was stirred at rt

for 1 h, filtered (+ EA) and the filtrate concentrated under reduced pressure to give the title compound as a yellow oil. TLC: rf (EA) = 0.18. LC-MS-conditions 05c: t_R = 0.22 min; $[M+H]^+$ = 186.30.

(2-(2-Methyl-[1,3]dioxolan-2-yl)oxazol-4-yl)methanamine:

- 5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of (2-(2-methyl-[1,3]dioxolan-2-yl)oxazol-4-yl)methanol (235 mg, 1.27 mmol) in dry CH_2Cl_2 (10 mL) was treated at 0 °C with Et_3N (0.24 mL, 1.68 mmol) followed by DMAP (16 mg, 0.13 mmol) and Ms-Cl (0.13 mL, 1.65 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over
- 10 $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give crude (2-(2-methyl-[1,3]dioxolan-2-yl)oxazol-4-yl)methyl methanesulfonate as a brown oil. The crude material was dissolved in dry DMF (6 mL) and treated with NaN_3 (93 mg, 1.41 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org.
- 15 layer dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 4-(azidomethyl)-2-(2-methyl-1,3-dioxolan-2-yl)oxazole as a brown oil. To a solution of the crude azide in THF (6 mL) were added polymer-supported Ph_3P (1.2 eq.) and water (2 mL). The reaction mixture was stirred at 60 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. $NaHCO_3$ and
- 20 the layers separated. The aq. layer was concentrated under reduced pressure, the residue triturated in EtOH and the solid filtered off. The filtrate was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title compound as an orange oil. LC-MS-conditions 01: t_R = 0.31 min; $[M+H]^+$ = 185.01.

(2-Bromo-thiazol-5-yl)methanamine:

- 25 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of (2-bromo-thiazol-5-yl)-methanol (621 mg, 3.20 mmol) in dry CH_2Cl_2 (10 mL) was treated at 0 °C with Et_3N (0.60 mL, 4.23 mmol) followed by DMAP (39 mg, 0.32 mmol) and Ms-Cl (0.33 mL, 4.15 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over $MgSO_4$, filtered, and the
- 30 solvents were removed under reduced pressure to give crude (2-bromothiazol-5-yl)methyl methanesulfonate as a colorless oil. The crude material was dissolved in dry DMF (15 mL) and treated with NaN_3 (223 mg, 3.40 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer washed with water (2x), dried over $MgSO_4$,

filtered and concentrated under reduced pressure to give crude 5-(azidomethyl)-2-bromothiazole as a yellow oil. To a solution of the crude azide in THF (12 mL) were added polymer-supported Ph_3P (1.2 eq.) and water (4 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was
5 partitioned between EA and aq. 1N NaOH/aq. sat. NaHCO_3 and the layers separated. The aq. layer was extracted with EA and the combined org. extracts dried over MgSO_4 , filtered and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 01: $t_R = 0.16$ min; $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+ = 233.91$.

(E)-2-Styryl-oxazole-4-carboxylic acid ethyl ester:

10 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a suspension of 3-phenyl-acrylamide (10.31 g, 67.95 mmol) and NaHCO_3 (28.47 g, 339.73 mmol) in THF (260 mL) was treated with 3-bromo-2-oxo-propionic acid ethyl ester (13.04 mL, 88.33 mmol) and the reaction mixture was heated at reflux for 15 h. 3-Bromo-2-oxo-propionic acid ethyl ester (13.04 mL, 88.33 mmol) was
15 added again and the reaction mixture was stirred at reflux for 15 h. The reaction mixture was then filtered over celite and the solvents were evaporated under reduced pressure. The residue was dissolved in THF (30 mL) and treated at 0 °C, dropwise, with trifluoroacetic anhydride (30.0 mL, 215.83 mmol). The reaction mixture was then stirred at rt overnight. Sat. aq. Na_2CO_3 was added and the mixture was extracted with EA (3×150
20 mL), dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. Purification of the residue by FC (1:9 EA–Hept) gave the title compound as a yellow solid. TLC: rf (1:9 EA–Hept) = 0.1. LC-MS-conditions 02: $t_R = 1.01$ min; $[\text{M}+\text{H}]^+ = 244.48$.

2-Formyl-oxazole-4-carboxylic acid ethyl ester:

25 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of NaIO_4 (3.21 g, 15.00 mmol) in water (26.0) mL was slowly added to a vigorously stirred suspension of silica gel (15.0 g) in acetone (60.0 mL). The mixture was then concentrated under reduced pressure and the lumpy solid slurried in CH_2Cl_2 and the solvent was evaporated under reduced pressure. CH_2Cl_2 (40.0 mL) was added and the reaction mixture was treated at rt with (E)-2-styryl-oxazole-4-carboxylic acid ethyl ester (1.22 g, 5.00 mmol) and RuCl_3 hydrate (82 mg, 0.15 mmol). The reaction
30 mixture was stirred at rt in the dark for 30 min, filtered and concentrated under reduced pressure. Purification of the residue by FC (1:9 to 1:2 EA–Hept) gave the title compound as a yellow solid. TLC: rf (3:2 EA–Hept) = 0.21. LC-MS-conditions 02: $t_R = 0.51$ min; $[\text{M}+\text{H}_2\text{O}+\text{H}]^+ = 188.50$.

2-Hydroxymethyl-oxazole-4-carboxylic acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), 2-formyl-oxazole-4-carboxylic acid ethyl ester (272 mg, 1.61 mmol) was dissolved in EtOH (5.0 mL). $NaBH_4$ (112 mg, 2.84 mmol) was added portionwise at 0 °C and the reaction mixture stirred at 0 °C for 1 h. Sat. aq. NH_4Cl was added and the mixture extracted with EA (5×10 mL). The combined org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure to give the title compound as a yellow oil. TLC: rf (EA) = 0.50. LC-MS-conditions 02: t_R = 0.58 min; $[M+H]^+$ = 172.03.

10 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-oxazole-4-carboxylic acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), 2-hydroxymethyl-oxazole-4-carboxylic acid ethyl ester (275 mg, 1.61 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL). *tert*-Butyldimethylsilyl chloride (510 mg, 3.22 mmol) was added at rt followed by imidazole (221 mg, 3.22 mmol). The reaction mixture was stirred at rt for 30 min. Water was added, the layers were separated and the org. layer was dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure. Purification of the residue by FC (1:20 to 1:9 EA–Hept) gave the title compound as a colorless oil. TLC: rf (9:1 hept–EA) = 0.15. LC-MS-conditions 02: t_R = 1.10 min; $[M+H]^+$ = 286.38.

20 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-oxazole-4-carbaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-oxazole-4-carboxylic acid ethyl ester (283 mg, 0.99 mmol) in CH_2Cl_2 (5.0 mL) was treated at -78 °C with DIBAL (1.85 mL of a 1M sol in toluene, 1.85 mmol) and the reaction mixture was stirred for 1 h at -78 °C. MeOH (70 μ L) and H_2O (100 μ L) were added and the reaction mixture was allowed to warm to rt. The reaction mixture was filtered, and the solvent removed under reduced pressure to give the title compound as a colorless oil. TLC: rf (1:1 hept–EA) = 0.61. LC-MS-conditions 02: t_R = 1.03 min; $[M+H_2O+H]^+$ = 260.50.

1-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-oxazol-4-yl]-ethanol:

30 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-oxazole-4-carbaldehyde (223 mg, 0.92 mmol) in CH_2Cl_2 (8.0 mL) was treated at 0 °C with trimethylaluminum (2.50 mL of a 2M solution in toluene, 5.00 mmol). The reaction mixture

was then stirred at 0 °C for 45 min. Sat. aq. NH₄Cl was then added and the aq. layer was extracted twice with CH₂Cl₂ and twice with EA. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure to give the title compound as a colorless oil. TLC: rf (1:1 hept-EA) = 0.32. LC-MS-conditions 02: t_R = 0.97 min, [M+H]⁺ = 258.30.

1-[2-(*tert*-Butyl-dimethyl-silyloxymethyl)-oxazol-4-yl]-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 1-[2-(*tert*-butyl-dimethyl-silyloxymethyl)-oxazol-4-yl]-ethanol (193 mg, 0.75 mmol) in AcCN (5.0 mL) was treated at rt with MnO₂ (362 mg, 3.75 mmol). The reaction mixture was stirred for 16 h at rt before being filtered through Celite. The solvent was removed under reduced pressure to give the title compound as a white solid. TLC: rf (1:1 hept-EA) = 0.69. LC-MS-conditions 02: t_R = 1.04 min, [M+H]⁺ = 255.84.

2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-(2-methyl-[1,3]dioxolan-2-yl)oxazole:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 1-[2-(*tert*-butyl-dimethyl-silyloxymethyl)-oxazol-4-yl]-ethanone (3.82 g, 14.96 mmol) in ethylene glycol (16 mL) was treated with trimethylorthoformate (3.35 mL, 30.51 mmol) followed by LiBF₄ (0.29 g, 2.99 mmol). The reaction mixture was heated at 95 °C until completion of the reaction. Aq. 0.5 M Na₂CO₃ was added and the mixture was extracted with Et₂O. The org. layer was washed with aq. 0.5 M Na₂CO₃ (2×), dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to give the title compound as a brown oil. LC-MS-conditions 01: t_R = 1.03 min; [M+H]⁺ = 300.08.

(4-(2-Methyl-[1,3]dioxolan-2-yl)-oxazol-2-yl)-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-(2-methyl-[1,3]dioxolan-2-yl)oxazole (3.50 g, 11.69 mmol) in dry THF (70 mL) was treated at 0 °C with TBAF (15.2 mL of a 1M solution in THF, 15.20 mmol). The reaction mixture was stirred at 0 °C for 1 h. Sat. aq. NH₄Cl was added, the layers separated and the aq. layer extracted with EA. The combined org. extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by FC (2:3 to 1:0 EA-Hept) gave the title compound as a pale yellow oil. TLC: rf (EA) = 0.20. LC-MS-conditions 01: t_R = 0.45 min, [M+H]⁺ = 186.00.

(4-(2-Methyl-[1,3]dioxolan-2-yl)-oxazol-2-yl)methanamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of (4-(2-methyl-[1,3]dioxolan-2-yl)-oxazol-2-yl)-methanol (230 mg, 1.24 mmol) in dry CH₂Cl₂ (10 mL) was treated at 0 °C with Et₃N (0.23 mL, 1.64 mmol) followed by DMAP (15 mg, 0.12 mmol) and Ms-Cl (0.13 mL, 1.61 mmol). After stirring at 0 °C for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-(2-methyl-[1,3]dioxolan-2-yl)oxazol-2-yl)methyl methanesulfonate as a colorless oil. The crude material was dissolved in dry DMF (6 mL) and treated with NaN₃ (93 mg, 1.41 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 2-(azidomethyl)-4-(2-methyl-[1,3]dioxolan-2-yl)oxazole as a colorless oil. To a solution of the crude azide in THF (9 mL) were added polymer-supported Ph₃P (1.4 eq.) and water (3 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃ and the layers separated. The aq. layer was concentrated under reduced pressure, the residue triturated in EtOH and the solid filtered off. The filtrate was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as an orange oil. LC-MS-conditions 01: t_R = 0.22 min; [M+H]⁺ = 185.00.

4-Chloromethyl-thiazole-2-carboxylic acid ethyl ester:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of amino-thioxo-acetic acid ethyl ester (7.29 g, 54.74 mmol) in toluene (58 mL) was treated with 1,3-dichloroacetone (8.41 g, 62.95 mmol). The resulting mixture was stirred at reflux for 2 h. EA (60 mL) was added and the org. layer was washed with sat. aq. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (70:30 hept-EA) gave the title compound as an orange oil. TLC: rf (4:1 hept-EA) = 0.26. LC-MS-conditions 02: t_R = 0.89 min; [M+H]⁺ = 206.45.

(4-Chloromethyl-thiazol-2-yl)-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-chloromethyl-thiazole-2-carboxylic acid ethyl ester (8.51 g, 41.38 mmol) in THF (413 mL) was treated at -78 °C with DiBAL (124 mL of a 1M sol in THF, 124 mmol) and the reaction mixture was stirred for 1 h at -78 °C. The mixture was

then allowed to warm up to rt and poured into a Rochelle's salt solution. After stirring for 1 h, the layers were separated and the aq. layer extracted with EA. The combined org. extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by FC (hept-EA) gave the title compound as a yellow oil.

5 TLC: rf (1:1 hept-EA) = 0.29. LC-MS-conditions 02: t_R = 0.59 min; $[\text{M}+\text{H}]^+$ = 164.08.

(4-Chloromethyl-thiazol-2-yl)-carbaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of (4-chloromethyl-thiazol-2-yl)-methanol (4.20 g, 25.67 mmol) in CH_3CN (257 mL) was treated at rt with MnO_2 (18.60 g, 192.55 mmol). The reaction

10 mixture was stirred at rt until completion of the reaction, and then filtered through Celite. The solvent was removed under reduced pressure to give the title compound as a pale yellow oil after purification by FC (hept-EA 4:1). TLC: rf (4:1 hept-EA) = 0.37. LC-MS-conditions 02: t_R = 0.77 min, $[\text{M}+\text{H}_2\text{O}+\text{H}]^+$ = 180.56.

1-(4-Chloromethyl-thiazol-2-yl)-ethanol:

15 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of (4-chloromethyl-thiazol-2-yl)-carbaldehyde (2.00 g, 12.37 mmol) in CH_2Cl_2 (124 mL) was treated at 0 °C with trimethylaluminum (62 mL of a 1M solution in heptane, 62.00 mmol). The reaction mixture was then stirred at 0 °C for 45 min. Sat. aq. NH_4Cl and aq. 1N HCl were then added and the aq. layer was extracted twice

20 with CH_2Cl_2 . The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 02: t_R = 0.66 min, $[\text{M}+\text{H}]^+$ = 178.54.

1-(4-Chloromethyl-thiazol-2-yl)-ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert

25 atmosphere (N_2), a solution of 1-(4-chloromethyl-thiazol-2-yl)-ethanol (2.19 g, 12.31 mmol) in CH_3CN (122 mL) was treated at rt with MnO_2 (5.94 g, 61.52 mmol). The reaction mixture was stirred at rt until completion of the reaction, and then filtered through Celite. The solvent was removed under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 02: t_R = 0.84 min.

30 **(2-Acetyl-thiazol-4-yl)-methanamine:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 1-(4-chloromethyl-thiazol-2-yl)-ethanone (1.08 g, 6.13 mmol) in dry DMF (21 mL) and treated with NaN_3 (1.20 g, 18.39 mmol) at 65 °C until

completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO_4 , filtered and concentrated under reduced pressure to give crude 1-(4-(azidomethyl)-thiazol-2-yl)-ethanone as a yellow oil. To a solution of the crude azide (200 mg, 1.10 mmol) in THF (6 mL) were added polymer-supported Ph_3P (2.0 eq.) and water (2 mL). The reaction mixture was stirred at 60 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO_3 and the layers separated. The org. layer was dried over MgSO_4 , filtered and concentrated under reduced pressure to give the title compound as a brown oil after purification by FC (CH_2Cl_2 -MeOH- Et_3N). LC-MS-conditions 01: t_R = 0.26 min; $[\text{M}+\text{H}]^+ = 157.04$.

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

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of 3-bromo-acetophenone (2.11 g, 10.60 mmol) in ethylene glycol (12 mL) was treated with trimethylorthoformate (2.3 mL, 21.02 mmol) followed by LiBF_4 (204 mg, 2.13 mmol). The reaction mixture was heated at 95 °C for 18 h. Sat. aq. Na_2CO_3 was added and the mixture was extracted twice with ether and the combined organic extracts were dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Purification of the residue by FC (20:1 hept-EA) gave the title compound as a pale yellow oil. TLC: rf (9:1 hept-EA) = 0.41. LC-MS-conditions 02: t_R = 1.01 min.

3-(2-Methyl-[1,3]dioxolan-2-yl)-benzaldehyde:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 2-(3-bromo-phenyl)-2-methyl-[1,3]dioxolane (2.37 g, 9.74 mmol) in THF (20.0 mL) at -78 °C was added dropwise *n*-BuLi (4 mL of a 2.5M solution in hexane, 10.00 mmol). The reaction mixture was then stirred for 30 min at -78 °C before DMF (1.0 mL, 12.92 mmol) was added dropwise. The reaction mixture was allowed to warm to rt over 1 h. Sat. aq. NH_4Cl was added and the mixture was extracted three times with Et_2O . The combined org. extracts were dried over NaSO_4 , filtered, and the solvent was removed under reduced pressure to give the crude title compound as a pale yellow oil. LC-MS-conditions 02: t_R = 0.87 min.

[3-(2-Methyl-[1,3]dioxolan-2-yl)-phenyl]-methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a ice-cold solution of 3-(2-methyl-[1,3]dioxolan-2-yl)-benzaldehyde

(1.84 g, 9.59 mmol) in MeOH (20 mL) was added NaBH₄ (456 mg, 12.05 mmol in four portions). The reaction mixture was then stirred for 1 h at 0 °C. Water was added and the mixture was extracted twice with EA. The combined org. extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to give the title compound as a pale yellow oil. TLC: rf (4:1 hept-EA) = 0.12. LC-MS-conditions 02: t_R = 0.74 min.

(3-(2-Methyl-[1,3]dioxolan-2-yl)-phenyl)methanamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of [3-(2-methyl-[1,3]dioxolan-2-yl)-phenyl]-methanol (1.68 g, 8.65 mmol) in dry CH₂Cl₂ (20 mL) was treated at 0 °C with Et₃N (1.60 mL, 11.38 mmol) followed by DMAP (109 mg, 0.88 mmol) and Ms-Cl (0.80 mL, 10.13 mmol). After stirring at 0 °C for 0.5 h, the reaction was quenched with water (10 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The crude residue was purified by FC (hept-EA 9:1 to 0:1) to give pure (3-(2-methyl-[1,3]dioxolan-2-yl)-phenyl)methyl methanesulfonate as a white solid. Part of this material (300 mg, 1.10 mmol) was dissolved in dry DMF (5 mL) and treated with NaN₃ (220 mg, 3.35 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 3-(azidomethyl)-(2-methyl-[1,3]dioxolan-2-yl)-benzene as a yellow oil. LC-MS-conditions 02: t_R = 0.99 min.

A mixture of the crude azide (194 mg, 0.88 mmol) in MeOH (5 mL) was hydrogenated in the presence of Pd/C (10%) at rt until completion of the reaction. The reaction mixture was filtered and concentrated under reduced pressure to give the title compound as a pale yellow solid. LC-MS-conditions 02: t_R = 0.59 min; [M+H]⁺ = 194.64.

(4-Bromo-2,6-difluorophenyl)-methanamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-2,6-difluorobenzyl alcohol (1.00 g, 4.48 mmol) in dry CH₂Cl₂ (20 mL) was treated at 0 °C with Et₃N (0.81 mL, 5.79 mmol) followed by DMAP (55 mg, 0.45 mmol) and Ms-Cl (0.37 mL, 4.71 mmol). After stirring at 0 °C for 0.5 h and at rt for 1 h, the reaction was quenched with water (10 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-bromo-2,6-difluorophenyl)methyl methanesulfonate as a yellow oil. This material was

dissolved in dry DMF (6 mL) and treated with NaN₃ (93 mg, 1.41 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 1-(azidomethyl)-4-bromo-2,6-difluorobenzene as a yellow oil. LC-MS-conditions 01: t_R = 1.00 min.

To a mixture of the crude azide (330 mg, 1.33 mmol) in THF (12 mL) were added polymer-supported Ph₃P (2.0 eq.) and water (2 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃ and the layers separated. The aq. layer was extracted with EA and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a yellow solid. LC-MS-conditions 02: t_R = 0.54 min; [M+CH₃CN+H]⁺ = 263.45.

4-Bromo-3-fluorobenzylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-3-fluorobenzoic acid (250 mg, 1.14 mmol) in dry THF (5 mL) was treated at 0 °C with Et₃N (0.16 mL, 1.14 mmol) and ethyl chloroformate (0.11 mL, 1.14 mmol). The reaction mixture was stirred at 0 °C for 15 min then aq. NH₃ (3 mL) was added. The reaction mixture was vigorously stirred at 0 °C for 30 min and at rt for 2 h and then concentrated under reduced pressure. The residue was partitioned between water and CH₂Cl₂, the layers separated and the aq. layer extracted with CH₂Cl₂ (2x). The combined org. extracts were dried (MgSO₄), filtered and concentrated under reduced pressure. The crude residue was purified by FC (EA-MeOH 1:0 to 10:1) and the corresponding carboxamide obtained as a white solid. TLC: rf (9:1 EA-MeOH) = 0.40. LC-MS-conditions 01: t_R = 0.73 min; [M+H]⁺ = 217.83.

Part of this material (150 mg, 0.69 mmol) was dissolved in dry THF (5 mL) and treated with BH₃.Me₂S complex (1.0 M in THF, 1.6 mL, 1.60 mmol) at 0 °C. The reaction mixture was then warmed to 50 °C and stirred at this temperature until completion of the reaction. The mixture was cooled to 0 °C and water was added followed by EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a white solid. LC-MS-conditions 07: t_R = 0.33 min; [M+CH₃CN+H]⁺ = 245.12.

1,4-Dibromo-2,3-difluorobenzene:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of lithium diisopropylamide (11.25 mmol) in dry THF (8 mL) was added a mixture of 1,3-difluorobenzene (600 mg, 5.26 mmol) and Me₃SiCl (1.48 mL, 11.57 mmol) at -78 °C. After stirring at -78 °C for 75 min, the reaction was quenched by the addition of aq. 1M H₂SO₄. The mixture was warmed to rt, diluted with TBME and saturated with solid NaCl. The layers were separated and the aq. layer extracted with TBME. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (2,3-difluoro-1,4-phenylene)-bis(trimethylsilane) as a white solid. This material (1.33 g, 5.15 mmol) was treated with bromine (1.06 mL, 20.58 mmol) at 0 °C. The reaction mixture was then warmed to 58 °C and stirred at this temperature until completion of the reaction. The reaction mixture was then cooled down to 0 °C and an ice-cold sat. NaHCO₃ solution was carefully added. The mixture was then extracted with TBME (2x) and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give 1,4-dibromo-2,3-difluorobenzene as a colorless oil after distillation (0.05 mbar, 90 °C). LC-MS-conditions 07: t_R = 0.93 min.

4-Bromo-2,3-difluorobenzyl alcohol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 1,4-dibromo-2,3-difluorobenzene (490 mg, 1.80 mmol) in dry Et₂O (6 mL) was added to a *n*-BuLi (0.72 mL of a 2.5M solution in hexanes, 1.80 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h before solid CO₂ was added. The reaction mixture was stirred at -78 °C for 10 min and then allowed to warm up to rt. The mixture was then diluted with EA and aq. 1N HCl was added. The layers separated and the org. layer dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give the crude carboxylic acid as a pale yellow solid. The crude material (360 mg, 1.52 mmol) was dissolved in dry THF (7 mL) and treated with BH₃.Me₂S complex (1.0 M in THF, 3.0 mL, 3.00 mmol) at 0 °C. The reaction mixture was then warmed to 50 °C and stirred at this temperature until completion of the reaction. The mixture was cooled to 0 °C and water was added followed by EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure.

The crude residue was purified by FC (hept-EA 9:1 to 2:1) to give the title compound as a colorless oil. TLC: r_f (1:1 EA-hept) = 0.50.

4-Bromo-2,3-difluorobenzylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-2,3-difluorobenzyl alcohol (175 mg, 0.70 mmol) in dry CH₂Cl₂ (2 mL) was treated at 0 °C with Et₃N (0.14 mL, 1.01 mmol) followed by DMAP (10 mg, 0.08 mmol) and Ms-Cl (0.06 mL, 0.82 mmol). After stirring at 0 °C for 0.5 h and at rt for 1 h, the reaction was quenched with water (2 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-bromo-2,3-difluorophenyl)methyl methanesulfonate as a yellow oil. This material was dissolved in dry DMF (3 mL) and treated with NaN₃ (46 mg, 0.71 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 1-(azidomethyl)-4-bromo-2,3-difluorobenzene as a colorless oil. LC-MS-conditions 07: t_R = 0.89 min.

To a mixture of the crude azide (164 mg, 0.60 mmol) in THF (3 mL) were added polymer-supported Ph₃P (2.0 eq.) and water (1 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃ and the layers separated. The aq. layer was extracted with EA and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 07: t_R = 0.42 min; $[M+CH_3CN+H]^+$ = 263.15.

4-Bromo-3,5-difluorobenzyl alcohol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-3,5-difluoroiodobenzene (790 mg, 2.48 mmol) in dry Et₂O (12 mL) was added to a *n*-BuLi (0.98 mL of a 2.5M solution in hexanes, 2.45 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h before solid CO₂ was added. The reaction mixture was stirred at -78 °C for 10 min and then allowed to warm up to rt. The mixture was then diluted with EA and aq. 1N HCl was added. The layers separated and the org. layer dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give the crude carboxylic acid as a pale yellow solid. The crude material (270 mg, 1.14 mmol) was dissolved in dry THF (6 mL) and treated with BH₃.Me₂S

complex (1.0 M in THF, 2.3 mL, 2.30 mmol) at 0 °C. The reaction mixture was then warmed to 50 °C and stirred at this temperature until completion of the reaction. The mixture was cooled to 0 °C and water was added followed by EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 9:1 to 2:1) to give the title compound as a white solid. TLC: rf (1:1 EA-hept) = 0.53.

4-Bromo-3,5-difluorobenzylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-3,5-difluorobenzyl alcohol (100 mg, 0.45 mmol) in dry CH₂Cl₂ (3 mL) was treated at 0 °C with Et₃N (0.081 mL, 0.58 mmol) followed by DMAP (5 mg, 0.045 mmol) and Ms-Cl (0.037 mL, 0.47 mmol). After stirring at 0 °C for 0.5 h and at rt for 0.5 h, the reaction was quenched with water (2 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-bromo-3,5-difluorophenyl)methyl methanesulfonate as a yellow oil. This material was dissolved in dry DMF (3 mL) and treated with NaN₃ (29 mg, 0.45 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 1-(azidomethyl)-4-bromo-3,5-difluorobenzene as a yellow oil. LC-MS-conditions 07: t_R = 0.90 min.

To a mixture of the crude azide (70 mg, 0.28 mmol) in THF (4 mL) were added polymer-supported Ph₃P (3.0 eq.) and water (1 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃ and the layers separated. The aq. layer was extracted with EA and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 07: t_R = 0.37 min; [M+CH₃CN+H]⁺ = 263.15.

4-Bromo-2,5-difluorobenzyl alcohol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 1,4-dibromo-2,5-difluorobenzene (600 mg, 2.21 mmol) in dry Et₂O (8 mL) was added to a *n*-BuLi (0.88 mL of a 2.5M solution in hexanes, 2.20 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h before solid CO₂ was

added. The reaction mixture was stirred at -78 °C for 10 min and then allowed to warm up to rt. The mixture was then diluted with EA and aq. 1N HCl was added. The layers separated and the org. layer dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give the crude carboxylic acid as a pale yellow solid. The crude material (530 mg, 2.24 mmol) was dissolved in dry THF (20 mL) and treated with BH₃.Me₂S complex (1.0 M in THF, 4.5 mL, 4.50 mmol) at 0 °C. The reaction mixture was then warmed to 50 °C and stirred at this temperature until completion of the reaction. The mixture was cooled to 0 °C and water was added followed by EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 3:1 to 1:1) to give the title compound as a white solid. TLC: rf (1:1 EA-hept) = 0.53.

4-Bromo-2,5-difluorobenzylamine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 4-bromo-2,5-difluorobenzyl alcohol (160 mg, 0.72 mmol) in dry CH₂Cl₂ (4 mL) was treated at 0 °C with Et₃N (0.13 mL, 0.93 mmol) followed by DMAP (9 mg, 0.07 mmol) and Ms-Cl (0.06 mL, 0.75 mmol). After stirring at 0 °C for 0.5 h and at rt for 1 h, the reaction was quenched with water (3 mL). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude (4-bromo-2,5-difluorophenyl)methyl methanesulfonate as a yellow oil. This material was dissolved in dry DMF (3 mL) and treated with NaN₃ (51 mg, 0.78 mmol) at 80 °C until completion of the reaction. The reaction mixture was then cooled down to rt and partitioned between EA and water. The layers were separated and the org. layer dried over MgSO₄, filtered and concentrated under reduced pressure to give crude 1-(azidomethyl)-4-bromo-2,5-difluorobenzene as a yellow oil. LC-MS-conditions 07: t_R = 0.89 min.

To a mixture of the crude azide (110 mg, 0.44 mmol) in THF (3 mL) were added polymer-supported Ph₃P (3.0 eq.) and water (1.5 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. sat. NaHCO₃ and the layers separated. The aq. layer was extracted with EA and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 07: t_R = 0.40 min; [M+CH₃CN+H]⁺ = 263.14.

5-Amino-2-bromo-3-fluoropyridine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of 3-amino-5-fluoropyridine (900 mg, 8.03 mmol) in dry DMF
5 (13 mL) was treated at 0 °C with *N*-bromo-succinimide (1.43 g, 8.03 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then partitioned between Et₂O and water. The layers were separated and the org. layer successively washed with water, sat. aq. NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 9:1
10 to 1:1) and the title compound obtained as an orange solid. LC-MS-conditions 07: t_R = 0.52 min; [M+H]⁺ = 191.30.

4-(Azetidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of trimethylene imine (300 mg, 5.25 mmol) and DBU (0.79
15 mL, 5.23 mmol) in dry Et₂O (4 mL) was added 4-bromobutyronitrile (0.54 mL, 5.27 mmol) at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. The mixture was filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (4 mL) and treated with LiAlH₄ (230 mg, 6.06 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction.
20 Aq. 1N NaOH (2 mL) was then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure to give crude 4-(azetidin-1-yl)butan-1-amine as a pale yellow oil. GC-MS-conditions 01: t_R = 1.35 min; [M+H]⁺ = 129.00.

25 2-(2-(Pyrrolidin-1-yl)ethoxy)ethanamine hydrochloride:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of 2-(2-aminoethoxy)ethanol (536 mg, 5.00 mmol) in THF (3 mL) was added aq. 2M NaOH (2.6 mL, 5.20 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and a solution of di-*tert*-butyl dicarbonate (1.16 g, 5.20 mmol) in
30 THF (3 mL) was then added dropwise. The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was diluted with CH₂Cl₂, filtered and the layers separated. The organic layer was dried over Na₂SO₄, filtered, and

the solvents were removed under reduced pressure. The crude alcohol was redissolved in dry CH_2Cl_2 (20 mL) and treated with triphenylphosphine on polystyrene (5.63 mmol) and imidazole (190 mg, 2.76 mmol). To this mixture cooled to 0 °C was added iodine (808 mg, 3.15 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, CH_2Cl_2 removed under reduced pressure. The residue was redissolved in EA, successively washed with 10% aq. Na_2SO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude iodide was redissolved in CH_3CN (15 mL) and treated with pyrrolidine (0.17 mL, 1.99 mmol) and K_2CO_3 (465 mg, 3.36 mmol). The reaction mixture was stirred at rt until completion of the reaction, filtered and concentrated under reduced pressure. The amine was purified by FC (hept-EA-acetone, 1:0:0 -> 0:0:1) and then the Boc group was removed by treatment with HCl (4.0 M in dioxane, 10 eq.) in dry CH_2Cl_2 (3 mL). The title compound was obtained after trituration in hot EA/acetone/MeOH as a beige solid. LC-MS-conditions 01: t_R = 0.13 min; $[\text{M}+\text{H}]^+$ = 159.11.

(3R,6S)-6-(Pyrrolidin-1-ylmethyl)tetrahydro-2H-pyran-3-amine hydrochloride:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to an ice-cold solution of (3R,6S)-6-hydroxymethyl-tetrahydro-2H-pyran-3-yl carbamic acid *tert*-butyl ester (328 mg, 1.40 mmol, H. S. Overkleeft *et al.* *Eur. J. Org. Chem.* **2003**, 2418), triphenylphosphine on polystyrene (6.16 mmol) and imidazole (203 mg, 2.95 mmol) in dry CH_2Cl_2 (14 mL) was added iodine (891 mg, 3.48 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, CH_2Cl_2 removed under reduced pressure. The residue was redissolved in EA, successively washed with 10% aq. Na_2SO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. After purification by FC, the iodide was redissolved in CH_3CN (15 mL) and treated with pyrrolidine (1.13 mL, 13.57 mmol) and K_2CO_3 (750 mg, 5.43 mmol). The reaction mixture was stirred at 85 °C until completion of the reaction, filtered and concentrated under reduced pressure. The amine was purified by FC (hept-EA-acetone, 1:0:0 -> 0:0:1) and then the Boc group was removed by treatment with HCl (4.0 M in dioxane, 9 eq.) in dry CH_2Cl_2 (2 mL). The title compound was obtained after trituration in hot EA/acetone/MeOH as an off-white solid. LC-MS-conditions 01: t_R = 0.15 min; $[\text{M}+\text{H}]^+$ = 185.06.

1-(4-(4-Aminobutyl)piperazin-1-yl)ethanone:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert

atmosphere (N₂), to a solution of 1-acetylpiperazine (256 mg, 2.00 mmol) and DBU (0.30 mL, 2.00 mmol) in dry Et₂O (2 mL) was added 4-bromobutyronitrile (0.21 mL, 2.00 mmol) at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. The mixture was filtered and concentrated under reduced pressure. A 0.087 mol/L solution of the crude nitrile in EtOH (10 mL) was hydrogenated at 50 °C using the H-Cube® (1 mL/min) with a Raney Nickel cartridge (30 mm) under 50 bar until completion of the reaction. The solution was then concentrated under reduced pressure to give crude 1-(4-(4-aminobutyl)piperazin-1-yl)ethanone as a colorless oil. GC-MS-conditions 01: t_R = 2.94 min; [M+H]⁺ = 200.40.

10 ***cis*-4-Benzylloxycarbonylaminocyclohexane-methanol:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of *cis*-4-benzylloxycarbonylaminocyclohexanecarboxylic acid (417 mg, 1.50 mmol) in THF (15 mL) was added BH₃.Me₂S complex (2.0 M in THF, 1.5 mL, 3.00 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h30. More BH₃.Me₂S complex (2.0 M in THF, 1.0 mL, 2.00 mmol) was added at 0 °C followed by NaBH₄ (12 mg, 0.30 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. MeOH was carefully added to quench the reaction, the volatiles were removed under reduced pressure and the residue co-evaporated with MeOH (2x). Purification by FC (hept-EA, 1:0 -> 3:2) gave pure *cis*-4-benzylloxycarbonylaminocyclohexane-methanol as a colorless oil. TLC: rf (1:2 hept-EA) = 0.45. LC-MS-conditions 01: t_R = 0.82 min; [M+H]⁺ = 264.07.

***cis*-4-(Pyrrolidin-1-ylmethyl)cyclohexanamine:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to an ice-cold solution of *cis*-4-benzylloxycarbonylaminocyclohexane-methanol (267 mg, 1.01 mmol), triphenylphosphine on polystyrene (3.20 mmol) and imidazole (97 mg, 1.42 mmol) in dry CH₂Cl₂ (40 mL) was added iodine (416 mg, 1.62 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, successively washed with 10% aq. Na₂SO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude iodide was redissolved in CH₃CN (15 mL) and treated with pyrrolidine (0.32 mL, 3.86 mmol) and K₂CO₃ (533 mg, 3.86 mmol). The reaction mixture was refluxed until completion of the reaction, filtered and concentrated under reduced pressure. The amine was purified by FC (hept-EA, 1:0 -> 1:1) and then the Cbz group was removed by

treatment with 10% Pd/C (116 mg) in EtOH (20 mL) under a H₂ atmosphere. The title compound was obtained as a white solid. LC-MS-conditions 04: t_R = 0.99 min; [M+H]⁺ = 183.35.

***trans*-4-Benzylloxycarbonylaminocyclohexane-methanol:**

- 5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of *trans*-4-benzylloxycarbonylaminocyclohexanecarboxylic acid (417 mg, 1.50 mmol) in THF (15 mL) was added BH₃.Me₂S complex (2.0 M in THF, 1.5 mL, 3.00 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1h30. More BH₃.Me₂S complex (2.0 M in THF, 1.0 mL, 2.00 mmol) was added at 0 °C followed by
- 10 NaBH₄ (12 mg, 0.30 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. MeOH was carefully added to quench the reaction, the volatiles were removed under reduced pressure and the residue co-evaporated with MeOH (2x). Purification by FC (hept-EA, 1:0 -> 3:2) gave pure *trans*-4-benzylloxycarbonylaminocyclohexane-methanol as a white solid. TLC: rf (1:2 hept-EA) =
- 15 0.35. LC-MS-conditions 01: t_R = 0.82 min; [M+H]⁺ = 264.05.

***trans*-4-(Pyrrolidin-1-ylmethyl)cyclohexanamine:**

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to an ice-cold solution of *trans*-4-benzylloxycarbonylaminocyclohexane-methanol (292 mg, 1.11 mmol), triphenylphosphine on polystyrene (3.52 mmol) and
- 20 imidazole (107 mg, 1.55 mmol) in dry CH₂Cl₂ (40 mL) was added iodine (455 mg, 1.77 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, successively washed with 10% aq. Na₂SO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude iodide was redissolved in CH₃CN (15 mL) and treated with pyrrolidine
- 25 (0.34 mL, 4.09 mmol) and K₂CO₃ (566 mg, 4.09 mmol). The reaction mixture was refluxed until completion of the reaction, filtered and concentrated under reduced pressure. The amine was purified by FC (hept-EA, 1:0 -> 1:1) and then the Cbz group was removed by treatment with 10% Pd/C (147 mg) in MeOH (10 mL) under a H₂ atmosphere. The title compound was obtained as a colorless oil. LC-MS-conditions 07d: t_R = 0.97 min; [M+H]⁺ =
- 30 183.37.

(R)-4-(3-Fluoropyrrolidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (*R*)-3-fluoropyrrolidine hydrochloride (400 mg, 3.09 mmol) and 4-bromobutyronitrile (0.32 mL, 3.09 mmol) in dry CH_3CN (16 mL) was added
5 K_2CO_3 (2.35 g, 16.99 mmol) at rt followed by KI (51 mg, 0.31 mmol). The reaction mixture was stirred at rt for 15 h. The mixture was filtered and the filtrate partitioned between water and CH_2Cl_2 . The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (23 mL) and treated with
10 $LiAlH_4$ (214 mg, 5.47 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction. Aq. 1N NaOH (7 mL) was then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure to give crude (*R*)-4-(3-fluoropyrrolidin-1-yl)butan-1-amine as a colorless oil. GC-MS-conditions 01: t_R = 1.71 min; $[M+H]^+$ = 161.10.

(S)-4-(3-Fluoropyrrolidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (*S*)-3-fluoropyrrolidine hydrochloride (200 mg, 1.54 mmol) and 4-bromobutyronitrile (0.16 mL, 1.54 mmol) in dry CH_3CN (8 mL) was added
20 K_2CO_3 (1.17 g, 8.50 mmol) at rt followed by KI (26 mg, 0.15 mmol). The reaction mixture was stirred at rt for 15 h. The mixture was filtered and the filtrate partitioned between water and CH_2Cl_2 . The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (10 mL) and treated with
25 $LiAlH_4$ (92 mg, 2.35 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction. Aq. 1N NaOH (3 mL) was then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure to give crude (*S*)-4-(3-fluoropyrrolidin-1-yl)butan-1-amine as a yellow oil. GC-MS-conditions 01: t_R = 1.70 min; $[M+H]^+$ = 161.10.

5-(Pyrrolidin-1-yl)pentan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a mixture of 5-bromovaleronitrile (0.21 mL, 1.80 mmol), pyrrolidine (0.15 mL, 1.81 mmol), K_2CO_3 (498 mg, 3.60 mmol) and KI (60 mg, 0.36 mmol) in dry CH_3CN

(15 mL) was refluxed for 1 h. The mixture was filtered and concentrated under reduced pressure. A 0.05 mol/L solution of the crude nitrile (59 mg, 0.39 mmol) in EtOH (8 mL) was hydrogenated at rt using the H-Cube® (1 mL/min) with a Raney Nickel cartridge (30 mm) under 50 bar until completion of the reaction. The solution was then concentrated under reduced pressure to give crude 5-(pyrrolidin-1-yl)pentan-1-amine as a colorless oil. LC-MS-conditions 01: $t_R = 0.16$ min; $[M+H]^+ = 157.19$.

4-(2,5-Dimethylpyrrolidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 2,5-dimethylpyrrolidine (250 mg, 2.34 mmol) and 4-bromobutyronitrile (0.24 mL, 2.34 mmol) in dry CH_3CN (12 mL) was added K_2CO_3 (1.78 g, 12.89 mmol) at rt followed by KI (39 mg, 0.23 mmol). The reaction mixture was stirred at rt for 15 h. The mixture was filtered and the filtrate partitioned between water and CH_2Cl_2 . The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (19 mL) and treated with $LiAlH_4$ (176 mg, 4.50 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction. Aq. 1N NaOH (7 mL) was then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give crude 4-(2,5-dimethylpyrrolidin-1-yl)butan-1-amine as a yellow oil. GC-MS-conditions 01: $t_R = 1.75$ and 1.83 min; $[M+H]^+ = 171.30$.

tert-Butyl (4-oxopentyl)carbamate:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 4-(tert-butoxycarbonyl-amino)butyric acid (1.00 g, 4.77 mmol) in dry CH_3CN (24 mL) were added *N,O*-dimethyl-hydroxylamine hydrochloride (475 mg, 4.77 mmol), EDC.HCl (934 mg, 4.77 mmol), HOBt (658 mg, 4.77 mmol) and *N*-methylmorpholine (2.68 mL, 23.86 mmol) at rt. The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure. The residue was redissolved in EA, successively washed with water, 10% aq. $KHSO_4$, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was dissolved in dry THF (20 mL) and treated with $MeMgBr$ (3.0M solution in Et_2O , 3.25 mL, 9.75 mmol) at 0 °C. The reaction mixture was stirred at 0 °C until completion of the reaction. 10% Aq. $KHSO_4$ was then carefully added, the layers

separated and the aq. layer extracted with EA (3x). The combined org. extracts were successively washed with aq. sat. NaHCO_3 and brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 3:2) to give the title compound as a colorless oil. TLC: rf (3:2 hept-EA) = 0.38.

5 **4-(Pyrrolidin-1-yl)pentan-1-amine hydrochloride:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of pyrrolidine (79 mg, 1.11 mmol) in dry CH_3CN (6 mL) was added *tert*-butyl (4-oxopentyl)carbamate (291 mg, 1.44 mmol) followed by $\text{Na}(\text{OAc})_3\text{BH}$ (680 mg, 2.88 mmol) at rt. The reaction mixture was stirred at rt until completion of the reaction. Sat. aq. NaHCO_3 was then added and the mixture extracted with EA (3x). The combined org. extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC (CH_2Cl_2 -MeOH- NH_3) to give pure *N-tert*-butoxycarbonyl-4-(pyrrolidin-1-yl)pentan-1-amine as a colorless oil. LC-MS-conditions 05c: t_R = 0.53 min; $[\text{M}+\text{H}]^+$ = 257.41. The title compound was obtained after Boc deprotection using 4N HCl in dioxane (10.0 eq.) in CH_2Cl_2 at rt as a colorless oil.

***tert*-Butyl (2-(oxiran-2-yl)ethyl)carbamate:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 4-amino-1-butene (2.00 g, 25.31 mmol) in dry CH_2Cl_2 (100 mL) were added di-*tert*-butyl dicarbonate (8.45 g, 37.96 mmol) and DIPEA (8.66 mL, 50.62 mmol) at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were washed with sat. aq. NaHCO_3 , dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC(hept-EA) and 4-(*N-tert*-butoxycarbonyl-amino)-1-butene was obtained as a colorless oil, which was redissolved in dry CH_2Cl_2 (175 mL) and treated with *m*-chloroperbenzoic acid (1.4 eq.) at rt. The reaction mixture was stirred at rt until completion of the reaction. Aq. 1N NaOH was then added, the layers separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 3:2) and the title compound obtained as a colorless oil. TLC: rf (3:2 hept-EA) = 0.33.

3-Fluoro-4-(pyrrolidin-1-yl)butan-1-amine hydrochloride:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), a solution of *tert*-butyl (2-(oxiran-2-yl)ethyl)carbamate (1.50 g, 8.01 mmol) in pyrrolidine (2 mL) was heated at 85 °C until completion of the reaction. The reaction mixture was evaporated to dryness to give a yellow oil. Part of this crude material (300 mg, 1.16 mmol) was dissolved in dry CH_2Cl_2 (34 mL) and treated with (diethylamino)sulphur trifluoride (0.18 mL, 1.37 mmol) at 0 °C. The reaction mixture was stirred at 0 °C until completion of the reaction. Sat. aq. $NaHCO_3$ was then added, the layers separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was then redissolved in dry CH_2Cl_2 (1 mL) and treated with 4N HCl in dioxane (1 mL) at rt. The reaction mixture was stirred at rt until completion of the reaction, and the solvents removed under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 07b: t_R = 0.14 min; $[M+H]^+$ = 161.18.

4-(2-(Methoxymethyl)pyrrolidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 2-(methoxymethyl)pyrrolidine (300 mg, 2.61 mmol) and 4-bromobutyronitrile (0.31 mL, 2.99 mmol) in dry CH_3CN (13 mL) was added K_2CO_3 (1.51 g, 10.94 mmol) at rt followed by KI (43 mg, 0.26 mmol). The reaction mixture was stirred at rt for 15 h. The mixture was filtered and the filtrate partitioned between water and CH_2Cl_2 . The layers were separated and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (21 mL) and treated with $LiAlH_4$ (192 mg, 5.07 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction. Sat. aq. Rochelle's salt solution and EA were then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give crude 4-(2-(methoxymethyl)pyrrolidin-1-yl)butan-1-amine as a pale yellow oil. GC-MS-conditions 01: t_R = 2.1 min; $[M+H]^+$ = 187.20.

4-(3,3-Difluoropyrrolidin-1-yl)butan-1-amine:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of 3,3-difluoropyrrolidine hydrochloride (250 mg, 1.69

mmol) and 4-bromobutyronitrile (0.17 mL, 1.69 mmol) in dry CH₃CN (9 mL) was added K₂CO₃ (1.28 g, 9.29 mmol) at rt followed by KI (28 mg, 0.17 mmol). The reaction mixture was stirred at rt for 15 h. The mixture was filtered and the filtrate partitioned between water and CH₂Cl₂. The layers were separated and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude nitrile was redissolved in dry THF (8 mL) and treated with LiAlH₄ (75 mg, 1.92 mmol) at 0 °C. The reaction mixture was warmed up to rt and stirred at this temperature until completion of the reaction. Sat. aq. Rochelle's salt solution and EA were then added, the layers separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give crude 4-(3,3-difluoropyrrolidin-1-yl)butan-1-amine as a colorless oil. GC-MS-conditions 01: t_R = 1.56 min; [M+H]⁺ = 179.10.

(*trans*-4-Aminocyclohexyl)methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of *trans*-4-benzyloxycarbonylaminocyclohexane-methanol (110 mg, 0.42 mmol) in MeOH (5 mL) was hydrogenated in the presence of Pd/C (10%) at rt until completion of the reaction. The mixture was then filtered and concentrated under reduced pressure. The title compound was obtained as a light brown solid. LC-MS-conditions 07: t_R = 0.11 min; [M+H]⁺ = 130.24.

(*cis*-4-Aminocyclohexyl)methanol:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a solution of *cis*-4-benzyloxycarbonylaminocyclohexane-methanol (235 mg, 0.89 mmol) in MeOH (5 mL) was hydrogenated in the presence of Pd/C (10%) at rt until completion of the reaction. The mixture was then filtered and concentrated under reduced pressure. The title compound was obtained as a colorless oil. LC-MS-conditions 07: t_R = 0.12 min; [M+H]⁺ = 130.26.

***tert*-Butyl ((*cis*-4-aminocyclohexyl)methyl)carbamate:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to an ice-cold solution of *cis*-4-benzyloxycarbonylaminocyclohexane-methanol (1.53 g, 5.81 mmol), triphenylphosphine on polystyrene (17.43 mmol) and imidazole (559 mg, 8.13 mmol) in dry CH₂Cl₂ (150 mL) was added iodine (2.38 g, 9.30

mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, successively washed with 10% aq. Na₂SO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude iodide (1.94 g, 5.20 mmol) was redissolved in DMF (15 mL) and
5 treated with sodium azide (358 mg, 5.46 mmol). The reaction mixture was heated to 80 °C until completion of the reaction. The mixture was then diluted with EA, washed with brine (3x), dried over MgSO₄, filtered and concentrated under reduced pressure. To a mixture of the crude azide (1.50 g, 5.20 mmol) in THF (27 mL) were added polymer-supported Ph₃P (2.0 eq.) and water (9 mL). The reaction mixture was stirred at 55 °C until completion of
10 the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. 0.5M Na₂CO₃ and the layers separated. The aq. layer was extracted with EA (2x) and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give benzyl (*cis*-4-(aminomethyl)cyclohexyl)carbamate as a yellow oil. LC-MS-conditions 07b: t_R = 0.57 min; [M+H]⁺ = 263.46.

15 To a solution of the crude amine (467 mg, 1.78 mmol) in THF (4 mL) was added aq. 1M NaOH (1.85 mL, 1.85 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and a solution of di-*tert*-butyl dicarbonate (412 mg, 1.85 mmol) in THF (3 mL) was then added dropwise. The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was diluted with CH₂Cl₂, filtered and the
20 layers separated. The organic layer was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The crude residue was purified by FC (hept-EA, 1:0 -> 7:3) and then the Cbz group was removed by treatment with 10% Pd/C (150 mg) in EA/MeOH 1:1 (10 mL) under a H₂ atmosphere. The title compound was obtained as a colorless oil. LC-MS-conditions 07b: t_R = 0.52 min; [M+H]⁺ = 229.46.

25 ***tert*-Butyl ((*trans*-4-aminocyclohexyl)methyl)carbamate:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to an ice-cold solution of *trans*-4-benzyloxycarbonylaminocyclohexane-methanol (1.32 g, 5.01 mmol), triphenylphosphine on polystyrene (15.04 mmol) and imidazole (483 mg, 7.02 mmol) in dry CH₂Cl₂ (150 mL) was added iodine (2.06 g, 8.02
30 mmol). The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was then filtered, successively washed with 10% aq. Na₂SO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude iodide (1.64 g, 4.39 mmol) was redissolved in DMF (15 mL) and

treated with sodium azide (303 mg, 4.61 mmol). The reaction mixture was heated to 80 °C until completion of the reaction. The mixture was then diluted with EA, washed with brine (3x), dried over MgSO₄, filtered and concentrated under reduced pressure. To a mixture of the crude azide (1.27 g, 4.40 mmol) in THF (21 mL) were added polymer-supported Ph₃P (2.0 eq.) and water (7 mL). The reaction mixture was stirred at 55 °C until completion of the reaction, cooled down to rt and filtered. The filtrate was partitioned between EA and aq. 0.5M Na₂CO₃ and the layers separated. The aq. layer was extracted with EA (2x) and the combined org. extracts dried over MgSO₄, filtered and concentrated under reduced pressure to give benzyl (*trans*-4-(aminomethyl)cyclohexyl)carbamate as a white solid. LC-MS-conditions 07b: t_R = 0.57 min; [M+H]⁺ = 263.46.

To a solution of the crude amine (466 mg, 1.78 mmol) in THF (4 mL) was added aq. 1M NaOH (1.85 mL, 1.85 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and a solution of di-*tert*-butyl dicarbonate (412 mg, 1.85 mmol) in THF (3 mL) was then added dropwise. The reaction mixture was warmed to rt and stirred at this temperature until completion of the reaction. The mixture was diluted with CH₂Cl₂, filtered and the layers separated. The organic layer was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The crude residue was purified by FC (hept-EA, 1:0 -> 7:3) and then the Cbz group was removed by treatment with 10% Pd/C (120 mg) in EA/MeOH 1:1 (10 mL) under a H₂ atmosphere. The title compound was obtained as a white solid. LC-MS-conditions 07b: t_R = 0.51 min; [M+H]⁺ = 229.47.

Amide coupling (with 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methylamine) – formation of (5*R*^{*})-*N*⁵-(2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (150 mg, 0.45 mmol) in dry CH₂Cl₂ (5 mL) were added HOBt (73 mg, 0.54 mmol), EDC.HCl (216 mg, 1.13 mmol), DMAP (14 mg, 0.11 mmol) and DIPEA (0.31 mL, 1.81 mmol). The reaction mixture was stirred at rt for 30 minutes, then a solution of 2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methylamine (116 mg, 0.45 mmol) in dry CH₂Cl₂ (4 mL) was added. The reaction mixture was stirred at rt until reaction completion. Water was added, the layers separated, and the org. layer dried over MgSO₄, filtered, and concentrated under reduced

pressure. The crude residue was purified by FC (9:1 CH₂Cl₂-MeOH + 1% NH₄OH) to give the title compound as a yellow oil. LC-MS-conditions 01: t_R = 0.88 min; [M+H]⁺ = 571.24.

Amide coupling (with 2-amino-5-methyl-thiazole) – formation of (5*R)-*N*⁵-(5-methyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (400 mg, 1.69 mmol) in dry CH₂Cl₂ (9 mL) were added EDC.HCl (828 mg, 4.23 mmol), DMAP (53 mg, 0.42 mmol) and DIPEA (1.45 mL, 8.46 mmol). The reaction mixture was stirred at rt for 30 minutes, then 2-amino-5-methyl-thiazole (197 mg, 1.69 mmol) was added. The reaction mixture was stirred at rt for 2 days. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (1:1 hept-EA) to give the title compound as a white solid. TLC: rf (1:1 hept-EA) = 0.37. LC-MS-conditions 02: t_R = 0.99 min; [M+H]⁺ = 333.41.

Amide coupling (with 4-bromo-benzylamine) – formation of (5*R)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (2.50 g, 10.58 mmol) in dry CH₂Cl₂ (53 mL) were added EDC.HCl (5.17 g, 26.45 mmol), DMAP (330 mg, 2.64 mmol) and DIPEA (9.1 mL, 52.91 mmol). The reaction mixture was stirred at rt for 30 minutes, then 4-bromo-benzylamine hydrochloride (2.40 g, 10.58 mmol) was added. The reaction mixture was stirred at rt for 2 days. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (3:2 hept-EA) to give the title compound as a yellow oil. TLC: rf (3:2 hept-EA) = 0.45. LC-MS-conditions 02: t_R = 1.06 min; [M+H]⁺ = 404.00.

Saponification – formation of (5*R)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (3.43 g, 8.48 mmol) in EtOH (85 mL) and 1N NaOH (85 mL) was stirred at rt until completion of the reaction. EtOH was removed under reduced pressure and the residue partitioned between 1N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 02: *t*_R = 0.94 min; [M+H]⁺ = 376.10.

Amide coupling (with 2-amino-5-bromo-thiazole) – formation of (5*R)-*N*⁵-(5-bromothiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxylic acid (500 mg, 2.12 mmol) in dry CH₂Cl₂ (5 mL) were added a few drops of DMF and oxalyl chloride (0.20 mL, 2.33 mmol). The reaction mixture was stirred at rt for 30 minutes. To the solution of the resulting acyl chloride was added a solution of 2-amino-5-bromo-thiazole hydrobromide (851 mg, 3.17 mmol) and DIPEA (1.45 mL, 8.47 mmol) in dry CH₂Cl₂ (2.5 mL). The reaction mixture was stirred at rt for 2 h. 1N HCl was added, the layers separated, and the aq. layer extracted with EA (2x). The combined org. extracts were successively washed with aq. sat. Na₂CO₃, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (7:3 hept-EA) to give the title compound as a white foam. TLC: *r*_f (7:3 hept-EA) = 0.30. LC-MS-conditions 02: *t*_R = 1.05 min; [M+H]⁺ = 397.25.

Saponification – formation of (5*R)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (1.13 g, 2.86 mmol) in EtOH (29 mL) and 1N NaOH (29 mL) was stirred at rt until completion of the reaction. EtOH was removed under reduced pressure and the residue partitioned between 1N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure

to give the title compound as a beige solid. LC-MS-conditions 02: t_R = 0.93 min; $[M+H]^+$ = 369.21.

Amide coupling (with (4-(2-methyl-[1,3]dioxolan-2-yl)thiazol-2-yl)methanamine) – formation of (5*R)-*N*⁵-(4-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl-methyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (970 mg, 4.11 mmol) in dry CH_2Cl_2 (15 mL) were added EDC.HCl (1.97 g, 10.26 mmol), DMAP (125 mg, 1.02 mmol) and DIPEA (2.81 mL, 16.42 mmol). The reaction mixture was stirred at rt for 30 minutes, then (4-(2-methyl-[1,3]dioxolan-2-yl)thiazol-2-yl)methanamine (822 mg, 4.11 mmol) in dry CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (5:1 → 1:4 hept-EA) to give the title compound as a yellow oil. LC-MS-conditions 02: t_R = 0.93 min; $[M+H]^+$ = 419.02.

Saponification/Acetal deprotection – formation of (5*R)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(4-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl-methyl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (1.50 g, 3.58 mmol) in EtOH (35 mL) and 1N NaOH (35 mL) was stirred at rt until completion of the reaction. EtOH was removed under reduced pressure and the residue partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude carboxylic acid as a yellow solid. Part of this crude material (800 mg, 2.05 mmol) was dissolved in THF (10 mL) and treated with aq. 1N HCl (6 mL) at rt. The reaction mixture was stirred at rt until completion of the reaction. Water was added and the product extracted with EA (3x). The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound as a yellow solid. LC-MS-conditions 02: t_R = 0.77 min; $[M+H]^+$ = 347.07.

Amide coupling (with 2-amino-4-acetyl-thiazole) – formation of (5*R)-*N*⁵-(4-acetyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (250 mg, 1.06 mmol) in dry CH₂Cl₂ (5 mL) were added EDC.HCl (517 mg, 2.64 mmol), DMAP (33 mg, 0.26 mmol) and DIPEA (0.91 mL, 5.29 mmol). The reaction mixture was stirred at rt for 30 minutes, then 2-amino-4-acetyl-thiazole hydrobromide (236 mg, 1.06 mmol) was added. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA 1:1) to give the title compound as a pale pink solid. TLC: rf (1:1 hept-EA) = 0.41. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 361.27.

Saponification – formation of (5*R)-*N*⁵-(4-acetyl-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

A mixture of (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (80 mg, 0.22 mmol) in EtOH (2.2 mL) and 1N NaOH (2.2 mL) was stirred at rt until completion of the reaction. EtOH was removed under reduced pressure and the residue partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as an off-white foam. LC-MS-conditions 02: t_R = 0.84 min; [M+H]⁺ = 333.29.

Amide coupling (with 4-methyl-1,3-oxazol-2-amine) – formation of (5*R)-*N*⁵-(4-methyl-oxazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (300 mg, 1.27 mmol) in dry CH₂Cl₂ (6.5 mL) were added EDC.HCl (621 mg, 3.17 mmol), DMAP (40 mg, 0.32 mmol) and DIPEA (1.09 mL, 6.35 mmol). The reaction mixture was stirred at rt for 30 minutes, then 4-methyl-1,3-oxazol-2-amine (138 mg, 1.27 mmol) was added. The reaction mixture was stirred at rt for 36 h. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x).

The combined org. extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (1:4 hept-EA) to give the title compound as a colorless oil. TLC: r_f (1:4 hept-EA) = 0.53. LC-MS-conditions 02: t_R = 0.88 min; $[\text{M}+\text{H}]^+$ = 317.50.

5 **Amide coupling (with 2-amino-4,5-dimethyl-thiazole) – formation of (5*R**)-*N*⁵-(4,5-dimethyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R**)-5-carboxylic acid (238 mg, 1.01 mmol) in dry CH_2Cl_2 (5 mL) were
 10 added EDC.HCl (493 mg, 2.52 mmol), DMAP (31 mg, 0.25 mmol) and DIPEA (0.86 mL, 5.04 mmol). The reaction mixture was stirred at rt for 30 minutes, then 2-amino-4,5-dimethyl-thiazole hydrochloride (169 mg, 1.01 mmol) was added. The reaction mixture was stirred at rt for 36 h. Water was added, the layers separated, and the aq. layer
 15 extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (3:2 hept-EA) to give the title compound as a colorless oil. TLC: r_f (3:2 hept-EA) = 0.25. LC-MS-conditions 02: t_R = 1.00 min; $[\text{M}+\text{H}]^+$ = 347.51.

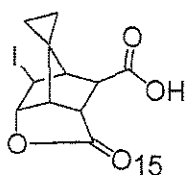
20 **Diels Alder reaction – formation of (5*R*,6*R*)-5,6-bis-[(1-(1*S*)-ethoxycarbonyl)-ethoxy-carbonyl]-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of (*E*)-1,2-bis-[(1*S*)-1-ethoxycarbonyl)-ethoxy-carbonyl]-ethene (7.40 g, 22.7 mmol) in *n*-hexane (76 mL) was added spiro[2.4]hepta-4,6-diene (3.14 g, 34.0 mmol) at rt. The reaction mixture was stirred at this temperature overnight.
 25 The mixture was concentrated under reduced pressure and the crude residue purified by FC (hept/EA, 9:1). The title compound was obtained as a pale yellow oil. TLC: r_f (9:1 hept-EA) = 0.25. LC-MS-conditions 02: t_R = 1.12 min; $[\text{M}+\text{H}]^+$ = 409.00. ^1H NMR (400 MHz, CDCl_3) δ 6.44 (dd, J = 5.5, 3.0 Hz, 1 H), 6.32 (dd, J = 5.5, 2.8 Hz, 1 H), 5.12 (q, J = 7.1 Hz, 1 H), 5.06 (q, J = 7.1 Hz, 1 H), 4.28-4.14 (m, 4 H), 3.76 (app. t, J = 4.0 Hz, 1 H), 2.92
 30 (d, J = 4.8 Hz, 1 H), 2.86 (m, 1 H), 2.80 (m, 1 H), 1.55-1.47 (m, 6 H), 1.29 (t, J = 7.3 Hz, 3 H), 1.29 (t, J = 7.3 Hz, 3 H), 0.70 (m, 1 H), 0.56-0.44 (m, 3 H).

Saponification – formation of (4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*,6*R*)-5,6-bis-carboxylic acid:

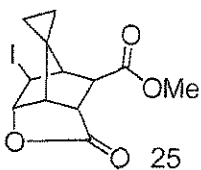
To a solution of (5*R*,6*R*)-5,6-bis-[(1-(1*S*)-ethoxycarbonyl)-ethoxy-carbonyl]-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane] (9.51 g, 23.28 mmol) in THF/H₂O (1:1, 232 mL) was added
 5 LiOH (3.91 g, 93.13 mmol). The reaction mixture was stirred at rt overnight. 1*N* HCl was added in order to adjust the pH of the reaction mixture to pH = 3, the layers separated and the aq. layer extracted with EA (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (CH₂Cl₂/MeOH, 9:1) to give the title compound as a colorless oil. TLC: *rf* (9:1
 10 CH₂Cl₂/MeOH) = 0.31. LC-MS-conditions 02: *t_R* = 0.72 min; [M+AcCN+H]⁺ = 250.18.

Iodolactonization – formation of enantiopure iodolactone 2:



To a solution of (4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*,6*R*)-5,6-bis-carboxylic acid (5.60 g, 22.32 mmol) in CH₂Cl₂ (33 mL) were added NaHCO₃ (2.06 g, 24.56 mmol), water (100 mL), KI (1.37 g, 82.60 mmol) and I₂ (6.80 g, 26.79 mmol). The reaction mixture was stirred at rt for 3 h. The reaction was quenched by the addition of sat. aq. Na₂S₂O₃. The layers were separated and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude foam was purified by FC (EA) to give enantiopure iodolactone 2 as a white solid. TLC: *rf* (EA) =
 20 0.33.

Esterification – formation of enantiopure iodolactone 1 (R¹⁰ = Me):



In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of enantiopure iodolactone 2 (5.00 g, 14.96 mmol) in dry MeOH (75 mL) was added TMSCH₂N₂ (2.0 M in hexanes, 37.0 mL, 74.83 mmol). The reaction mixture was stirred at rt overnight, concentrated under reduced pressure and purified by FC (hept-EA, 4:1) to give enantiopure iodolactone 1 (R¹⁰ = Me) as a white solid. TLC: *rf* (4:1 hept-EA) = 0.18.

Retro-iodolactonization – formation of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of enantiopure iodolactone 1 (*R*¹⁰ = Me) (2.86 g, 8.21 mmol) in acetic acid (29 mL) was added zinc powder (8.06 g, 123.23 mmol). The reaction mixture was stirred at 65 °C for 4 h, cooled down to rt, filtered and partitioned between water and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 1:1) and the title compound was obtained as a colorless oil. TLC: *r*_f (1:1 hept-EA) = 0.41.

Amide coupling (with 4-bromo-aniline) – formation of (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (80 mg, 0.36 mmol) in dry toluene (2 mL) were added a few drops of DMF and oxalyl chloride (0.048 mL, 0.54 mmol). The reaction mixture was stirred at reflux for 40 minutes, cooled down to rt, concentrated under reduced pressure and the residue dried under high vacuum.

To a solution of this acyl chloride in dry CH₂Cl₂ (2 mL) were added 4-bromoaniline (96 mg, 0.54 mmol) and DIPEA (0.18 mL, 1.08 mmol). The reaction mixture was stirred at rt for 1 h. 1N HCl was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (3:2 hept-EA) to give the title compound as an orange solid. TLC: *r*_f (3:2 hept-EA) = 0.50. LC-MS-conditions 02: *t*_R = 1.06 min; [M+H]⁺ = 376.20.

Amide coupling (with 1-(5-aminomethyl-furan-2-yl)-ethanone) – formation of (5*R*)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (200 mg, 0.90 mmol) in dry CH₂Cl₂ (3 mL) were added EDC.HCl (440 mg, 2.25 mmol), DMAP (28 mg, 0.22 mmol) and DIPEA (0.46 mL, 2.70 mmol). The reaction mixture was stirred at rt for 30 minutes, then 1-(5-aminomethyl-

furan-2-yl)-ethanone (125 mg, 0.90 mmol) was added. The reaction mixture was stirred at rt for 16 h. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (4:6 hept-
5 EA) to give the title compound as a colorless oil. TLC: rf (4:6 hept-EA) = 0.21. LC-MS-conditions 02: t_R = 0.89 min; [M+H]⁺ = 344.49.

(5*R*)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-
10 [4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (210 mg, 0.61 mmol) in EtOH (6.1 mL) was added aq. 1N NaOH (6.1 mL, 6.10 mmol). The reaction mixture was stirred at rt overnight and concentrated under reduced pressure. The residue was partitioned between 1N HCl and EA, the layers separated and the aq. layer extracted with EA (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced
15 pressure to give the title compound as a yellow foam. TLC: rf (9:1 CH₂Cl₂/MeOH) = 0.38. LC-MS-conditions 02: t_R = 0.79 min; [M+H]⁺ = 329.94.

(5*R*)-*N*⁵-(4-Bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

A mixture of (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-ethoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (prepared from the racemic compound using chiral
20 HPLC, 500 mg, 1.28 mmol) and 1N aq. NaOH (13 mL) in EtOH (13 mL) was stirred at rt overnight. The reaction mixture was then concentrated under reduced pressure and partitioned between 2M HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined organic extracts were washed with brine, dried over
25 MgSO₄, filtered and concentrated under reduced pressure to give the title compound as a white solid. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 362.20.

Double bond reduction – formation of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert
30 atmosphere (N₂), a deoxygenated suspension of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (220 mg, 0.99 mmol), Pd/C 10% (44 mg) and cyclohexene (0.20 mL, 1.98 mmol) in dry THF (2.5 mL) was stirred at reflux for 2 h. The reaction mixture was filtered through celite and the filter cake washed with THF.

The filtrate was concentrated under reduced pressure and the title compound obtained as a white solid. TLC: rf (2:3 hept-EA) = 0.48.

Amide coupling (with 4-bromo-aniline) – formation of (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (220 mg, 0.98 mmol) in dry toluene (5 mL) were added a few drops of DMF and oxalyl chloride (0.13 mL, 1.47 mmol). The reaction mixture was stirred at reflux for 40 minutes, cooled down to rt, concentrated under reduced
10 pressure and the residue dried under high vacuum.

To a solution of this acyl chloride in dry CH₂Cl₂ (5 mL) were added 4-bromoaniline (261 mg, 1.47 mmol) and DIPEA (0.50 mL, 2.94 mmol). The reaction mixture was stirred at rt for 1 h. 1N HCl was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and
15 concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 4:1) and the title compound obtained as a white foam. TLC: rf (4:1 hept-EA) = 0.35. LC-MS-conditions 02: t_R = 1.10 min; [M+H]⁺ = 378.22.

Amide coupling (with 1-(5-aminomethyl-furan-2-yl)-ethanone) – formation of (5*R*)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

20 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (200 mg, 0.89 mmol) in dry CH₂Cl₂ (3 mL) were added EDC.HCl (436 mg, 2.23 mmol), DMAP (28 mg, 0.22 mmol) and DIPEA (0.46 mL,
25 2.68 mmol). The reaction mixture was stirred at rt for 30 minutes, then 1-(5-aminomethyl-furan-2-yl)-ethanone (124 mg, 0.89 mmol) was added. The reaction mixture was stirred at rt for 16 h. Water was added, the layers separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (4:6 hept-
30 EA) to give the title compound as a colorless oil. TLC: rf (4:6 hept-EA) = 0.35. LC-MS-conditions 01: t_R = 0.88 min; [M+H]⁺ = 346.05.

(5*R*)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (110 mg, 0.32 mmol) in EtOH (3.2 mL) was added aq. 1N NaOH (3.2 mL, 3.20 mmol). The reaction mixture was stirred at rt overnight and concentrated under reduced pressure. The residue was partitioned between
5 1N HCl and EA, the layers separated and the aq. layer extracted with EA (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow foam. TLC: rf (9:1 CH₂Cl₂/MeOH) = 0.38. LC-MS-conditions 02: t_R = 0.82 min; [M+H]⁺ = 332.37.

10 **Amide coupling (with 2-amino-5-bromo-thiazole) – formation of (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (1.11 g, 5.00 mmol) in dry CH₂Cl₂ (20 mL) were
15 added a few drops of DMF and oxalyl chloride (0.48 mL, 5.50 mmol). The reaction mixture was stirred at rt for 30 minutes, concentrated under reduced pressure and the residue dried under high vacuum.

To a suspension of 2-amino-5-bromo-thiazole monohydrobromide (1.34 g, 5.00 mmol) in dry THF (10 mL) was added a solution of the acyl chloride in dry THF (10 mL) followed by
20 Et₃N (1.4 mL, 10.0 mmol). The reaction mixture was stirred at rt for 1 h, diluted with EA and washed with brine. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1) and the title compound obtained as a pale yellow oil. TLC: rf (1:1 hept-EA) = 0.60. LC-MS-conditions
25 01: t_R = 0.98 min; [M+H]⁺ = 382.92.

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (2.14 g, 5.58 mmol) in THF (30 mL) was
30 added aq. 2N NaOH (11 mL, 22.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then washed with Et₂O, the aq. layer acidified and extracted with EA (3x). The combined org. extracts were washed with brine, dried

over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow solid. LC-MS-conditions 01: t_R = 0.88 min; [M+H]⁺ = 368.87.

Amide coupling (with 5-amino-2-bromo-pyridine) – formation of (5*R*)-*N*⁵-(2-bromopyrid-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (222 mg, 1.00 mmol) in dry CH₂Cl₂ (4 mL) were added a few drops of DMF and oxalyl chloride (0.10 mL, 1.13 mmol). The reaction mixture was stirred at rt for 30 minutes and a solution of 5-amino-2-bromo-pyridine (265 mg, 1.50 mmol) and DIPEA (0.70 mL, 4.00 mmol) in dry CH₂Cl₂ (2 mL). The reaction mixture was stirred at rt for 20 minutes, diluted with EA and washed with aq. 1N HCl. The layers were separated and the aq. layer extracted with EA (2x). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 -> 3:1) and the title compound obtained as a colorless oil. LC-MS-conditions 01: t_R = 0.95 min; [M+H]⁺ = 376.97.

(5*R*)-*N*⁵-(2-Bromo-pyrid-5-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (323 mg, 0.86 mmol) in THF (4 mL) was added aq. 2N NaOH (1.7 mL, 3.40 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow foam. LC-MS-conditions 02: t_R = 0.87 min; [M+H]⁺ = 362.93.

Amide coupling (with 4-bromo-3-fluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-3-fluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-3-fluoroaniline (95 mg, 0.50 mmol) in dry CH₂Cl₂

(1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a colorless solid. TLC: rf (1:1 hept-EA) = 0.55. LC-MS-conditions 02: t_R = 1.07 min; [M+H]⁺ = 393.86.

Amide coupling (with 4-bromo-2-fluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

10 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (59 mg, 0.26 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (129 mg, 0.66 mmol) and DMAP (6 mg, 0.05 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-2-fluoroaniline (50 mg, 0.26 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.18 mL, 1.05 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a yellow oil. LC-MS-conditions 02: t_R = 1.07 min; [M+H]⁺ = 393.65.

20 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

To a solution of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (20 mg, 0.05 mmol) in EtOH (1 mL) was added aq. 1N NaOH (0.5 mL, 0.50 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure, the residue partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 380.22.

Amide coupling (with 4-bromo-2-methylaniline) – formation of (5*R*)-*N*⁵-(4-bromo-2-methylphenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-2-methylaniline (93 mg, 0.50 mmol) in dry
10 CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a yellow oil. LC-MS-conditions 02: t_R = 1.06 min; [M+H]⁺ =
15 389.98.

(5*R*)-*N*⁵-(4-Bromo-2-methylphenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-2-methylphenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (93 mg, 0.24 mmol) in EtOH (2 mL) was
20 added aq. 1N NaOH (1.0 mL, 1.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure, the residue partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound
25 as a pale brown foam. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 376.26.

Amide coupling (with 5-amino-2-chloropyridine) – formation of (5*R*)-*N*⁵-(2-chloro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert
30 atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-3-fluoroaniline (66 mg, 0.50 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was

stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a white foam. LC-MS-conditions 02: t_R = 0.96 min; $[M+H]^+$ = 333.27.

Amide coupling (with 2-amino-5-bromopyridine) – formation of (5*R*)-*N*⁵-(5-bromo-pyridin-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 2-amino-5-bromopyridine (86 mg, 0.50 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a yellow oil. LC-MS-conditions 02: t_R = 1.03 min; $[M+H]^+$ = 376.72.

(5*R*)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(5-bromo-pyridin-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (29 mg, 0.08 mmol) in EtOH (1 mL) was added aq. 1N NaOH (0.5 mL, 0.50 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure, the residue partitioned between 2N HCl and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow solid. LC-MS-conditions 02: t_R = 0.94 min.

Amide coupling (with 2-amino-5-methylpyridine) – formation of (5*R*)-*N*⁵-(5-methyl-pyridin-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

- 5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (222 mg, 1.00 mmol) in dry CH₂Cl₂ (4 mL) were added 2-amino-5-methylpyridine (109 mg, 1.00 mmol), EDC.HCl (489 mg, 2.50 mmol) and DMAP (25 mg, 0.20 mmol). The mixture was cooled to 0 °C and DIPEA (0.70 mL, 4.00
- 10 mmol) was added. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 2:1) and the title compound obtained as a yellow oil. TLC: rf (2:1 hept-EA) = 0.43. LC-MS-conditions 02: t_R = 0.79 min; [M+H]⁺ = 313.40.

15 **(5*R*)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- To a solution of (5*R*)-*N*⁵-(5-methyl-pyridin-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (56 mg, 0.18 mmol) in THF (1 mL) was added aq. 2N NaOH (0.4 mL, 0.80 mmol). The reaction mixture was stirred at rt until
- 20 completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow solid. LC-MS-conditions 02: t_R = 0.71 min; [M+H]⁺ = 298.61.

25 **Amide coupling (with 4-bromo-2,5-difluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were
- 30 added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-2,5-difluoroaniline (104 mg, 0.50 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated

under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 3:1) and the title compound obtained as a yellow oil. LC-MS-conditions 02: t_R = 1.09 min; $[M+H]^+$ = 412.39.

(5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (170 mg, 0.41 mmol) in THF (2 mL) was added aq. 1N NaOH (0.8 mL, 0.80 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (CH₂Cl₂-MeOH-NH₄OH) gave the title compound as a pale yellow oil. LC-MS-conditions 02: t_R = 1.00 min; $[M+H]^+$ = 398.40.

Amide coupling (with 4-bromo-2,6-difluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-2,6-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (200 mg, 0.90 mmol) in dry CH₂Cl₂ (4 mL) were added 3 drops of DMF and oxalyl chloride (0.09 mL, 1.02 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-2,6-difluoroaniline (187 mg, 0.90 mmol) in pyridine (1.1 mL) was added a solution of the acyl chloride in acetone (5 mL). The reaction mixture was stirred at rt for 2 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 3:1) and the title compound obtained as a colorless oil. TLC: r_f (2:3 hept-EA) = 0.40. LC-MS-conditions 02: t_R = 1.03 min; $[M+H]^+$ = 411.86.

(5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-2,6-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (240 mg, 0.58 mmol) in THF (2 mL) was added aq. 1N NaOH (1.1 mL, 1.10 mmol). The reaction mixture was stirred at rt until

completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white foam. LC-MS-conditions 02: t_R = 0.94 min; $[M+H]^+$ = 398.02.

5 **Amide coupling (with 4-bromo-2,3-difluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-2,3-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

10 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (150 mg, 0.67 mmol) in dry CH₂Cl₂ (4 mL) were added 3 drops of DMF and oxalyl chloride (0.07 mL, 0.77 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

15 To a suspension of 4-bromo-2,3-difluoroaniline (140 mg, 0.67 mmol) in pyridine (0.8 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound obtained as a yellow oil. TLC: rf (1:1 hept–EA) = 0.63, LC-MS-conditions 02: t_R = 1.08 min; $[M+H]^+$ = 411.93.

20 **(5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

25 To a solution of (5*R*)-*N*⁵-(4-bromo-2,3-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (260 mg, 0.63 mmol) in THF (2.5 mL) was added aq. 1N NaOH (1.2 mL, 1.20 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white foam. LC-MS-conditions 02: t_R = 0.99 min; $[M+H]^+$ = 398.38.

30 **Amide coupling (with 4-bromo-3,5-difluoroaniline) – formation of (5*R*)-*N*⁵-(4-bromo-3,5-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were

added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-3,5-difluoroaniline (109 mg, 0.50 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a yellow oil. LC-MS-conditions 01: *t_R* = 1.06 min; [M+H]⁺ = 411.90.

Amide coupling (with 4-bromo-3-(trifluoromethyl)aniline) – formation of (5*R*)-*N*⁵-(4-bromo-3-trifluoromethylphenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (111 mg, 0.50 mmol) in dry CH₂Cl₂ (2 mL) were added EDC.HCl (244 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was cooled to 0 °C and a solution of 4-bromo-3-(trifluoromethyl)aniline (120 mg, 0.50 mmol) in dry CH₂Cl₂ (1 mL) was added followed by DIPEA (0.35 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated and the org. layer washed with aq. 1N HCl, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 1:1) and the title compound obtained as a colorless oil. LC-MS-conditions 02: *t_R* = 1.11 min; [M+H]⁺ = 443.88.

Amide coupling (with 4-bromo-2-fluorobenzylamine) – formation of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (150 mg, 0.67 mmol) in dry CH₂Cl₂ (4 mL) were added 3 drops of DMF and oxalyl chloride (0.07 mL, 0.77 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-2-fluorobenzylamine hydrochloride (162 mg, 0.67 mmol) in pyridine (0.80 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq.

1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound obtained as a yellow oil. LC-MS-conditions 01: t_R = 0.99 min; $[M+H]^+$ = 407.94.

(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (250 mg, 0.61 mmol) in THF (5 mL) was added aq. 1N NaOH (2.9 mL, 2.90 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white foam. LC-MS-conditions 02: t_R = 0.94 min; $[M+H]^+$ = 394.00.

Amide coupling (with 4-bromo-3-fluorobenzylamine) – formation of (5*R*)-*N*⁵-(4-bromo-3-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (80 mg, 0.36 mmol) in dry CH₂Cl₂ (4 mL) were added 3 drops of DMF and oxalyl chloride (0.04 mL, 0.41 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-3-fluorobenzylamine (90 mg, 0.44 mmol) in pyridine (0.43 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (hept-EA 1:1 to 1:2) gave the title compound as a colorless oil. LC-MS-conditions 07: t_R = 0.84 min; $[M+H]^+$ = 408.01.

Amide coupling (with 4-bromo-2,3-difluorobenzylamine) – formation of (5*R*)-*N*⁵-(4-bromo-2,3-difluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (120 mg, 0.54 mmol) in dry CH₂Cl₂ (4 mL) were

added 3 drops of DMF and oxalyl chloride (0.05 mL, 0.62 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-2,3-difluorobenzylamine (120 mg, 0.54 mmol) in pyridine (0.64 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 2 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (hept-EA 9:1 to 1:1) gave the title compound as a yellow oil. TLC: rf (1:1 hept-EA) = 0.65. LC-MS-conditions 07: t_R = 0.86 min; [M+H]⁺ = 426.05.

10 **(5R)-N⁵-(4-Bromo-2,3-difluorophenyl-methyl)-(6R)-6-hydroxycarbonyl-(4S,7R)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

To a solution of (5R)-N⁵-(4-bromo-2,3-difluorophenyl-methyl)-(6R)-6-methoxycarbonyl-(4S,7R)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (120 mg, 0.28 mmol) in THF (4 mL) was added aq. 1N NaOH (1.3 mL, 1.30 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white foam. LC-MS-conditions 07: t_R = 0.77 min; [M+H]⁺ = 411.93.

20 **Amide coupling (with 4-bromo-3,5-difluorobenzylamine) – formation of (5R)-N⁵-(4-bromo-3,5-difluorophenyl-methyl)-(6R)-6-methoxycarbonyl-(4S,7R)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6R)-6-methoxycarbonyl-(4S,7R)-[4,7-ethenylene-spiro[2.4]heptane]-(5R)-5-carboxylic acid (55 mg, 0.25 mmol) in dry CH₂Cl₂ (4 mL) were added 2 drops of DMF and oxalyl chloride (0.025 mL, 0.28 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-3,5-difluorobenzylamine (55 mg, 0.25 mmol) in pyridine (0.24 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 2 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. TLC: rf (1:1 hept-EA) = 0.65. LC-MS-conditions 07: t_R = 0.85 min; [M+H]⁺ = 426.08.

(5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-3,5-difluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (80 mg, 0.19 mmol) in THF (2 mL) was added aq. 1N NaOH (1.5 mL, 1.50 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a brown foam. LC-MS-conditions 07: *t*_R = 0.75 min; [M+H]⁺ = 412.08.

10 Amide coupling (with 4-bromo-2,5-difluorobenzylamine) – formation of (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (90 mg, 0.40 mmol) in dry CH₂Cl₂ (4 mL) were added 2 drops of DMF and oxalyl chloride (0.04 mL, 0.46 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 4-bromo-2,5-difluorobenzylamine (90 mg, 0.40 mmol) in pyridine (0.39 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 2 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. TLC: *r*_f (1:1 hept–EA) = 0.65. LC-MS-conditions 07: *t*_R = 0.86 min; [M+H]⁺ = 426.08.

25 (5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (170 mg, 0.40 mmol) in THF (4 mL) was added aq. 1N NaOH (1.6 mL, 1.60 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a brown foam. LC-MS-conditions 07: *t*_R = 0.76 min; [M+H]⁺ = 412.08.

Amide coupling (with 5-amino-2-bromo-3-fluoropyridine) – formation of (5*R*)-*N*⁵-(2-bromo-3-fluoro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (120 mg, 0.54 mmol) in dry CH₂Cl₂ (2 mL) were added 2 drops of DMF and oxalyl chloride (0.054 mL, 0.61 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 5-amino-2-bromo-3-fluoropyridine (103 mg, 0.54 mmol) in pyridine (0.64 mL) was added a solution of the acyl chloride in acetone (3 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (hept-EA 9:1 to 4:1) gave the title compound as a white foam. TLC: rf (2:3 hept-EA) = 0.51. LC-MS-conditions 07: t_R = 0.86 min; [M+H]⁺ = 395.30.

Amide coupling (with 2-(4-chlorophenyl)ethylamine) – formation of (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (800 mg, 3.60 mmol) in dry CH₂Cl₂ (10 mL) were added a few drops of DMF and oxalyl chloride (0.33 mL, 3.96 mmol). The reaction mixture was stirred at rt for 30 minutes and a solution of 2-(4-chlorophenyl)ethylamine (857 mg, 5.40 mmol) and DIPEA (2.5 mL, 14.40 mmol) in dry CH₂Cl₂ (5 mL) was added. The reaction mixture was stirred at rt for 10 min, diluted with CH₂Cl₂ and washed with aq. 1N HCl. The layers were separated and the aq. layer extracted with CH₂Cl₂ (2x). The combined org. extracts were successively washed with aq. Na₂CO₃ and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 4:1 to 1:1) and the title compound obtained as a yellow oil. TLC: rf (1:1 hept-EA) = 0.55. LC-MS-conditions 01: t_R = 1.00 min; [M+H]⁺ = 360.03.

(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-

ethenylene-spiro[2.4]heptane]-5-carboxamide (550 mg, 1.53 mmol) in EtOH (15 mL) was added aq. 1N NaOH (7.5 mL, 7.50 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure and the residue partitioned between EA and aq. 2N HCl. The layers were separated and
5 the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow solid. LC-MS-conditions 01: t_R = 0.91 min; $[M+H]^+$ = 346.00.

Amide coupling (with 2-(2,4-dichlorophenyl)ethylamine) – formation of (5*R*)-*N*⁵-(2-(2,4-dichlorophenyl)ethyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

10 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (110 mg, 0.50 mmol) in dry DMF (5 mL) were added HATU (188 mg, 0.50 mmol) and DIPEA (0.13 mL, 0.75 mmol) at rt. The reaction
15 mixture was stirred at rt for 1 h and a solution of 2-(2,4-dichlorophenyl)ethylamine (94 mg, 0.50 mmol) in dry DMF (2.5 mL) was added. The reaction mixture was stirred at rt for 30 min, diluted with EA and washed with water. The layers were separated and the org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 to 3:2) and the title compound obtained as a
20 colorless oil. LC-MS-conditions 01: t_R = 1.03 min; $[M+H]^+$ = 394.02.

(5*R*)-*N*⁵-(2-(2,4-Dichlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(2-(2,4-dichlorophenyl)ethyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (170 mg, 0.43 mmol) in EtOH (4 mL)
25 was added aq. 1N NaOH (2 mL, 2.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then concentrated under reduced pressure and the residue partitioned between EA and aq. 2N HCl. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title
30 compound as a white foam. LC-MS-conditions 02: t_R = 0.97 min; $[M+H]^+$ = 380.36.

Amide coupling (with 4-bromo-2-fluorobenzylamine) – formation of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

- 5 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (160 mg, 0.71 mmol) in dry CH₂Cl₂ (4 mL) were added 3 drops of DMF and oxalyl chloride (0.07 mL, 0.81 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.
- 10 To a suspension of 4-bromo-2-fluorobenzylamine hydrochloride (171 mg, 0.71 mmol) in pyridine (0.84 mL) was added a solution of the acyl chloride in acetone (4 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound obtained as a yellow oil.
- 15 LC-MS-conditions 02: t_R = 1.06 min; [M+H]⁺ = 410.67.

(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

- To a solution of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (290 mg, 0.71 mmol) in THF (5 mL) was added aq. 1N NaOH (2.8 mL, 2.80 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white foam. LC-MS-conditions 01: t_R = 0.93 min; [M+H]⁺ = 395.95.
- 20

- 25 **Amide coupling (with 2-amino-5-bromo-thiazole) – formation of (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:**

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (4.70 g, 20.9 mmol) in dry CH₂Cl₂ (80 mL) were added 10 drops of DMF and oxalyl chloride (2.2 mL, 25.1 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.
- 30

To a suspension of 2-amino-5-bromo-thiazole monohydrobromide (5.67 g, 21.1 mmol) in pyridine (5 mL) was added a solution of the acyl chloride in acetone (80 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1) and the title compound obtained as a pale yellow solid. TLC: rf (2:1 hept-EA) = 0.38. LC-MS-conditions 07c: t_R = 0.98 min; [M+H]⁺ = 385.12.

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (2.90 g, 7.53 mmol) in THF (60 mL) was added aq. 2N NaOH (15 mL, 30.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then washed with Et₂O, the aq. layer acidified and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a light brown solid. LC-MS-conditions 07c: t_R = 0.84 min; [M+H]⁺ = 371.11.

Amide coupling (with 5-amino-2-bromo-pyridine) – formation of (5*R*)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (2.55 g, 11.37 mmol) in dry CH₂Cl₂ (60 mL) were added 10 drops of DMF and oxalyl chloride (1.20 mL, 13.65 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 5-amino-2-bromo-pyridine (1.97 g, 11.37 mmol) in pyridine (2.75 mL) was added a solution of the acyl chloride in acetone (60 mL). The reaction mixture was stirred at rt for 30 minutes, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 1:0 -> 1:1) and the title compound obtained as a white solid. TLC: rf (2:1 hept-EA) = 0.44. LC-MS-conditions 07: t_R = 0.84 min; [M+H]⁺ = 379.04.

(5*R*)-*N*⁵-(2-Bromo-pyrid-5-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

To a solution of (5*R*)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (3.81 g, 10.05 mmol) in THF (100 mL) was added aq. 2N NaOH (20 mL, 40.00 mmol). The reaction mixture was stirred at rt until completion of the reaction. The mixture was then poured into aq. 1N HCl and extracted with EA (3x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white solid. LC-MS-conditions 07: *t*_R = 0.72 min; [M+H]⁺ = 365.22.

Amide coupling (with 5-amino-2-bromo-3-fluoropyridine) – formation of (5*R*)-*N*⁵-(2-bromo-3-fluoro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-(5*R*)-5-carboxylic acid (121 mg, 0.54 mmol) in dry CH₂Cl₂ (2 mL) were added 2 drops of DMF and oxalyl chloride (0.054 mL, 0.61 mmol). The reaction mixture was stirred at rt for 60 minutes and concentrated under reduced pressure.

To a suspension of 5-amino-2-bromo-3-fluoropyridine (103 mg, 0.54 mmol) in pyridine (0.64 mL) was added a solution of the acyl chloride in acetone (3 mL). The reaction mixture was stirred at rt for 1 h, diluted with EA and successively washed with aq. 1N HCl, sat. aq. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (hept-EA 9:1 to 4:1) gave the title compound as a white foam. TLC: *r*_f (2:3 hept-EA) = 0.52. LC-MS-conditions 07: *t*_R = 0.91 min; [M+H]⁺ = 397.18.

Amide coupling (with beta-alanine methyl ester hydrochloride) – formation of enantiopure iodolactone 3 (R² = 2-methoxycarbonyl-ethyl and R³ = H):

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of enantiopure iodolactone 2 (3.40 g, 10.18 mmol) in dry toluene (32 mL) were added a few drops of DMF and oxalyl chloride (1.11 mL, 12.58 mmol). The reaction mixture was stirred at rt for 60 min, concentrated under reduced pressure and the residue co-evaporated with toluene (2x). The residue was then redissolved in CH₂Cl₂ (32 mL) and beta-alanine methyl ester hydrochloride (1.59 g, 11.19 mmol) and DIPEA (5.37 mL, 30.53 mmol) were added at rt. The reaction mixture was stirred at rt for 25 minutes, diluted with CH₂Cl₂ and washed with sat. aq. NH₄Cl. The layers were separated, and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts

were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 5:1 $\rightarrow$ 1:1) and the title compound obtained as a pale yellow foam. TLC: rf (95:5 hept-EA) = 0.38. LC-MS-conditions 02: t_R = 0.87 min; $[\text{M}+\text{H}]^+$ = 420.00.

5 **Retro-iodolactonization – formation of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of enantiopure iodolactone 3 (R^2 = 2-methoxycarbonyl-ethyl and R^3 = H) (3.21 g, 7.66 mmol) in acetic acid (15 mL) was added zinc powder (0.60 g, 9.20 mmol). The reaction mixture was stirred at 65 °C for 2 h, cooled down to rt, filtered and the filter cake rinsed with EA. The filtrate was washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by FC (hept-EA, 1:1 $\rightarrow$ 1:2) and the title compound was obtained as a colorless oil. TLC: rf (EA) = 0.27. LC-MS-conditions 02: t_R = 0.71 min; $[\text{M}+\text{H}]^+$ = 294.00.

15 **Amide coupling (with 4-pyrrolidin-1-yl-butylamine) – formation of enantiopure iodolactone 3 (R^2 = 4-pyrrolidin-1-yl-butyl and R^3 = H):**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of enantiopure iodolactone 2 (1.59 g, 4.76 mmol) in dry CH_2Cl_2 (30 mL) were added a few drops of DMF and oxalyl chloride (0.45 mL, 5.23 mmol). The reaction mixture was stirred at rt for 2 h, after which 4-(1-pyrrolidino)-butylamine (0.69 g, 4.76 mmol) and DIPEA (0.81 mL, 4.76 mmol) were added. The reaction mixture was stirred at rt for 30 minutes, diluted with CH_2Cl_2 and washed with sat. aq. NH_4Cl . The layers were separated, and the aq. layer extracted with CH_2Cl_2 (3x). The combined org. extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) and the title compound obtained as a pale yellow oil. TLC: rf (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) = 0.22. LC-MS-conditions 01: t_R = 0.68 min; $[\text{M}+\text{H}]^+$ = 458.65.

Retro-iodolactonization – formation of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide:

30 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N_2), to a solution of enantiopure iodolactone 3 (R^2 = 4-pyrrolidin-1-yl-butyl and R^3 = H) (1.29 g, 2.81 mmol) in acetic acid (5 mL) was added zinc powder (276 mg, 4.22 mmol). The reaction mixture was stirred at 65 °C for 0.5 h, cooled down to rt, filtered,

washed with EA and the filtrate concentrated under reduced pressure. The crude residue was purified by FC (C-18 reverse phase silica, H₂O/MeOH, 1:0 then 0:1) and the title compound was obtained as a white foam. LC-MS-conditions 02: t_R = 0.64 min; $[M+H]^+$ = 333.54.

5 **Double bond reduction – formation of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-6-carboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), a deoxygenated suspension of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (500 mg, 1.70 mmol), Pd/C 10% (181 mg) and cyclohexene (0.80 mL, 7.80 mmol) in dry THF (15 mL) was stirred at reflux for 16 h. The reaction mixture was filtered through celite and the filter cake washed with THF. The filtrate was concentrated under reduced pressure and the title compound obtained as a colorless oil. TLC: r_f (EA) = 0.37. LC-MS-conditions 02: t_R = 0.77 min; $[M+H]^+$ = 296.26.

15 **Amide coupling (with 4-bromo-benzylamine) – formation of (5*R*)-*N*⁵-(4-bromophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (59 mg, 0.20 mmol) in dry CH₂Cl₂ (2 mL) was added 4-bromo-benzylamine (39 mg, 0.20 mmol) in dry CH₂Cl₂ (0.5 mL) at rt followed by EDC.HCl (98 mg, 0.50 mmol) and DMAP (5 mg, 0.04 mmol). DIPEA (0.14 mL, 0.80 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale brown oil. TLC: r_f (1:2 hept–EA) = 0.31. LC-MS-conditions 02: t_R = 0.92 min; $[M+H]^+$ = 461.08.

30 **Amide coupling (with 2-amino-5-bromopyridine) – formation of (5*R*)-*N*⁵-(5-bromopyrid-2-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in

dry CH₂Cl₂ (2 mL) was added 2-amino-5-bromopyridine (58 mg, 0.33 mmol) in dry CH₂Cl₂ (0.5 mL) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. TLC: rf (1:1 hept-EA) = 0.37. LC-MS-conditions 02: t_R = 0.96 min; [M+H]⁺ = 448.40.

Amide coupling (with 5-amino-2-chloropyridine) – formation of (5*R*)-*N*⁵-(2-chloropyrid-5-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (2 mL) was added 5-amino-2-chloropyridine (44 mg, 0.33 mmol) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow solid. TLC: rf (1:1 hept-EA) = 0.13. LC-MS-conditions 02: t_R = 0.88 min; [M+H]⁺ = 404.06.

Amide coupling (with 4-bromo-2-fluoro-benzylamine hydrochloride) – formation of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (3 mL) was added 4-bromo-2-fluoro-benzylamine hydrochloride (72 mg, 0.30 mmol) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow oil. TLC: rf (1:2 hept-EA) = 0.42. LC-MS-conditions 02: t_R = 0.96 min; [M+H]⁺ = 479.10.

Amide coupling (with (2-bromothiazol-5-yl)methylamine) – formation of (5*R*)-*N*⁵-[(2-bromothiazol-5-yl)methyl]-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (2 mL) was added (2-bromo-thiazol-5-yl)methanamine (58 mg, 0.30 mmol) in dry CH₂Cl₂ (0.5 mL) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a brown oil. TLC: rf (1:2 hept–EA) = 0.21. LC-MS-conditions 02: t_R = 0.85 min; [M+H]⁺ = 467.57.

Amide coupling (with 4-methoxy-aniline) – formation of (5*R*)-*N*⁵-(4-methoxy-phenyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (2 mL) was added 4-methoxy-aniline (41 mg, 0.33 mmol) in dry CH₂Cl₂ (0.5 mL) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a yellow oil. TLC: rf (1:2 hept–EA) = 0.37. LC-MS-conditions 02: t_R = 0.90 min; [M+H]⁺ = 399.02.

Amide coupling (with 4-bromo-benzylamine) – formation of (5*R*)-*N*⁵-(4-bromophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (2 mL) was added 4-bromo-benzylamine (64 mg, 0.33 mmol) in dry CH₂Cl₂ (0.5

mL) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow solid. TLC: rf (1:2 hept-EA) = 0.39. LC-MS-conditions 02: t_R = 0.97 min; [M+H]⁺ = 462.80.

Amide coupling (with 5-amino-2-chloropyridine) – formation of (5*R*)-*N*⁵-(2-chloropyrid-5-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (2 mL) was added 5-amino-2-chloropyridine (44 mg, 0.33 mmol) in dry CH₂Cl₂ (1 mL) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a light brown solid. LC-MS-conditions 02: t_R = 0.92 min; [M+H]⁺ = 406.25.

Amide coupling (with 4-bromo-2-fluoro-benzylamine hydrochloride) – formation of (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (3 mL) was added 4-bromo-2-fluoro-benzylamine hydrochloride (80 mg, 0.33 mmol) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as a white solid. TLC: rf (1:2 hept-EA) = 0.45. LC-MS-conditions 02: t_R = 0.98 min; [M+H]⁺ = 481.00.

Amide coupling (with 4-methoxy-aniline) – formation of (5*R*)-*N*⁵-(4-methoxy-phenyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-6-carboxamide (88 mg, 0.30 mmol) in dry CH₂Cl₂ (3 mL) was added 4-methoxy-aniline (41 mg, 0.33 mmol) at rt followed by EDC.HCl (147 mg, 0.75 mmol) and DMAP (7 mg, 0.06 mmol). DIPEA (0.21 mL, 1.20 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. Water was added, the layers separated, and the org. layer successively washed with aq. 1N HCl (2x), brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give the title compound as an orange oil. TLC: rf (1:2 hept–EA) = 0.45. LC-MS-conditions 02: t_R = 0.93 min; [M+H]⁺ = 401.28.

15 Preparation of Examples

Example 1:

(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(5-amino-pentyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **A** then **H**, starting from (5*R*^{*})-*N*⁵-(4-bromo-phenyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-(*tert*-butoxycarbonyl-amino)-pentylamine.

LC-MS-conditions 05c: t_R = 0.55 min; [M+H]⁺ = 446.12.

Example 2:

25 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **F**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)-butylamine.

LC-MS-conditions 02: t_R = 0.85 min; [M+H]⁺ = 486.21.

Example 3:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-(4-amino)-piperidine.

LC-MS-conditions 05c: *t*_R = 0.54 min; [M+H]⁺ = 444.00.

Example 4:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and isobutylamine.

LC-MS-conditions 05c: *t*_R = 0.84 min; [M+H]⁺ = 417.18.

Example 5:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(*tert*-butoxycarbonyl-amino)-butylamine.

LC-MS-conditions 05c: *t*_R = 0.54 min; [M+H]⁺ = 432.05.

Example 6:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-*N,N*-dimethyl-amino-ethyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(dimethylamino)-ethylamine.

LC-MS-conditions 02: *t*_R = 0.82 min; [M+H]⁺ = 432.24.

Example 7:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-((3-aminomethyl-phenyl)-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(*tert*-butoxycarbonyl-aminomethyl)-benzylamine.

LC-MS-conditions 05c: *t_R* = 0.58 min; [M+H]⁺ = 479.90.

Example 8:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-piperidiny-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N-tert*-butoxycarbonyl-4-(amino-methyl)-piperidine.

- 15 LC-MS-conditions 05c: *t_R* = 0.55 min; [M+H]⁺ = 458.00.

Example 9:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (±)-1-*tert*-butoxycarbonyl-3-amino-pyrrolidine.

LC-MS-conditions 05c: *t_R* = 0.54 min; [M+H]⁺ = 429.97.

Example 10:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N-tert*-butoxycarbonyl-3-amino-2,2-dimethyl-propylamine.

LC-MS-conditions 05c: *t_R* = 0.57 min; [M+H]⁺ = 446.08.

Example 11:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-(*N,N*-diethyl-amino)-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(diethylamino)-butylamine.

LC-MS-conditions 05b: *t_R* = 0.56 min; [M+H]⁺ = 488.28.

Example 12:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3-hydroxy-propyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-1-propanol.

LC-MS-conditions 02: *t_R* = 0.92 min; [M+H]⁺ = 418.92.

Example 13:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-carbamoyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and beta-alaninamide hydrochloride.

LC-MS-conditions 02: *t_R* = 0.88 min; [M+H]⁺ = 432.20.

Example 14:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-tert-butoxycarbonyl-pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (±)-3-amino-*N*-tert-butoxycarbonyl-pyrrolidine.

LC-MS-conditions 05c: *t_R* = 0.78 min; [M+H]⁺ = 530.03.

Example 15:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and cyclopentylamine.

LC-MS-conditions 05b: *t*_R = 0.85 min; [M+H]⁺ = 429.15.

Example 16:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-tert-butoxycarbonyl-3-amino-propylamine.

LC-MS-conditions 05c: *t*_R = 0.53 min; [M+H]⁺ = 417.99.

Example 17:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-ethoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-ethoxypropylamine.

LC-MS-conditions 05b: *t*_R = 0.79 min; [M+H]⁺ = 447.17.

Example 18:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidinyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-tert-butoxycarbonyl-2-(amino-methyl)-pyrrolidine.

LC-MS-conditions 05c: *t*_R = 0.55 min; [M+H]⁺ = 444.06.

Example 19:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2,2-trifluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2,2,2-trifluoro-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.80 min; [M+H]⁺ = 443.07.

Example 20:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-fluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-fluoro-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.73 min; [M+H]⁺ = 407.10.

Example 21:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-methyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-tert-butoxycarbonyl-*N*-methyl-2-amino-ethylamine.

LC-MS-conditions 05c: *t_R* = 0.54 min; [M+H]⁺ = 418.17.

Example 22:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-tetrahydrofuranyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-tetrahydrofuranyl-methylamine.

LC-MS-conditions 05b: *t_R* = 1.10 min; [M+H]⁺ = 445.31.

Example 23:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *trans*-4-amino-cyclohexanol hydrochloride.

LC-MS-conditions 05: *t_R* = 0.83 min; [M+H]⁺ = 459.20.

Example 24:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-ethylsulfanyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-ethylsulfanyl-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.83 min; [M+H]⁺ = 449.20.

Example 25:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(*N,N*-diethyl-amino)-pent-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(*N,N*-diethyl-amino)-1-methyl-butylamine.

LC-MS-conditions 05b: *t_R* = 0.92 min; [M+H]⁺ = 502.11.

Example 26:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (±)-*N*-*tert*-butoxycarbonyl-(3-amino)-piperidine.

LC-MS-conditions 05c: *t_R* = 0.55 min; [M+H]⁺ = 444.01.

Example 27:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-*tert*-butoxycarbonyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-*tert*-butoxycarbonyl-amino-ethylamine.

LC-MS-conditions 05c: *t*_R = 0.75 min; [M+H]⁺ = 504.02.

Example 28:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-hydroxy-prop-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and D,L-2-amino-1-propanol.

- 15 LC-MS-conditions 05: *t*_R = 0.81 min; [M+H]⁺ = 419.07.

Example 29:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-imidazolidin-2-on-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-imidazolidin-2-on-1-yl-ethylamine.

LC-MS-conditions 05b: *t*_R = 0.96 min; [M+H]⁺ = 472.98.

Example 30:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide :**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1-pyrrolidino)-propylamine.

LC-MS-conditions 05b: *t*_R = 0.86 min; [M+H]⁺ = 472.10.

Example 31:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-methoxy-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 5 Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-methoxy-ethylamine.

LC-MS-conditions 02: *t_R* = 0.98 min; [M+H]⁺ = 418.98.

Example 32:

- 10 **(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R*^{*})-*N*⁵-(4-bromo-phenyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-benzoimidazol-2-yl)-propylamine.

- 15 LC-MS-conditions 05b: *t_R* = 0.59 min; [M+H]⁺ = 519.28.

Example 33:

(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 20 Following general procedure **A**, starting from (5*R*^{*})-*N*⁵-(4-bromo-phenyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(1-methyl-pyrrolidin-2-yl)-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.85 min; [M+H]⁺ = 472.17.

Example 34:

- 25 **(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(2-hydroxy-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*^{*})-*N*⁵-(4-bromo-phenyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-amino-ethanol.

LC-MS-conditions 02: *t_R* = 0.90 min; [M+H]⁺ = 405.26.

Example 35:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and bis-(2-methoxy-ethyl)-amine.

LC-MS-conditions 05b: *t_R* = 0.78 min; [M+H]⁺ = 477.20.

Example 36:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyano-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and amino-acetonitrile.

- 15 LC-MS-conditions 05b: *t_R* = 0.70 min; [M+H]⁺ = 400.09.

Example 37:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-pyrazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-1*H*-pyrazol-1-yl-propylamine.

LC-MS-conditions 05b: *t_R* = 0.73 min; [M+H]⁺ = 469.15.

Example 38:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-aminomethyl-phenyl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(*tert*-butoxycarbonyl-aminomethyl)-benzylamine.

LC-MS-conditions 05c: *t_R* = 0.57 min; [M+H]⁺ = 480.04.

Example 39:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-ethyl-*N*⁶-(2-diethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-ethyl-2-(*N,N*-diethyl-amino)-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.60 min; [M+H]⁺ = 488.21.

Example 40:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-imidazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-imidazol-1-yl)-propylamine.

LC-MS-conditions 05b: *t_R* = 0.54 min; [M+H]⁺ = 469.20.

Example 41:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-([1,4]-dioxan-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and [1,4]-dioxan-2-yl-methylamine.

LC-MS-conditions 05b: *t_R* = 1.06 min; [M+H]⁺ = 460.97.

Example 42:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-butanol.

LC-MS-conditions 05: *t_R* = 0.81 min; [M+H]⁺ = 433.21.

Example 43:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(4-methyl-piperazin-1-yl)-propylamine.

LC-MS-conditions 05b: *t*_R = 0.74 min; [M+H]⁺ = 501.10.

5 Example 44:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-tert-butoxycarbonyl-2-amino-ethylamine.

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LC-MS-conditions 05c: *t*_R = 0.53 min; [M+H]⁺ = 404.06.

Example 45:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

15 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-methyl-2-(*N,N*-dimethyl-amino)-ethylamine.

LC-MS-conditions 05b: *t*_R = 0.55 min; [M+H]⁺ = 446.17.

Example 46:

20 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-tert-butoxycarbonyl-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-tert-butoxycarbonyl-amino-butylamine.

25 LC-MS-conditions 05c: *t*_R = 0.78 min; [M+H]⁺ = 532.07.

Example 47:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methyl-tert-butoxycarbonyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-tert-butoxycarbonyl-*N*-methyl-2-amino-ethylamine.

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LC-MS-conditions 05c: *t*_R = 0.78 min; [M+H]⁺ = 517.63.

Example 48:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidin-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-pyrrolidino-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.54 min; [M+H]⁺ = 458.14.

Example 49:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-1*H*-[1,2,4]-triazol-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-1*H*-[1,2,4]-triazol-1-yl-ethylamine.

LC-MS-conditions 05: *t_R* = 0.78 min; [M+H]⁺ = 456.13.

Example 50:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(furan-3-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and furan-3-yl-methylamine.

LC-MS-conditions 05b: *t_R* = 0.79 min; [M+H]⁺ = 441.18.

Example 51:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-dimethyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-dimethyl-amino-pentylamine.

LC-MS-conditions 02: *t_R* = 0.84 min; [M+H]⁺ = 474.32.

Example 52:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-dimethyl-amino-propylamine.

LC-MS-conditions 02: *t*_R = 0.82 min; [M+H]⁺ = 446.09.

Example 53:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-methoxy-propylamine.

- 15 LC-MS-conditions 02: *t*_R = 1.00 min; [M+H]⁺ = 432.99.

Example 54:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1-ethyl-pyrrolidin-2-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (1-ethyl-pyrrolidin-2-yl)-methylamine.

LC-MS-conditions 05b: *t*_R = 0.88 min; [M+H]⁺ = 472.12.

Example 55:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-[1,2,4]-triazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-1*H*-[1,2,4]-triazol-1-yl-propylamine.

LC-MS-conditions 05b: *t*_R = 0.63 min; [M+H]⁺ = 470.22.

Example 56:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (±)-3-amino-*N*-*tert*-butoxycarbonyl-piperidine.

LC-MS-conditions 05c: *t*_R = 0.81 min; [M+H]⁺ = 544.06.

Example 57:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(*N*-*tert*-butoxycarbonyl-amino)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-*tert*-butoxycarbonyl-amino-propylamine.

- 15 LC-MS-conditions 05c: *t*_R = 0.77 min; [M+H]⁺ = 517.58.

Example 58:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-methyl-butylamine.

LC-MS-conditions 05b: *t*_R = 0.89 min; [M+H]⁺ = 431.13.

Example 59:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-1-hydroxy-4-methyl-pent-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2*S*)-2-amino-4-methyl-pentan-1-ol.

LC-MS-conditions 05: *t*_R = 0.93 min; [M+H]⁺ = 461.21.

Example 60:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methoxy-carbonyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and beta-alanine methylester hydrochloride.

LC-MS-conditions 02: *t_R* = 0.99 min; [M+H]⁺ = 446.94.

Example 61:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(4-aminosulfonyl-phenyl)-ethylamine.

- 15 LC-MS-conditions 05b: *t_R* = 1.06 min; [M+H]⁺ = 544.03.

Example 62:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-5-methyl-1*H*-pyrazol-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(1-ethyl-5-methyl-1*H*-pyrazol-3-yl)-ethylamine.

LC-MS-conditions 05: *t_R* = 0.87 min; [M+H]⁺ = 497.14.

- 25 **Example 63:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and bis-(2-

- 30 methoxy-ethyl)-amine. LC-MS-conditions 02: *t_R* = 1.02 min; [M+H]⁺ = 477.24.

Example 64:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.88 min; [M+H]⁺ = 483.00.

Example 65:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2*S*)-2-amino-propionamide.

15 LC-MS-conditions 02: *t_R* = 0.89 min; [M+H]⁺ = 431.92.

Example 66:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-diethyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-diethyl-amino-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.86 min; [M+H]⁺ = 460.09.

Example 67:

25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and
30 pentylamine.

LC-MS-conditions 05b: *t_R* = 0.89 min; [M+H]⁺ = 431.10.

Example 68:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-*tert*-butoxycarbonyl-amino-pentylamine.

LC-MS-conditions 05c: *t*_R = 0.80 min; [M+H]⁺ = 546.04.

10 **Example 69:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-(3-methyl-butyl)-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-1-isopentyl-piperidine.

15

LC-MS-conditions 05b: *t*_R = 0.96 min; [M+H]⁺ = 514.10.

Example 70:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyridin-2-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-pyridin-2-yl-ethylamine.

LC-MS-conditions 02: *t*_R = 0.83 min; [M+H]⁺ = 465.93.

25

Example 71:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-*N*-*tert*-butoxycarbonyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2,2-dimethyl-3-*tert*-butoxycarbonyl-amino-propylamine.

30

LC-MS-conditions 05c: *t*_R = 0.84 min; [M+H]⁺ = 546.02.

Example 72:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-phenyl-1*H*-pyrazol-5-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-phenyl-2*H*-pyrazol-3-ylamine. LC-MS-conditions 05b: *t*_R = 1.15 min; [M+H]⁺ = 503.04.

Example 73:

- 10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide (1.0 eq.) in DMF (0.2 M)
15 were added cyclopropylamine (1.5 eq.), PyBOP (1.5 eq.) and DIPEA (3.0 eq.). The reaction mixture was stirred at rt until completion of the reaction. The reaction mixture was then partitioned between water and EA. The layers were separated and the aq. layer extracted with EA (3x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC or
20 HPLC gave the desired compound.
LC-MS-conditions 02: *t*_R = 1.00 min; [M+H]⁺ = 401.13.

Example 74:

- 25 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and butylamine.
LC-MS-conditions 02: *t*_R = 1.07 min; [M+H]⁺ = 416.25.

Example 75:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(hexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and hexylamine.

LC-MS-conditions 05b: *t*_R = 1.25 min; [M+H]⁺ = 445.11.

10 **Example 76:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-ethylamine.

LC-MS-conditions 05b: *t*_R = 1.04 min; [M+H]⁺ = 497.09.

Example 77:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-phenyl-2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-phenyl-2-morpholino-ethylamine.

LC-MS-conditions 05b: *t*_R = 0.94 min; [M+H]⁺ = 550.09.

25

Example 78:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-diethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-diethylamino-propylamine.

LC-MS-conditions 05b: *t*_R = 0.88 min; [M+H]⁺ = 474.07.

30

Example 79:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-pyrrolidin-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-pyrrolidin-2-yl-methylamine.

LC-MS-conditions 05c: *t*_R = 0.83 min; [M+H]⁺ = 544.06.

10 **Example 80:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-

15 morpholino-ethylamine.

LC-MS-conditions 05b: *t*_R = 0.83 min; [M+H]⁺ = 474.05.

Example 81:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *cis*-2-amino-cyclohexane-carboxylic acid amide.

LC-MS-conditions 05b: *t*_R = 1.05 min; [M+H]⁺ = 486.06.

25

Example 82:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-piperidin-1-yl-propan-1-on-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-
- 30 amino-1-piperidin-1-yl-propan-1-one.

LC-MS-conditions 05b: *t*_R = 1.13 min; [M+H]⁺ = 500.08.

Example 83:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-benzyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-*N*-benzyl-piperidine.

LC-MS-conditions 05b: *t_R* = 0.60 min; [M+H]⁺ = 534.24.

Example 84:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-hexyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-methyl-hexylamine.

15 LC-MS-conditions 05b: *t_R* = 0.97 min; [M+H]⁺ = 459.15.

Example 85:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3,3-dimethyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3,3-dimethyl-butylamine.

LC-MS-conditions 05b: *t_R* = 0.93 min; [M+H]⁺ = 445.13.

25 **Example 86:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-methyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-*N*-methyl-piperidine.

30 LC-MS-conditions 05b: *t_R* = 0.83 min; [M+H]⁺ = 458.11.

Example 87:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-morpholino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-morpholino-propylamine.

LC-MS-conditions 05b: *t*_R = 0.84 min; [M+H]⁺ = 488.15.

10 **Example 88:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(5-methyl-1*H*-pyrazol-4-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(5-methyl-1*H*-pyrazol-4-yl)-propylamine.

- 15

LC-MS-conditions 05b: *t*_R = 0.97 min; [M+H]⁺ = 483.05.

Example 89:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-*tert*-butoxycarbonyl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-*tert*-butoxycarbonyl-propylamine.

LC-MS-conditions 05b: *t*_R = 1.21 min; [M+H]⁺ = 503.06.

25

Example 90:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-{[(3-*N*-*tert*-butoxycarbonyl-aminomethyl)-phenyl]-methyl}-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(*tert*-butoxycarbonyl-aminomethyl)-benzylamine.

30

LC-MS-conditions 05c: *t*_R = 0.82 min; [M+H]⁺ = 580.00.

Example 91:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-propyl-*N*⁶-(cyclopropylmethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-(cyclopropyl-methyl)-propylamine.

LC-MS-conditions 05b: *t_R* = 0.93 min; [M+H]⁺ = 457.16.

Example 92:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-4-(amino-methyl)-piperidine.

15 LC-MS-conditions 05c: *t_R* = 0.81 min; [M+H]⁺ = 558.03:

Example 93:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and cyclohexylamine.

LC-MS-conditions 05b: *t_R* = 1.22 min; [M+H]⁺ = 443.05.

25 **Example 94:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-*N*-*tert*-butoxycarbonyl-piperidine.

30 LC-MS-conditions 05c: *t_R* = 0.80 min; [M+H]⁺ = 544.04.

Example 95:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-2-phenyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2*S*)-2-amino-3-phenyl-propionamide.

LC-MS-conditions 05b: *t_R* = 1.08 min; [M+H]⁺ = 508.04.

10 **Example 96:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2*S*)-2-amino-3,3,*N*-trimethyl-butyramide.

- 15 LC-MS-conditions 05b: *t_R* = 1.11 min; [M+H]⁺ = 488.11.

Example 97:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-*N*-tert-butoxycarbonyl-aminomethyl-phenyl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(*tert*-butoxycarbonyl-aminomethyl)-benzylamine.

LC-MS-conditions 05c: *t_R* = 0.82 min; [M+H]⁺ = 580.03.

25

Example 98:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-tert-butoxycarbonyl-azetidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 30 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-*N*-tert-butoxycarbonyl-azetidine.

LC-MS-conditions 05c: *t_R* = 0.77 min; [M+H]⁺ = 516.07.

Example 99:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-ethylamine.

LC-MS-conditions 05b: *t*_R = 1.25 min; [M+H]⁺ = 572.15.

Example 100:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-2-methoxy-1-benzyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (1*S*)-1-benzyl-2-methoxy-ethylamine.

15 LC-MS-conditions 05b: *t*_R = 1.19 min; [M+H]⁺ = 509.01.

Example 101:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (5-methyl-3-phenyl-isoxazol-4-yl)-methylamine.

LC-MS-conditions 05b: *t*_R = 0.86 min; [M+H]⁺ = 531.77.

Example 102:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-ethyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropionamide.

30 LC-MS-conditions 05b: *t*_R = 0.63 min; [M+H]⁺ = 433.63.

Example 103:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-methoxy-propylamine.

LC-MS-conditions 05b: *t_R* = 0.77 min; [M+H]⁺ = 435.12.

Example 104:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(tetrahydrofuran-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and tetrahydrofuran-2-yl-methylamine.

15 LC-MS-conditions 05b: *t_R* = 0.78 min; [M+H]⁺ = 447.12.

Example 105:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2-imidazolidin-2-on-1-yl)-ethyl]-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-imidazolidin-2-on-1-yl-ethylamine.

LC-MS-conditions 05b: *t_R* = 0.65 min; [M+H]⁺ = 475.14.

25 **Example 106:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

30 In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide (1.0 eq.) in DMF (0.1 M) were added cyclopropylamine (1.0 eq.), HATU (1.5 eq.), DMAP (0.25 eq.) and DIPEA (5.0 eq.). The reaction mixture was stirred at rt until completion of the reaction. The reaction mixture was then partitioned between sat. aq. NH₄Cl and CH₂Cl₂. The layers were separated and the aq. layer extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over

MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC or HPLC gave the desired compound.

LC-MS-conditions 02: t_R = 1.03 min; $[M+H]^+$ = 403.00.

5 **Example 107:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-hydroxy-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-
10 propanol.

LC-MS-conditions 05: t_R = 0.84 min; $[M+H]^+$ = 421.07.

Example 108:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(1*H*-imidazol-1-yl)-propyl)-(4*S**,7*R**)-[4,7-
15 ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-imidazol-1-yl)-propylamine.

LC-MS-conditions 05b: t_R = 0.57 min; $[M+H]^+$ = 471.18.

20 **Example 109:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(dimethyl-amino)-pentyl)-(4*S**,7*R**)-[4,7-
ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 5-
25 dimethyl-amino-pentylamine.

LC-MS-conditions 05b: t_R = 0.58 min; $[M+H]^+$ = 476.20.

Example 110:

30 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-pyrrolidino-propylamine.

35 LC-MS-conditions 05b: t_R = 0.58 min; $[M+H]^+$ = 474.20.

Example 111:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-(4-methyl-piperazin-1-yl)-propylamine.

LC-MS-conditions 05b: *t_R* = 0.50 min; [M+H]⁺ = 503.22.

Example 112:

10 **(5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethylamine.

15 LC-MS-conditions 05b: *t_R* = 0.59 min; [M+H]⁺ = 485.20.

Example 113:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **F**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-methoxycarbonyl-(4*S*,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)-butylamine.

LC-MS-conditions 02: *t_R* = 0.87 min; [M+H]⁺ = 487.96.

25 **Example 114:**

(5*R)-*N*⁵-(2-Bromopyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-2-bromo-pyridine.

30 LC-MS-conditions 05: *t_R* = 0.68 min; [M+H]⁺ = 487.04.

Example 115:

(5*R)-*N*⁵-(4-Methoxyphenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-methoxy-phenylamine.

LC-MS-conditions 05c: $t_R = 0.55$ min; $[M+H]^+ = 438.29$.

Example 116:

10 **(5*R**)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-2-chloro-pyridine.

15 LC-MS-conditions 05: $t_R = 0.66$ min; $[M+H]^+ = 443.15$.

Example 117:

(5*R)-*N*⁵-(Benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-benzothiazole.

LC-MS-conditions 05: $t_R = 0.65$ min; $[M+H]^+ = 465.18$.

Example 118:

25 **(5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and *p*-bromo-benzylamine hydrochloride.

30 LC-MS-conditions 05: $t_R = 0.72$ min; $[M+H]^+ = 500.17$.

Example 119:

(5*R)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-bromo-pyridine.

LC-MS-conditions 05: *t_R* = 0.69 min; [M+H]⁺ = 487.16.

Example 120:

10 **(5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-bromo-thiazole.

15 LC-MS-conditions 05: *t_R* = 0.73 min; [M+H]⁺ = 493.03.

Example 121:

(5*R)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-methyl-pyridine.

LC-MS-conditions 05c: *t_R* = 0.40 min; [M+H]⁺ = 423.32.

Example 122:

25 **(5*R**)-*N*⁵-Pentyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and
30 pentylamine.

LC-MS-conditions 05c: *t_R* = 0.56 min; [M+H]⁺ = 401.96.

Example 123:

(5*R)-*N*⁵-[(4-Methyl-phenyl)-methyl]-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-methyl-benzylamine.

LC-MS-conditions 05: *t*_R = 0.72 min; [M+H]⁺ = 435.88.

Example 124:

10 **(5*R**)-*N*⁵-(2-Methoxycarbonyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-methoxycarbonyl-ethylamine.

15 LC-MS-conditions 05c: *t*_R = 0.45 min; [M+H]⁺ = 417.83.

Example 125:

(5*R)-*N*⁵-(Cyclohexyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and cyclohexyl-methylamine.

LC-MS-conditions 05c: *t*_R = 0.56 min; [M+H]⁺ = 428.38.

25 **Example 126:**

(5*R)-*N*⁵-(4-Methyl-cyclohex-1-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-methyl-cyclohexylamine.

30 LC-MS-conditions 05c: *t*_R = 0.57 min; [M+H]⁺ = 428.39.

Example 127:

(5*R*^{*})-*N*⁵-(5-Oxo-hexyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 5 Following general procedures **E** then **G**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-(2-methyl-[1,3]dioxolan-2-yl)-butylamine.

LC-MS-conditions 02: *t*_R = 0.70 min; [M+H]⁺ = 430.02.

10 **Example 128:**

(5*R*^{*})-*N*⁵-(5-Nitro-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- Following general procedure **C**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-nitro-thiazole.

LC-MS-conditions 05: *t*_R = 0.66 min; [M+H]⁺ = 460.09.

Example 129:

(5*R*^{*})-*N*⁵-(5-Chloro-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 20 Following general procedure **C**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-chloro-thiazole.

LC-MS-conditions 05: *t*_R = 0.68 min; [M+H]⁺ = 449.13.

25

Example 130:

(5*R*^{*})-*N*⁵-(5-Cyano-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- Following general procedure **C**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-5-cyano-thiazole.

LC-MS-conditions 05: *t*_R = 0.63 min; [M+H]⁺ = 440.23.

30

Example 131:

(5*R*^{*})-*N*⁵-(Furan-2-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **A**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and furan-2-yl-methylamine.

LC-MS-conditions 05c: $t_R = 0.47$ min; $[M+H]^+ = 412.32$.

Example 132:

10 **(5*R*^{*})-*N*⁵-(1-(4-Bromophenyl)-ethyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 1-(4-Bromophenyl)-ethylamine.

15 LC-MS-conditions 05: $t_R = 0.77$ min; $[M+H]^+ = 513.73$.

Example 133:

(5*R*^{*})-*N*⁵-(4-Trifluoromethoxyphenyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **B**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-trifluoromethoxy-aniline.

LC-MS-conditions 05: $t_R = 0.81$ min; $[M+H]^+ = 492.15$.

25 **Example 134:**

(5*R*^{*})-*N*⁵-(2-Phenoxy-ethyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **A**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-phenoxy-ethylamine.

30 LC-MS-conditions 05c: $t_R = 0.53$ min; $[M+H]^+ = 452.30$.

Example 135:

(5*R)-*N*⁵-(3-Methyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and isopentylamine.

LC-MS-conditions 05c: *t*_R = 0.52 min; [M+H]⁺ = 401.97.

Example 136:

10 **(5*R**)-*N*⁵-Butyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and butylamine.

15 LC-MS-conditions 05c: *t*_R = 0.52 min; [M+H]⁺ = 388.38.

Example 137:

(5*R)-*N*⁵-(5-Methyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (5-methyl-furan-2-yl)-methylamine.

LC-MS-conditions 05c: *t*_R = 0.50 min; [M+H]⁺ = 426.33.

Example 138:

25 **(5*R**)-*N*⁵-(2-Methyl-benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-2-methyl-benzothiazole.

30 LC-MS-conditions 05: *t*_R = 0.68 min; [M+H]⁺ = 479.17.

Example 139:

(5*R)-*N*⁵-(2-Phenyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-phenyl-ethylamine.

LC-MS-conditions 05c: *t*_R = 0.53 min; [M+H]⁺ = 436.32.

Example 140:

10 **(5*R**)-*N*⁵-(4-Oxo-pentyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **E** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-(2-methyl-[1,3]dioxolan-2-yl)-propylamine.

15 LC-MS-conditions 02: *t*_R = 0.68 min; [M+H]⁺ = 416.47.

Example 141:

(5*R)-*N*⁵-(3-(1*H*-Imidazol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-1*H*-imidazol-1-yl-propylamine.

LC-MS-conditions 05c: *t*_R = 0.32 min; [M+H]⁺ = 440.36.

25 **Example 142:**

(5*R)-*N*⁵-(2-Chloro-pyrimidin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-2-chloro-pyrimidine.

30 LC-MS-conditions 05: *t*_R = 0.63 min; [M+H]⁺ = 444.13.

Example 143:

(5*R)-*N*⁵-(3-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-bromo-benzylamine.

LC-MS-conditions 05: *t*_R = 0.74 min; [M+H]⁺ = 499.62.

Example 144:

10 **(5*R**)-*N*⁵-(Benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-benzothiazole.

15 LC-MS-conditions 05: *t*_R = 0.74 min; [M+H]⁺ = 465.18.

Example 145:

(5*R)-*N*⁵-(5-*tert*-Butyl-isoxazol-3-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-amino-5-*tert*-butyl-isoxazole.

LC-MS-conditions 05: *t*_R = 0.76 min; [M+H]⁺ = 455.21.

25 **Example 146:**

(5*R)-*N*⁵-(3-Methyl-benzo[d]isothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-3-methyl-benzoisothiazole.

30 LC-MS-conditions 05: *t*_R = 0.71 min; [M+H]⁺ = 479.19.

Example 147:

(5*R)-*N*⁵-(1*H*-Indol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-1*H*-indole.

LC-MS-conditions 05: *t*_R = 0.65 min; [M+H]⁺ = 447.17.

Example 148:

10 **(5*R**)-*N*⁵-(6-Fluoro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-6-fluoro-benzothiazole.

15 LC-MS-conditions 05: *t*_R = 0.76 min; [M+H]⁺ = 483.10.

Example 149:

(5*R)-*N*⁵-(2-Ethyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-ethyl-butylamine.

LC-MS-conditions 05: *t*_R = 0.75 min; [M+H]⁺ = 416.28.

25 **Example 150:**

(5*R)-*N*⁵-(4-(4-Chlorophenyl)-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-4-(4-chlorophenyl)-thiazole.

30 LC-MS-conditions 05: *t*_R = 0.86 min; [M+H]⁺ = 525.10.

Example 151:

(5*R)-*N*⁵-(Benzo[2,1,3]oxadiazol-4-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-amino-benzo[2,1,3]oxadiazole.

LC-MS-conditions 05: *t*_R = 0.73 min; [M+H]⁺ = 450.19.

Example 152:

10 **(5*R**)-*N*⁵-(4-*tert*-Butyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-4-*tert*-butyl-thiazole.

15 LC-MS-conditions 05: *t*_R = 0.81 min; [M+H]⁺ = 471.19.

Example 153:

(5*R)-*N*⁵-(3-Phenyl-[1,2,4]thiadiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-3-phenyl-[1,2,4]thiadiazole.

LC-MS-conditions 05: *t*_R = 0.80 min; [M+H]⁺ = 492.17.

25 **Example 154:**

(5*R)-*N*⁵-(6-Chloro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-amino-6-chloro-benzothiazole.

30 LC-MS-conditions 05: *t*_R = 0.82 min; [M+H]⁺ = 499.01.

Example 155:

(5*R)-*N*⁵-(3-(2-Methyl-1*H*-indol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-(2-methyl-1*H*-indol-1-yl)-propylamine.

LC-MS-conditions 05: *t_R* = 0.79 min; [M+H]⁺ = 503.30.

Example 156:

10 **(5*R**)-*N*⁵-(2-(1-Methyl-1*H*-benzimidazol-2-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(1-methyl-1*H*-benzimidazol-2-yl)-ethylamine.

15 LC-MS-conditions 05: *t_R* = 0.48 min; [M+H]⁺ = 490.19.

Example 157:

(5*R)-*N*⁵-(2-(1*H*-Indol-1-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(1*H*-indol-1-yl)-ethylamine.

LC-MS-conditions 05: *t_R* = 0.70 min; [M+H]⁺ = 475.19.

Example 158:

25 **(5*R**)-*N*⁵-(2-(2-Methoxy-phenyl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(2-methoxy-phenyl)-ethylamine.

30 LC-MS-conditions 05: *t_R* = 0.72 min; [M+H]⁺ = 466.22.

Example 159:

(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(3,5-dimethyl-pyrazol-1-yl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(3,5-dimethyl-pyrazol-1-yl)-propionic acid.

LC-MS-conditions 05: *t*_R = 0.84 min; [M+H]⁺ = 497.18.

Example 160:

10 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[5-phenyl-isoxazole-4-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-phenyl-isoxazole-4-carboxylic acid.

15 LC-MS-conditions 05: *t*_R = 1.09 min; [M+H]⁺ = 518.11.

Example 161:

(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-(2-oxo-pyrrolidin-1-yl)-butyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

20 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(2-oxo-pyrrolidin-1-yl)-butyric acid.

LC-MS-conditions 05: *t*_R = 0.80 min; [M+H]⁺ = 499.65.

25 **Example 162:**

(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-chloro-phenyl)-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2-chloro-phenyl)-acetic acid.

30 LC-MS-conditions 05: *t*_R = 1.00 min; [M+H]⁺ = 499.18.

Example 163:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-methoxy-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 5 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-methoxy-propionic acid.

LC-MS-conditions 05: *t_R* = 0.85 min; [M+H]⁺ = 433.13.

10 **Example 164:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(*N,N*-dimethyl-aminocarbonyl)-propionyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N,N*-dimethyl-succinamic acid.

- 15

LC-MS-conditions 05: *t_R* = 0.81 min; [M+H]⁺ = 474.17.

Example 165:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[2,2-dichloro-1-methyl-cyclopropylcarbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 20

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2,2-dichloro-1-methyl-cyclopropanecarboxylic acid.

LC-MS-conditions 05: *t_R* = 1.00 min; [M+H]⁺ = 497.04.

- 25

Example 166:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-methoxycarbonyl-butanoyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and pentanedioic acid monomethyl ester.

- 30

LC-MS-conditions 05: *t_R* = 0.88 min; [M+H]⁺ = 475.14.

Example 167:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-(pentanoylamino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 5 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and pentanoic acid. LC-MS-conditions 05: *t*_R = 0.96 min; [M+H]⁺ = 431.20.

Example 168:

- 10 **(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2,5-dimethyl-thiazol-4-yl)-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2,5-dimethylthiazol-4-yl)-acetic acid.

- 15 LC-MS-conditions 05: *t*_R = 0.89 min; [M+H]⁺ = 499.54.

Example 169:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[1-phenyl-1*H*-pyrazole-5-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 20 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-phenyl-2*H*-pyrazole-3-carboxylic acid.

LC-MS-conditions 05: *t*_R = 0.97 min; [M+H]⁺ = 517.14.

- 25 **Example 170:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-aminocarbonyl-propionyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(aminomethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and succinamic acid.

- 30 LC-MS-conditions 05: *t*_R = 0.75 min; [M+H]⁺ = 446.14.

Example 171:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[(4-methyl-pyridine-3-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 5 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-methyl-nicotinic acid.

LC-MS-conditions 05: $t_R = 0.75$ min; $[M+H]^+ = 466.20$.

10 **Example 172:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(isobutyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and isobutyric acid.

- 15 LC-MS-conditions 05: $t_R = 0.92$ min; $[M+H]^+ = 417.18$.

Example 173:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[(N-ethyl-piperidine-4-carbonyl)-amino]-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 20 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-ethyl-piperidine-4-carboxylic acid.

LC-MS-conditions 05: $t_R = 0.72$ min; $[M+H]^+ = 486.20$.

25 **Example 174:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[(3-pyridin-3-yl-propionylamino)-methyl]-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-pyridin-3-yl-propionic acid.

- 30 LC-MS-conditions 05: $t_R = 0.71$ min; $[M+H]^+ = 480.16$.

Example 175:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[(N-(3-methoxy-propionyl)-N-methyl-amino)-
methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 35

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-[(methyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-methoxy-propionic acid.

LC-MS-conditions 05: *t*_R = 0.90 min; [M+H]⁺ = 447.15.

5

Example 176:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[2-chloro-3-fluoro-phenyl-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-chloro-3-fluoro-benzoic acid.

LC-MS-conditions 05: *t*_R = 0.98 min; [M+H]⁺ = 503.04.

Example 177:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-pyrrolidin-1-yl-butanoylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-pyrrolidin-1-yl-butyric acid.

LC-MS-conditions 05: *t*_R = 0.73 min; [M+H]⁺ = 486.23.

Example 178:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[1,5-dimethyl-1*H*-pyrazole-3-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid.

LC-MS-conditions 05: *t*_R = 0.93 min; [M+H]⁺ = 468.91.

Example 179:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(cyclopentyl-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and cyclopentanecarboxylic acid.

35

LC-MS-conditions 05: $t_R = 0.97$ min; $[M+H]^+ = 443.15$.

Example 180:

5 **(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-methyl-thiazol-4-yl)-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2-methyl-thiazol-4-yl)-acetic acid.

LC-MS-conditions 05: $t_R = 0.89$ min; $[M+H]^+ = 485.96$.

10

Example 181:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(*N,N*-dimethyl-amino)-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

15 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and dimethylamino-acetic acid.

LC-MS-conditions 05: $t_R = 0.75$ min; $[M+H]^+ = 432.13$.

Example 182:

20 **(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[*N*-(2-(2-chloro-phenyl)-acetyl)-*N*-methyl-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-6-[(methyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (2-chloro-phenyl)-acetic acid.

25 LC-MS-conditions 05: $t_R = 1.06$ min; $[M+H]^+ = 513.13$.

Example 183:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[*N*-(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-*N*-methyl-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

30 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-6-[(methyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1,5-dimethyl-1*H*-pyrazole-3-carboxylic acid.

LC-MS-conditions 05: $t_R = 0.91$ min; $[M+H]^+ = 483.27$.

Example 184:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-cyclopropyl-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 5 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and cyclopropyl-acetic acid.

LC-MS-conditions 05: $t_R = 0.92$ min; $[M+H]^+ = 429.20$.

10 **Example 185:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(1-methyl-1*H*-benzoimidazol-2-yl)-propionyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1-methyl-1*H*-benzoimidazol-2-yl)-propionic acid.

LC-MS-conditions 05: $t_R = 0.78$ min; $[M+H]^+ = 533.12$.

Example 186:

- 20 **(5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-1*H*-indol-3-yl-propionyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-indol-3-yl)-propionic acid.

- 25 LC-MS-conditions 05: $t_R = 0.96$ min; $[M+H]^+ = 518.20$.

Example 187:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(butanoyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 30 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and butyric acid.

LC-MS-conditions 02: $t_R = 1.02$ min; $[M+H]^+ = 417.45$.

Example 188:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(4-fluoro-phenyl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

- 5 Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(4-fluoro-phenyl)-propionic acid.

LC-MS-conditions 05: *t_R* = 0.99 min; [M+H]⁺ = 497.16.

10 **Example 189:**

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-phenyl-acryloylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-phenyl-acrylic acid.

15

LC-MS-conditions 05: *t_R* = 0.99 min; [M+H]⁺ = 477.13.

Example 190:

(5*R)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide:**

20

Following general procedure **D**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-6-(6*R**)-(amino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carboxylic acid.

LC-MS-conditions 05: *t_R* = 0.95 min; [M+H]⁺ = 502.99.

25

Example 191:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

30

Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and [4-(2-methyl-[1,3]dioxolan-2-yl)-thiazol-2-yl]-methylamine.

LC-MS-conditions 01: *t_R* = 0.66 min; [M+H]⁺ = 471.17.

Example 192:

(5*R)-*N*⁵-(4-Acetyl-phenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 1-(4-amino-phenyl)-ethanone.

LC-MS-conditions 02: $t_R = 0.78$ min; $[M+H]^+ = 450.55$.

10 **Example 193:**

(5*R)-*N*⁵-(5-Methyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedure **F**, starting from (5*R**)-*N*⁵-(5-methyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)-butylamine.

LC-MS-conditions 02: $t_R = 0.77$ min; $[M+H]^+ = 429.17$.

Example 194:

(5*R)-*N*⁵-(5-Acetyl-thiophen-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and [5-(2-methyl-[1,3]dioxolan-2-yl)-thiophen-2-yl]-methylamine.

LC-MS-conditions 02: $t_R = 0.74$ min; $[M+H]^+ = 470.48$.

25

Example 195:

(5*R)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedure **J**, starting from (5*R**)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)-butylamine.

LC-MS-conditions 02: $t_R = 0.71$ min; $[M+H]^+ = 454.27$.

30

Example 196:

(5*R*)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 5 Following general procedure J, starting from (5*R*)-*N*⁵-(5-acetyl-furan-2-yl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)-butylamine.

LC-MS-conditions 02: *t*_R = 0.73 min; [M+H]⁺ = 456.18.

10 **Example 197:**

(5*R*^{*})-*N*⁵-(4-Trifluoromethyl-phenyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-

- 15 aminobenzotrifluoride.

LC-MS-conditions 01: *t*_R = 0.85 min; [M+H]⁺ = 476.13.

Example 198:

(5*R*^{*})-*N*⁵-(2-Acetyl-oxazol-5-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 20

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a solution of (5*R*^{*})-*N*⁵-(2-[1-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-oxazol-5-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide (1.0 eq.) in THF (0.05 M) was added a 1 M solution of TBAF in THF (1.5 eq.) at 0 °C. The reaction mixture was stirred at rt until completion of the reaction. The reaction mixture was diluted with EA, washed with brine (3x), dried over MgSO₄, filtered, and the solvents were removed under reduced pressure in order to give (5*R*^{*})-*N*⁵-(2-(1-hydroxy-ethyl)-oxazol-5-yl-methyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide. The crude material was

25 dissolved in AcCN (0.06 M) and treated with MnO₂ (5.5 eq.) at 50 °C. Once the reaction was completed, the mixture was filtered and concentrated under reduced pressure. Purification by HPLC gave the title compound.

- 30

LC-MS-conditions 01: *t*_R = 0.66 min; [M+H]⁺ = 455.23.

Example 199:

(5*R)-*N*⁵-(2-(4,5-Dimethyl-1*H*-imidazol-2-yl)-ethyl)-(6*R**)-*N*⁶-(4-bromophenyl)-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-bromo-
5 phenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(4,5-dimethyl-
1*H*-imidazol-2-yl)-ethylamine.

LC-MS-conditions 05c: *t*_R = 0.59 min; [M+H]⁺ = 483.20.

Example 200:

10 **(5*R**)-*N*⁵-(4-Iodophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-
ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-
pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-
iodo-benzylamine hydrochloride.

15 LC-MS-conditions 06: *t*_R = 0.68 min; [M+H]⁺ = 547.75.

Example 201:

(5*R)-*N*⁵-(5-(iso-Butyl)-isoxazol-3-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-
(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-
pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 1-
(5-isobutyl-isoxazol-3-yl)-methylamine.

LC-MS-conditions 06: *t*_R = 0.64 min; [M+H]⁺ = 468.89.

25 **Example 202:**

(5*R)-*N*⁵-(2-Bromo-thiophen-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-
[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-
pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-
30 bromothiophen-4-yl)-methylamine.

LC-MS-conditions 06: *t*_R = 0.67 min; [M+H]⁺ = 506.49.

Example 203:

(5*R)-*N*⁵-(2-Fluoro-4-bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 5 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromo-2-fluorobenzylamine hydrochloride.

LC-MS-conditions 06: $t_R = 0.69$ min; $[M+H]^+ = 517.75$.

10 **Example 204:**

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethylamino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **J**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-*N,N*-dimethylpropanamide.

15

LC-MS-conditions FA: $t_R = 0.94$ min; $[M+H]^+ = 460.11$.

Example 205:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-4-oxobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

20

Following general procedure **J**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-aminobutanamide hydrochloride.

LC-MS-conditions FA: $t_R = 0.87$ min; $[M+H]^+ = 446.08$.

25

Example 206:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **J**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-1-(pyrrolidin-1-yl)propan-1-one hydrochloride.

30

LC-MS-conditions FA: $t_R = 0.98$ min; $[M+H]^+ = 486.11$.

Example 207:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-2-oxoethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **J**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-aminoacetamide hydrochloride.

LC-MS-conditions FA: *t_R* = 0.84 min; [M+H]⁺ = 418.04.

Example 208:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-ethyl-piperazin-1-yl)-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(4-ethylpiperazin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t_R* = 0.57 min; [M+H]⁺ = 529.20.

Example 209:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-piperidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(piperidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t_R* = 0.67 min; [M+H]⁺ = 500.14.

Example 210:

25 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(azetidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(azetidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t_R* = 0.64 min; [M+H]⁺ = 472.12.

Example 211:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-morpholino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-morpholinobutan-1-amine.

LC-MS-conditions TFA: *t_R* = 0.63 min; [M+H]⁺ = 502.19.

Example 212:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-1,4-diazepan-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **K**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(4-methyl-1,4-diazepan-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t_R* = 0.56 min; [M+H]⁺ = 529.19.

Example 213:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **K**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(4-methylpiperazin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t_R* = 0.58 min; [M+H]⁺ = 515.17.

25 **Example 214:**

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-4-oxobutyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-1-(pyrrolidin-1-yl)butan-1-one hydrochloride.

30 LC-MS-conditions FA: *t_R* = 1.00 min; [M+H]⁺ = 500.13.

Example 215:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-(2-(pyrrolidin-1-yl)ethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **K**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(2-(pyrrolidin-1-yl)ethoxy)ethanamine hydrochloride.

LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 502.15.

Example 216:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3*R*,6*S*)-6-(pyrrolidin-1-ylmethyl)tetrahydro-2*H*-pyran-3-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **K**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (3*R*,6*S*)-6-(pyrrolidin-1-ylmethyl)tetrahydro-2*H*-pyran-3-amine hydrochloride.

15 LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 528.20.

Example 217:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-acetyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **I**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(4-(4-aminobutyl)piperazin-1-yl)ethanone.

LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 543.15.

Example 218:

25 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **L**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *cis*-4-(pyrrolidin-1-ylmethyl)cyclohexanamine.

30 LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 526.25.

Example 219:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*R*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (*R*)-4-(3-fluoropyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 504.18.

Example 220:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*S*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and (*S*)-4-(3-fluoropyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 504.16.

Example 221:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(5-pyrrolidino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **K**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 5-(pyrrolidin-1-yl)pentan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 500.14.

25 **Example 222:**

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **L**, starting from (5*R*)-*N*⁵-(4-bromo-phenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *trans*-4-(pyrrolidin-1-ylmethyl)cyclohexanamine.

30 LC-MS-conditions TFA: *t*_R = 0.69 min; [M+H]⁺ = 526.19.

Example 223:

(5*R)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methylamino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **N**, starting from (5*R**)-*N*⁵-(4-bromo-phenyl)-(6*R**)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and methylamine.

LC-MS-conditions FA: *t_R* = 0.88 min; [M+H]⁺ = 446.10.

Example 224:

10 **(5*R**)-*N*⁵-(2-Acetyl-thiazol-5-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-(2-methyl-[1,3]dioxolan-2-yl)thiazol-5-yl)methanamine.

15 LC-MS-conditions TFA: *t_R* = 0.48 min; [M+H]⁺ = 471.25.

Example 225:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **K**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-pyrrolidin-1-yl-butylamine.

LC-MS-conditions TFA: *t_R* = 0.61 min; [M+H]⁺ = 493.09.

Example 226:

(5*R)-*N*⁵-(2,6-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **I**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,6-difluoro-4-methoxybenzylamine.

30 LC-MS-conditions TFA: *t_R* = 0.59 min; [M+H]⁺ = 488.26.

Example 227:

(5*R)-*N*⁵-(2,3-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,3-difluoro-4-methoxybenzylamine.

LC-MS-conditions FA: *t*_R = 0.73 min; [M+H]⁺ = 488.28.

Example 228:

10 **(5*R**)-*N*⁵-(3-Fluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-fluoro-4-methoxybenzylamine.

15 LC-MS-conditions TFA: *t*_R = 0.56 min; [M+H]⁺ = 470.28.

Example 229:

(5*R)-*N*⁵-(3,5-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

20 Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3,5-difluoro-4-methoxybenzylamine.

LC-MS-conditions FA: *t*_R = 0.74 min; [M+H]⁺ = 488.29.

Example 230:

25 **(5*R**)-*N*⁵-(4-Chloro-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-chlorobenzylamine.

30 LC-MS-conditions FA: *t*_R = 0.77 min; [M+H]⁺ = 456.24.

Example 231:

(5*R)-*N*⁵-(4-Fluoro-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-fluorobenzylamine.

LC-MS-conditions FA: *t*_R = 0.70 min; [M+H]⁺ = 440.27.

Example 232:

10 **(5*R**)-*N*⁵-(4-Trifluoromethoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-trifluoromethoxybenzylamine.

15 LC-MS-conditions FA: *t*_R = 0.86 min; [M+H]⁺ = 506.26.

Example 233:

(5*R)-*N*⁵-(4-Isopropoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

20 Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-isopropoxybenzylamine.

LC-MS-conditions FA: *t*_R = 0.81 min; [M+H]⁺ = 480.33.

25 **Example 234:**

(5*R)-*N*⁵-(4-Bromo-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (4-bromothiazol-2-yl)methanamine.

30 LC-MS-conditions TFA: *t*_R = 0.52 min; [M+H]⁺ = 507.12.

Example 235:

(5*R)-*N*⁵-(2-Acetyl-oxazol-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

5 Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-(2-methyl-[1,3]dioxolan-2-yl)oxazol-4-yl)methanamine.

LC-MS-conditions TFA: *t*_R = 0.47 min; [M+H]⁺ = 455.33.

Example 236:

10 **(5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(pyrrolidin-1-yl)propan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 486.17.

Example 237:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(pyrrolidin-1-yl)propan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 479.09.

Example 238:

25 **(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **F**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 495.19.

Example 239:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

LC-MS-conditions FA: *t_R* = 0.84 min; [M+H]⁺ = 441.06.

Example 240:

10 **(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

15 LC-MS-conditions FA: *t_R* = 0.79 min; [M+H]⁺ = 439.04.

Example 241:

(5*R*)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-bromophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t_R* = 0.81 min; [M+H]⁺ = 446.11.

25 **Example 242:**

(5*R*)-*N*⁵-(2-Bromo-pyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

30 LC-MS-conditions FA: *t_R* = 0.70 min; [M+H]⁺ = 433.07.

Example 243:

(5*R)-*N*⁵-(4-Acetyl-oxazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (4-(2-methyl-[1,3]dioxolan-2-yl)-oxazol-2-yl)methanamine.

LC-MS-conditions TFA: *t*_R = 0.43 min; [M+H]⁺ = 455.23.

Example 244:

10 **(5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and isobutylamine.

15 LC-MS-conditions FA: *t*_R = 0.83 min; [M+H]⁺ = 402.18.

Example 245:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and isobutylamine.

LC-MS-conditions FA: *t*_R = 1.10 min; [M+H]⁺ = 424.06.

Example 246:

25 **(5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and
30 isobutylamine.

LC-MS-conditions FA: *t*_R = 1.10 min; [M+H]⁺ = 431.12.

Example 247:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-benzo[d]imidazol-2-yl)propan-1-amine.

LC-MS-conditions FA: *t_R* = 0.63 min; [M+H]⁺ = 504.18.

Example 248:

10 **(5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-benzo[d]imidazol-2-yl)propan-1-amine.

15 LC-MS-conditions FA: *t_R* = 0.83 min; [M+H]⁺ = 526.05.

Example 249:

(5*R)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(1*H*-benzo[d]imidazol-2-yl)propan-1-amine.

LC-MS-conditions FA: *t_R* = 0.86 min; [M+H]⁺ = 533.15.

Example 250:

(5*R)-*N*⁵-(2-Methoxy-pyrid-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

25 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 6-methoxypyridin-3-amine.

30 LC-MS-conditions TFA: *t_R* = 0.48 min; [M+H]⁺ = 439.27.

Example 251:

(5*R)-*N*⁵-(2-Bromo-pyrazin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-bromopyrazin-2-amine.

LC-MS-conditions TFA: *t*_R = 0.58 min; [M+H]⁺ = 488.15.

Example 252:

10 **(5*R**)-*N*⁵-(5-Trifluoromethyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-(trifluoromethyl)pyridin-2-amine.

15 LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 477.26.

Example 253:

(5*R)-*N*⁵-(2-Methyl-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 6-methylpyridin-3-amine.

LC-MS-conditions TFA: *t*_R = 0.40 min; [M+H]⁺ = 423.28.

25 **Example 254:**

(5*R)-*N*⁵-(Benzo[d]oxazol-6-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and

30 benzo[d]oxazol-6-amine.

LC-MS-conditions TFA: *t*_R = 0.51 min; [M+H]⁺ = 449.26.

Example 255:

(5*R)-*N*⁵-(5-Methyl-isoxazol-3-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (5-methylisoxazol-3-yl)methanamine.

LC-MS-conditions TFA: *t_R* = 0.47 min; [M+H]⁺ = 427.25.

Example 256:

10 **(5*R**)-*N*⁵-(4-Methyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-methylthiazol-2-amine.

15 LC-MS-conditions TFA: *t_R* = 0.52 min; [M+H]⁺ = 429.24.

Example 257:

(5*R)-*N*⁵-(5-Trifluoromethyl-1,3,4-thiadiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:**

20 Following general procedure **B**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine.

LC-MS-conditions TFA: *t_R* = 0.62 min; [M+H]⁺ = 484.21.

Example 258:

(5*R)-*N*⁵-(2-Bromo-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

25 Following general procedure **E**, starting from (5*R**)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-pyrrolidino-butylamine.

30 LC-MS-conditions TFA: *t_R* = 0.56 min; [M+H]⁺ = 487.20.

Example 259:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2-fluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-fluoroethanamine.

LC-MS-conditions FA: *t_R* = 0.94 min; [M+H]⁺ = 414.02.

Example 260:

10 **(5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(2-aminoethyl)imidazolidin-2-one.

15 LC-MS-conditions FA: *t_R* = 0.82 min; [M+H]⁺ = 480.05.

Example 261:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

LC-MS-conditions FA: *t_R* = 0.54 min; [M+H]⁺ = 417.14.

Example 262:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

25 Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(diethylamino)butylamine.

30 LC-MS-conditions TFA: *t_R* = 0.46 min; [M+H]⁺ = 473.30.

Example 263:

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-ethoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-ethoxy-propylamine.

LC-MS-conditions FA: *t_R* = 1.03 min; [M+H]⁺ = 461.12.

Example 264:

10 **(5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-pyrrolidino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(3-aminopropyl)pyrrolidine.

15 LC-MS-conditions TFA: *t_R* = 0.44 min; [M+H]⁺ = 457.22.

Example 265:

(5*R)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(3-aminopropyl)-4-methylpiperazine.

LC-MS-conditions TFA: *t_R* = 0.53 min; [M+H]⁺ = 508.14.

Example 266:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-dimethylamino-ethylamine.

30 LC-MS-conditions TFA: *t_R* = 0.43 min; [M+H]⁺ = 417.18.

Example 267:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-dimethylamino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-dimethylamino-1-propylamine.

LC-MS-conditions TFA: *t*_R = 0.43 min; [M+H]⁺ = 431.24.

Example 268:

10 **(5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(3-aminopropyl)-4-methyl-piperazine.

15 LC-MS-conditions TFA: *t*_R = 0.40 min; [M+H]⁺ = 486.22.

Example 269:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(2-aminoethyl)imidazolidin-2-one.

LC-MS-conditions FA: *t*_R = 0.58 min; [M+H]⁺ = 458.19.

Example 270:

25 **(5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(diethylamino)butylamine.

30 LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 495.13.

Example 271:

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-fluoroethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-fluoroethylamine hydrochloride.

LC-MS-conditions FA: *t*_R = 0.95 min; [M+H]⁺ = 421.08.

Example 272:

10 **(5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-diethylamino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(diethylamino)butylamine.

15 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 502.16.

Example 273:

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(3-aminopropyl)-4-methyl-piperazine.

LC-MS-conditions TFA: *t*_R = 0.55 min; [M+H]⁺ = 515.21.

Example 274:

25 **(5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-dimethylamino-ethylamine.

30 LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 446.16.

Example 275:

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(2-aminoethyl)imidazolidin-2-one.

LC-MS-conditions FA: *t_R* = 0.84 min; [M+H]⁺ = 487.12.

Example 276:

10 **(5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-methoxy-ethylamine.

15 LC-MS-conditions FA: *t_R* = 0.93 min; [M+H]⁺ = 426.04.

Example 277:

(5*R)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(3-dimethylamino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **B**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-dimethylamino-1-propylamine.

LC-MS-conditions TFA: *t_R* = 0.58 min; [M+H]⁺ = 453.10.

25 **Example 278:**

(5*R)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R**)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R**)-6-hydroxycarbonyl-(4*S*,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

30 LC-MS-conditions FA: *t_R* = 0.76 min; [M+H]⁺ = 435.10.

Example 279:

(5*R*)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(2-bromo-pyrid-5-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(1-pyrrolidino)butylamine.

LC-MS-conditions TFA: *t_R* = 0.60 min; [M+H]⁺ = 489.17.

Example 280:

10 **(5*R*)-*N*⁵-(5-Bromopyrid-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **M**, starting from (5*R*)-*N*⁵-(5-bromopyrid-2-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

15 LC-MS-conditions FA: *t_R* = 0.79 min; [M+H]⁺ = 433.08.

Example 281:

(5*R*)-*N*⁵-(2-Chloropyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **M**, starting from (5*R*)-*N*⁵-(2-chloropyrid-5-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t_R* = 0.68 min; [M+H]⁺ = 389.14.

Example 282:

25 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

30 LC-MS-conditions FA: *t_R* = 0.83 min; [M+H]⁺ = 464.06.

Example 283:

(5*R*)-*N*⁵-(2-Bromothiazol-5-yl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **M**, starting from (5*R*)-*N*⁵-[(2-bromothiazol-5-yl)methyl]-(6*R*)-

- 5 *N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t*_R = 0.64 min; [M+H]⁺ = 453.01.

Example 284:

- 10 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromo-2-fluorobenzylamine hydrochloride.

- 15 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 518.13.

Example 285:

(5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

- 20 Following general procedure **I**, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-amino-anisole.

LC-MS-conditions TFA: *t*_R = 0.56 min; [M+H]⁺ = 438.25.

- 25 **Example 286:**

(5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **I**, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromo-

- 30 benzylamine.

LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 500.10.

Example 287:

(5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-hydroxyl-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

A solution of (5*R*)-*N*⁵-(4-methoxy-phenyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide in THF (0.09 M) was treated with aq. 1N NaOH (4.0 eq.) at rt until completion of the reaction. The reaction mixture was poured into aq. 2N HCl and extracted with EA (3x). The combined organic extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to give the title compound as a brown oil.

LC-MS-conditions FA: *t*_R = 0.75 min; [M+H]⁺ = 385.15.

Example 288:

(5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **F**, starting from (5*R*)-*N*⁵-(4-bromo-3-fluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 504.13.

Example 289:

(5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **F**, starting from (5*R*)-*N*⁵-(2-chloro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.54 min; [M+H]⁺ = 443.21.

Example 290:

(5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-methoxy-phenyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t*_R = 0.69 min; [M+H]⁺ = 384.19.

Example 291:

(5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-bromophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t*_R = 0.86 min; [M+H]⁺ = 448.11.

Example 292:

10 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

15 LC-MS-conditions FA: *t*_R = 0.88 min; [M+H]⁺ = 466.10.

Example 293:

(5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **M**, starting from (5*R*)-*N*⁵-(4-methoxy-phenyl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide and NH₄OH.

LC-MS-conditions FA: *t*_R = 0.76 min; [M+H]⁺ = 386.20.

Example 294:

25 **(5*R*)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R*)-*N*⁵-(5-bromo-pyridin-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 487.16.

Example 295:

(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 504.16.

Example 296:

10 **(5*R*)-*N*⁵-(4-Bromo-2-methylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure E, starting from (5*R*)-*N*⁵-(4-bromo-2-methylphenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 500.14.

Example 297:

(5*R*)-*N*⁵-(4-Bromo-3-chlorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure L, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromo-3-chloroaniline.

LC-MS-conditions TFA: *t*_R = 0.72 min; [M+H]⁺ = 520.16.

Example 298:

25 **(5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure M, starting from (5*R*)-*N*⁵-(2-chloropyrid-5-yl)-(6*R*)-*N*⁶-(2-methoxycarbonyl-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide and 30 NH₄OH.

LC-MS-conditions FA: *t*_R = 0.74 min; [M+H]⁺ = 391.15.

Example 299:

(5*R)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,3-propanediamine.

LC-MS-conditions TFA: *t*_R = 0.41 min; [M+H]⁺ = 403.18.

Example 300:

10 **(5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-*tert*-butoxycarbonyl-4-(aminomethyl)piperidine.

15 LC-MS-conditions TFA: *t*_R = 0.45 min; [M+H]⁺ = 443.20.

Example 301:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2-methylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-*N*-methylethylenediamine.

LC-MS-conditions TFA: *t*_R = 0.56 min; [M+H]⁺ = 425.03.

Example 302:

25 **(5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(5-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromo-2-fluorobenzylamine hydrochloride.

30 LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 453.04.

Example 303:

(5*R)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(*N*-*tert*-butoxycarbonyl-aminomethyl)-4-(aminomethyl)benzene.

LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 487.09.

Example 304:

- 10 **(5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(*tert*-butoxycarbonyl-amino)-2,2-dimethyl-propylamine.

- 15 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 453.09.

Example 305:

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2-methylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- 20 Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-*N*-methylethylenediamine.

LC-MS-conditions TFA: *t*_R = 0.59 min; [M+H]⁺ = 432.18.

- 25 **Example 306:**

(5*R)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

- Following general procedures **B** then **H**, starting from (5*R**)-*N*⁵-(4-bromophenyl-methyl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-*tert*-butoxycarbonyl-4-aminopiperidine.

30 LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 458.17.

Example 307:

(5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-amino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **B** then **H**, starting from (5*R*^{*})-*N*⁵-(4-bromophenyl-methyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,3-propanediamine.

LC-MS-conditions TFA: *t*_R = 0.59 min; [M+H]⁺ = 432.06.

Example 308:

10 **(5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-(aminomethyl)phenyl-methyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **B** then **H**, starting from (5*R*^{*})-*N*⁵-(4-bromophenyl-methyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(*N*-*tert*-butoxycarbonyl-aminomethyl)-3-(aminomethyl)benzene.

15 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 494.17.

Example 309:

(5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures **B** then **H**, starting from (5*R*^{*})-*N*⁵-(4-bromophenyl-methyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(*N*-*tert*-butoxycarbonyl-aminomethyl)-4-(aminomethyl)benzene.

LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 494.12.

25 **Example 310:**

(5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **B** then **H**, starting from (5*R*^{*})-*N*⁵-(4-bromophenyl-methyl)-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-(*tert*-butoxycarbonyl-amino)-2,2-dimethyl-propylamine.

30 LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 460.13.

Example 311:

(5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **B** then **H**, starting from (5*R*)-*N*⁵-(4-bromophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-*tert*-butoxycarbonyl-4-(aminomethyl)piperidine.

LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 472.16.

Example 312:

10 **(5*R*)-*N*⁵-(2-Bromo-thiazol-5-yl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-bromo-thiazol-5-yl)methanamine.

15 LC-MS-conditions TFA: *t*_R = 0.52 min; [M+H]⁺ = 507.13.

Example 313:

(5*R*)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **E**, starting from (5*R*)-*N*⁵-(5-methyl-pyridin-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropanamide hydrochloride.

LC-MS-conditions FA: *t*_R = 0.56 min; [M+H]⁺ = 369.19.

25 **Example 314:**

(5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.70 min; [M+H]⁺ = 522.17.

Example 315:

(5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-2,6-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 522.17.

Example 316:

10 **(5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromo-2,3-difluorophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.69 min; [M+H]⁺ = 522.14.

Example 317:

(5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **E**, starting from (5*R*)-5-hydroxycarbonyl-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (4-bromo-2,6-difluorophenyl)-methanamine.

LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 536.12.

Example 318:

25 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 520.20.

Example 319:

(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,5-pentanediamine.

LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 478.13.

Example 320:

10 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,4-butanediamine.

15 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 464.12.

Example 321:

(5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **F**, starting from (5*R*)-*N*⁵-(4-bromo-3-fluorophenyl-methyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 518.16.

25 **Example 322:**

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,5-pentanediamine.

30 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 453.05.

Example 323:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-1-*tert*-butoxycarbonyl-piperidine.

LC-MS-conditions TFA: *t*_R = 0.57 min; [M+H]⁺ = 451.10.

Example 324:

10 **(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(aminomethyl)-1-*tert*-butoxycarbonyl-piperidine.

15 LC-MS-conditions TFA: *t*_R = 0.58 min; [M+H]⁺ = 465.16.

Example 325:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶,*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(*tert*-butoxycarbonyl-aminomethyl)piperidine.

LC-MS-conditions TFA: *t*_R = 0.57 min; [M+H]⁺ = 465.07.

Example 326:

25 **(5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures I then H, starting from (5*R*)-*N*⁵-(4-bromo-2-fluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,5-pentanediamine.

30 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 480.12.

Example 327:

(5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(4-bromo-2,3-difluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 536.17.

Example 328:

10 **(5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R*)-*N*⁵-(4-bromo-3,5-difluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 536.12.

Example 329:

(5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure I, starting from (5*R*)-*N*⁵-(4-bromo-2,5-difluorophenyl-methyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 536.22.

Example 330:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

25 Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-amino-1-*tert*-butoxycarbonyl-piperidine.

30 LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 453.04.

Example 331:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(isobutyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and isobutylamine.

LC-MS-conditions FA: *t*_R = 1.15 min; [M+H]⁺ = 426.08.

Example 332:

10 **(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-*tert*-butoxycarbonyl-amino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N-tert*-butoxycarbonyl-1,4-butanediamine.

15 LC-MS-conditions FA: *t*_R = 1.16 min; [M+H]⁺ = 541.09.

Example 333:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N-tert*-butoxycarbonyl-1,5-pentanediamine.

LC-MS-conditions FA: *t*_R = 1.20 min; [M+H]⁺ = 555.12.

25 **Example 334:**

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N-tert*-butoxycarbonyl-1,5-pentanediamine.

30 LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 455.11.

Example 335:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-1,4-butanediamine.

LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 441.10.

Example 336:

10 **(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶,*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(*tert*-butoxycarbonyl-aminomethyl)piperidine.

15 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 467.15.

Example 337:

(5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 1-*tert*-butoxycarbonyl-4-(aminomethyl)piperidine.

LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 467.12.

Example 338:

25 **(5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **F**, starting from (5*R*)-*N*⁵-(2-bromo-3-fluoro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 505.12.

Example 339:

(5*R)-*N*⁵-(4-Aminobutyl)-(6*R**)-*N*⁶-(4-bromophenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-bromo-phenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and *N*-*tert*-butoxycarbonyl-1,4-butanediamine.

LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 432.12.

Example 340:

10 **(5*R**)-*N*⁵-(5-Aminopentyl)-(6*R**)-*N*⁶-(4-bromophenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **A** then **H**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-bromo-phenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and *N*-*tert*-butoxycarbonyl-1,5-pentanediamine.

15 LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 446.14.

Example 341:

(5*R)-*N*⁵-(2-(Cyclohexen-1-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(1-cyclohexenyl)ethylamine.

LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 440.36.

25 **Example 342:**

(5*R)-*N*⁵-(4-*tert*-Butyl-cyclohexyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-*tert*-butylcyclohexylamine.

30 LC-MS-conditions TFA: *t*_R = 0.78 min; [M+H]⁺ = 470.39.

Example 343:

(5*R)-*N*⁵-(2-(Pyridin-2-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(2-aminoethyl)pyridine.

LC-MS-conditions TFA: *t*_R = 0.35 min; [M+H]⁺ = 437.27.

Example 344:

10 **(5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R**)-*N*⁵-(4-acetyl-thiazol-2-yl)-(6*R**)-6-hydroxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.50 min; [M+H]⁺ = 457.26.

Example 345:

(5*R)-*N*⁵-(4-Trifluoromethyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **C**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-trifluoromethyl-thiazole-2-ylamine.

LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 483.20.

Example 346:

25 **(5*R**)-*N*⁵-(2,4,6-Trifluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,4,6-trifluorobenzylamine.

30 LC-MS-conditions TFA: *t*_R = 0.58 min; [M+H]⁺ = 476.24.

Example 347:

(5*R)-*N*⁵-(2,4-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,4-dimethylbenzylamine.

LC-MS-conditions TFA: *t*_R = 0.649 min; [M+H]⁺ = 450.31.

Example 348:

10 **(5*R**)-*N*⁵-[(2-Acetyl-thiazol-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-acetyl-thiazol-4-yl)-methanamine.

15 LC-MS-conditions TFA: *t*_R = 0.49 min; [M+H]⁺ = 471.23.

Example 349:

(5*R)-*N*⁵-(3-Chloro-2-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-chloro-2-fluorobenzylamine.

LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 474.23.

Example 350:

(5*R)-*N*⁵-(4-Methyl-oxazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **F**, starting from (5*R**)-*N*⁶-(4-methyl-oxazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.46 min; [M+H]⁺ = 413.25.

Example 351:

(5*R)-*N*⁵-[(5-Acetyl-thiazol-2-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (5-(2-methyl-[1,3]dioxolan-2-yl)thiazol-2-yl)methanamine.

LC-MS-conditions TFA: *t*_R = 0.46 min; [M+H]⁺ = 471.23.

Example 352:

10 **(5*R**)-*N*⁵-(3-Acetylphenyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **I**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 1-(3-aminophenyl)ethanone.

15 LC-MS-conditions TFA: *t*_R = 0.55 min; [M+H]⁺ = 450.28.

Example 353:

(5*R)-*N*⁵-(2-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-bromo-4-fluorobenzylamine hydrochloride.

LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 518.18.

25 **Example 354:**

(5*R)-*N*⁵-(3-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-bromo-4-fluorobenzylamine hydrochloride.

30 LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 518.21.

Example 355:

(5*R)-*N*⁵-(2,3,5-Trifluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,3,5-trifluorobenzylamine.

LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 476.26.

Example 356:

10 **(5*R**)-*N*⁵-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (4-methyl-1,2,5-oxadiazol-3-yl)methanamine hydrochloride.

15 LC-MS-conditions TFA: *t*_R = 0.48 min; [M+H]⁺ = 428.26.

Example 357:

(5*R)-*N*⁵-(2-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-fluoro-3-(trifluoromethyl)benzylamine.

LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 508.25.

Example 358:

25 **(5*R**)-*N*⁵-(3,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3,5-dimethylbenzylamine.

30 LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 450.31.

Example 359:

(5*R)-*N*⁵-(3-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **G**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (3-(2-methyl-[1,3]dioxolan-2-yl)-phenyl)methanamine.

LC-MS-conditions TFA: *t_R* = 0.52 min; [M+H]⁺ = 464.28.

Example 360:

10 **(5*R**)-*N*⁵-(3-Difluoromethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-(difluoromethoxy)benzylamine.

15 LC-MS-conditions TFA: *t_R* = 0.60 min; [M+H]⁺ = 488.27.

Example 361:

(5*R)-*N*⁵-[(2-Methoxypyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-methoxypyridin-4-yl)methanamine.

LC-MS-conditions TFA: *t_R* = 0.40 min; [M+H]⁺ = 453.25.

25 **Example 362:**

(5*R)-*N*⁵-(3-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-fluoro-5-(trifluoromethyl)benzylamine.

30 LC-MS-conditions TFA: *t_R* = 0.66 min; [M+H]⁺ = 508.27.

Example 363:

(5*R)-*N*⁵-(4-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 1-(4-(aminomethyl)phenyl)ethanone.

LC-MS-conditions TFA: *t*_R = 0.51 min; [M+H]⁺ = 464.24.

Example 364:

10 **(5*R**)-*N*⁵-(2-Chloro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure A, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-chloro-5-(trifluoromethyl)benzylamine.

15 LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 524.22.

Example 365:

(5*R)-*N*⁵-(2-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure A, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-fluoro-5-(trifluoromethyl)benzylamine.

LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 508.24.

Example 366:

25 **(5*R**)-*N*⁵-(4-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure A, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-fluoro-3-(trifluoromethyl)benzylamine.

30 LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 508.26.

Example 367:

(5*R)-*N*⁵-[(2,6-Dichloropyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2,6-dichloropyridin-4-yl)methanamine.

LC-MS-conditions TFA: *t*_R = 0.58 min; [M+H]⁺ = 491.18.

Example 368:

10 **(5*R**)-*N*⁵-(2,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,5-dimethylbenzylamine.

15 LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 450.30.

Example 369:

(5*R)-*N*⁵-(4,5-Dimethyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **F**, starting from (5*R**)-*N*⁵-(4,5-dimethyl-thiazol-2-yl)-(6*R**)-6-ethoxycarbonyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.55 min; [M+H]⁺ = 443.25.

Example 370:

25 **(5*R**)-*N*⁵-(2-Methoxy-5-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-methoxy-5-methylphenyl)methanamine hydrochloride.

30 LC-MS-conditions TFA: *t*_R = 0.62 min; [M+H]⁺ = 466.32.

Example 371:

(5*R)-*N*⁵-(2-Chloro-3,6-difluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-chloro-3,6-difluorobenzylamine.

LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 492.20.

Example 372:

10 **(5*R**)-*N*⁵-(2-Isopropoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and (2-isopropoxyphenyl)methanamine.

15 LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 480.31.

Example 373:

(5*R)-*N*⁵-(2-Chloro-6-fluoro-3-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **A**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-chloro-6-fluoro-3-methylbenzylamine.

LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 488.27.

Example 374:

(5*R)-*N*⁵-(3-Chloro-4-methoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-chloro-4-methoxybenzylamine hydrochloride.

30 LC-MS-conditions FA: *t*_R = 0.75 min; [M+H]⁺ = 486.24.

Example 375:

(5*R)-*N*⁵-(3,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

5 Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3,4-dimethoxybenzylamine.

LC-MS-conditions FA: *t_R* = 0.64 min; [M+H]⁺ = 482.32.

Example 376:

10 **(5*R**)-*N*⁵-(2,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,4-dimethoxybenzylamine.

15 LC-MS-conditions FA: *t_R* = 0.73 min; [M+H]⁺ = 482.30.

Example 377:

(5*R)-*N*⁵-(2-(3,4-Dimethoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

20 Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(3,4-dimethoxyphenyl)ethylamine.

LC-MS-conditions TFA: *t_R* = 0.56 min; [M+H]⁺ = 496.30.

25 **Example 378:**

(5*R)-*N*⁵-(2-(4-Methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(4-methoxyphenyl)ethylamine.

30 LC-MS-conditions TFA: *t_R* = 0.58 min; [M+H]⁺ = 466.32.

Example 379:

(5*R)-*N*⁵-(2-(4-Bromophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-bromophenethylamine.

LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 514.23.

Example 380:

10 **(5*R**)-*N*⁵-(2-(3,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3,4-Dimethylphenethylamine hydrochloride.

15 LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 464.28.

Example 381:

(5*R)-*N*⁵-(2-(4-Methylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

20 Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2-(*p*-tolyl)ethylamine.

LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 450.33.

25 **Example 382:**

(5*R)-*N*⁵-(2-(4-Fluorophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-fluorophenethylamine.

30 LC-MS-conditions TFA: *t*_R = 0.59 min; [M+H]⁺ = 454.29.

Example 383:

(5*R)-*N*⁵-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3,4-methylenedioxyphenethylamine hydrochloride.

LC-MS-conditions TFA: *t*_R = 0.57 min; [M+H]⁺ = 480.28.

Example 384:

10 **(5*R**)-*N*⁵-(2-(3-Bromo-4-methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 3-bromo-4-methoxyphenethylamine.

15 LC-MS-conditions TFA: *t*_R = 0.63 min; [M+H]⁺ = 544.22.

Example 385:

(5*R)-*N*⁵-(2-(2,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

20 Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 2,4-dimethylphenethylamine.

LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 464.32.

25 **Example 386:**

(5*R)-*N*⁵-(4-Ethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **N**, starting from (5*R**)-5-hydroxycarbonyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 4-ethoxybenzylamine.

30 LC-MS-conditions TFA: *t*_R = 0.60 min; [M+H]⁺ = 466.32.

Example 387:

(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **I**, starting from (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.64 min; [M+H]⁺ = 470.25.

Example 388:

10 **(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-dimethylamino-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **D**, starting from (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-dimethylamino-ethylamine.

15 LC-MS-conditions TFA: *t*_R = 0.61 min; [M+H]⁺ = 416.21.

Example 389:

(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(pyridin-2-yl)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure **D**, starting from (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 2-(2-aminoethyl)pyridine.

LC-MS-conditions FA: *t*_R = 0.80 min; [M+H]⁺ = 450.21.

Example 390:

25 **(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **D**, starting from (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(2-aminoethyl)benzene sulfonamide.

30 LC-MS-conditions FA: *t*_R = 0.95 min; [M+H]⁺ = 528.16.

Example 391:

(5*R*)-*N*⁵-(2-(2,4-Dichlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(2-(2,4-dichlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.69 min; [M+H]⁺ = 504.22.

Example 392:

10 **(5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(*N*-isopentyl-piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R*)-*N*⁵-(2-(4-chlorophenyl)ethyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 1-(3-methyl-butyl)-piperidin-4-ylamine hydrochloride.

15 LC-MS-conditions TFA: *t*_R = 0.70 min; [M+H]⁺ = 498.30.

Example 393:

(5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure F, starting from (5*R*)-*N*⁵-(4-bromo-3,5-difluorophenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.71 min; [M+H]⁺ = 522.13.

Example 394:

25 **(5*R*)-*N*⁵-(4-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

In a flame dried round-bottomed flask equipped with a magnetic stir bar and under inert atmosphere (N₂), to a freshly prepared solution of lithium di-isopropylamide (3.4 eq.) in THF (0.3 M) was added a 0.1 M solution of (5*R*)-*N*⁵-(5-bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide at 0 °C. The reaction mixture was stirred at 0 °C until completion of the reaction. Water (3.0 eq.) was added and the mixture stirred at rt for 15 h, diluted with EA, washed with brine, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure.

35 Purification by FC gave the title compound.

LC-MS-conditions TFA: t_R = 0.59 min; $[M+H]^+$ = 493.15.

Example 395:

5 **(5*R*)-*N*⁵-(4-Bromo-3-trifluoromethylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **F**, starting from (5*R*)-*N*⁵-(4-bromo-3-trifluoromethylphenyl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: t_R = 0.75 min; $[M+H]^+$ = 554.16.

10

Example 396:

(5*R*^{*})-*N*⁵-[(4-Acetyl-thiazol-2-yl)methyl]-(6*R*^{*})-*N*⁶-(2-methylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

15 Following general procedures **B** then **H**, starting from (5*R*^{*})-*N*⁵-[(4-acetyl-thiazol-2-yl)methyl]-(6*R*^{*})-6-hydroxycarbonyl-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-*N*-methylethylenediamine.

LC-MS-conditions TFA: t_R = 0.42 min; $[M+H]^+$ = 403.19.

Example 397:

20 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2,5-dimethylpyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(2,5-dimethylpyrrolidin-1-yl)butan-1-amine.

25 LC-MS-conditions TFA: t_R = 0.69 min; $[M+H]^+$ = 514.19.

Example 398:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(pyrrolidin-1-yl)pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:

30 Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)pentan-1-amine hydrochloride.

LC-MS-conditions TFA: t_R = 0.67 min; $[M+H]^+$ = 500.16.

35

Example 399:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3-fluoro-4-(pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 3-fluoro-4-(pyrrolidin-1-yl)butan-1-amine hydrochloride.

LC-MS-conditions TFA: *t*_R = 0.66 min; [M+H]⁺ = 504.15.

Example 400:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2-(methoxymethyl)pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:**

Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(2-(methoxymethyl)pyrrolidin-1-yl)butan-1-amine.

15 LC-MS-conditions TFA: *t*_R = 0.68 min; [M+H]⁺ = 530.20.

Example 401:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(3,3-difluoropyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, formate salt:

20 Following general procedure **E**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and 4-(3,3-difluoropyrrolidin-1-yl)butan-1-amine.

LC-MS-conditions TFA: *t*_R = 0.67 min; [M+H]⁺ = 522.14.

25 **Example 402:**

(5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure **F**, starting from (5*R*)-*N*⁵-(2-bromo-3-fluoro-pyridin-5-yl)-(6*R*)-6-methoxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-(pyrrolidin-1-yl)butan-1-amine.

30 LC-MS-conditions TFA: *t*_R = 0.65 min; [M+H]⁺ = 507.17.

Example 403:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-hydroxyethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and ethanolamine.

LC-MS-conditions FA: *t*_R = 0.87 min; [M+H]⁺ = 414.03.

Example 404:

10 **(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-hydroxypropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-aminopropan-1-ol.

15 LC-MS-conditions FA: *t*_R = 0.90 min; [M+H]⁺ = 428.03.

Example 405:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxybutyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 4-aminobutan-1-ol.

LC-MS-conditions FA: *t*_R = 0.92 min; [M+H]⁺ = 442.06.

25 **Example 406:**

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-methyl-3-hydroxyprop-2-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-amino-2-methylpropan-1-ol.

30 LC-MS-conditions FA: *t*_R = 1.00 min; [M+H]⁺ = 442.06.

Example 407:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(2-hydroxyethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-(2-aminoethoxy)ethanol.

LC-MS-conditions FA: *t*_R = 0.88 min; [M+H]⁺ = 458.05.

Example 408:

10 **(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *trans*-4-amino-cyclohexanol hydrochloride.

15 LC-MS-conditions FA: *t*_R = 0.96 min; [M+H]⁺ = 468.06.

Example 409:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(1-hydroxy-cyclohexyl)methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 1-aminomethyl-1-cyclohexanol hydrochloride.

LC-MS-conditions FA: *t*_R = 1.08 min; [M+H]⁺ = 482.08.

25 **Example 410:**

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*trans*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and (*trans*-4-aminocyclohexyl)methanol.

30 LC-MS-conditions FA: *t*_R = 1.01 min; [M+H]⁺ = 482.09.

Example 411:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*cis*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedure I, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and (*cis*-4-aminocyclohexyl)methanol.

LC-MS-conditions FA: *t_R* = 0.99 min; [M+H]⁺ = 482.08.

Example 412:

10 **(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(pyrrolidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-1-*tert*-butoxycarbonyl-pyrrolidine hydrochloride.

15 LC-MS-conditions 07: *t_R* = 0.60 min; [M+H]⁺ = 439.41.

Example 413:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(*N*-methylamino)-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N*-*tert*-butoxycarbonyl-*N*-methylethylenediamine.

LC-MS-conditions 07: *t_R* = 0.60 min; [M+H]⁺ = 427.16.

25 **Example 414:**

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-(*N*-methylamino)-propyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures I then H, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and *N*-(3-aminopropyl)-*N*-methylcarbamic acid *tert*-butyl ester.

30 LC-MS-conditions 07: *t_R* = 0.61 min; [M+H]⁺ = 441.16.

Example 415:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-*N*-*tert*-butoxycarbonyl-piperidine.

LC-MS-conditions 07: *t*_R = 0.61min; [M+H]⁺ = 453.20.

Example 416:

10 **(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(pyrrolidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-aminomethyl-*N*-*tert*-butoxycarbonyl-pyrrolidine.

15 LC-MS-conditions 07: *t*_R = 0.62 min; [M+H]⁺ = 453.20.

Example 417:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 2-aminomethyl-*N*-*tert*-butoxycarbonyl-piperidine.

LC-MS-conditions 07: *t*_R = 0.63 min; [M+H]⁺ = 467.23.

Example 418:

25 **(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-3-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-aminomethyl-*N*-*tert*-butoxycarbonyl-piperidine.

30 LC-MS-conditions 07: *t*_R = 0.62 min; [M+H]⁺ = 467.22.

Example 419:

(5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(azetidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide:

Following general procedures **I** then **H**, starting from (5*R*)-*N*⁵-(5-bromothiazol-2-yl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5-carboxamide and 3-amino-*N*-*tert*-butoxycarbonyl-azetidine.

LC-MS-conditions 07: *t_R* = 0.60 min; [M+H]⁺ = 425.15.

Example 420:

10 **(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:**

Following general procedures **L** then **H**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *tert*-butyl ((*cis*-4-aminocyclohexyl)methyl)carbamate.

15 LC-MS-conditions 07b: *t_R* = 0.69 min; [M+H]⁺ = 472.07.

Example 421:

(5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide:

20 Following general procedures **L** then **H**, starting from (5*R*)-*N*⁵-(4-bromophenyl)-(6*R*)-6-hydroxycarbonyl-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide and *tert*-butyl ((*trans*-4-aminocyclohexyl)methyl)carbamate.

LC-MS-conditions 07b: *t_R* = 0.70 min; [M+H]⁺ = 472.09.

Example 422:

(5*R*^{*})-*N*⁵-(2-Trifluoromethyl-pyridin-5-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide, hydrochloride:

Following general procedure **B**, starting from (5*R*^{*})-5-hydroxycarbonyl-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-6-carboxamide and 5-amino-2-(trifluoromethyl)pyridine.

30 LC-MS-conditions TFA: *t_R* = 0.60 min; [M+H]⁺ = 477.20.

II. Biological assays

In vitro assay

The ALX receptor and FPRL2 agonistic activities of the compounds of formula (I) are determined in accordance with the following experimental method.

5 Experimental method:

Intracellular calcium measurements:

Cells expressing recombinant human ALX receptor and the G-protein G α 16 (HEK293-hALXR-G α 16) were grown to 80% confluency in Growing Medium (GM). Cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and
10 collected by centrifugation at 1'000 rpm at rt for 5 min in Assay Buffer (AB) (equal parts of Hank's BSS (Gibco, 14065-049) and DMEM without Phenol Red (Gibco, 11880-028)). After 60 min incubation at 37°C under 5% CO₂ in AB supplemented with 1 μ M Fluo-4 (AM) (Invitrogen, F14202), and 20 mM HEPES (Gibco, 15630-056), the cells were washed and resuspended in AB. They were then seeded onto 384-well FLIPR assay plates (Greiner,
15 781091) at 50'000 cells in 70 μ l per well and sedimented by centrifugation at 1'000 rpm for 1 min. Stock solutions of test compounds were made up at a concentration of 10 mM in DMSO, and serially diluted in AB to concentrations required for activation dose response curves. WKYMVm (Phoenix Peptides) was used as a reference agonist. FLIPR384 or FLIPR Tetra instruments (Molecular Devices) were operated according to the
20 manufacturer's standard instructions, adding 4 μ l of test compound dissolved at 10 mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final concentration. Changes in fluorescence were monitored before and after the addition of test compounds at λ_{ex} =488 nm and λ_{em} =540 nm. Emission peak values above base level after compounds addition were exported after base line subtraction. Values were
25 normalized to high-level control (WKYMVm compound, 10 nM final concentration) after subtraction of the base line value (AB addition).

Cells expressing recombinant human FPRL2 and the G-protein G α 16 (HEK293-hFPRL2-G α 16) were grown to 80% confluency in Growing Medium (GM). Cells were detached from culture dishes with a cell dissociation buffer (Invitrogen, 13151-014), and collected by
30 centrifugation at 1'000 rpm at rt for 5 min in Assay Buffer (AB) (equal parts of Hank's BSS (Gibco, 14065-049) and DMEM without Phenol Red (Gibco, 11880-028)). After 60 min incubation at 37°C under 5% CO₂ in AB supplemented with 1 μ M Fluo-4 (AM) (Invitrogen,

F14202), and 20 mM HEPES (Gibco, 15630-056), the cells were washed and resuspended in AB. They were then seeded onto 384-well FLIPR assay plates (Greiner, 781091) at 50'000 cells in 70 μ l per well and sedimented by centrifugation at 1'000 rpm for 1 min. Stock solutions of test compounds were made up at a concentration of 10 mM in DMSO, and serially diluted in AB to concentrations required for activation dose response curves. Gly14-Humanin (Humanin peptide with replacement of Serine by Glycine at position 14, Phoenix Peptides) was used as a reference agonist. FLIPR384 or FLIPR Tetra instruments (Molecular Devices) were operated according to the manufacturer's standard instructions, adding 4 μ l of test compound dissolved at 10 mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final concentration. Changes in fluorescence were monitored before and after the addition of test compounds at λ_{ex} =488 nm and λ_{em} =540 nm. Emission peak values above base level after compounds addition were exported after base line subtraction. Values were normalized to high-level control (GLY14-Humanin compound, 100 nM final concentration) after subtraction of the base line value (AB addition).

Agonistic activities of exemplified compounds are displayed in *Table 1*.

Table 1

Compound	ALX receptor EC ₅₀ [nM]	FPRL2 EC ₅₀ [nM]	Compound	ALX receptor EC ₅₀ [nM]	FPRL2 EC ₅₀ [nM]
Example 1	0.16	571	Example 216	2.7	297
Example 2	0.10	46	Example 217	38	61
Example 3	0.20	2000	Example 218	2.1	356
Example 4	0.24	5310	Example 219	0.30	174
Example 5	0.34	1160	Example 220	0.35	235
Example 6	0.41	1260	Example 221	0.66	41
Example 7	0.55	413	Example 222	208	398
Example 8	0.82	2600	Example 223	3.2	1210
Example 9	0.94	1510	Example 224	994	1860
Example 10	0.98	726	Example 225	6.4	143
Example 11	1.0	329	Example 226	912	356
Example 12	1.0	1300	Example 227	290	89
Example 13	1.1	4620	Example 228	389	308

Example 14	1.2	1690	Example 229	119	67
Example 15	1.3	4400	Example 230	31	65
Example 16	1.4	3920	Example 231	514	159
Example 17	1.8	2010	Example 232	1260	112
Example 18	2.0	551	Example 233	7220	197
Example 19	2.4	2480	Example 234	73	176
Example 20	2.7	2860	Example 235	153	181
Example 21	2.8	1690	Example 236	49	292
Example 22	3.2	4640	Example 237	305	542
Example 23	3.3	>25000	Example 238	22	142
Example 24	3.7	4120	Example 239	15	>25000
Example 25	3.9	365	Example 240	8.1	>25000
Example 26	4.2	744	Example 241	240	>25000
Example 27	4.2	1960	Example 242	5.9	6140
Example 28	4.5	>25000	Example 243	170	2300
Example 29	4.8	5584	Example 244	369	>25000
Example 30	4.9	405	Example 245	3.9	8240
Example 31	5.0	1410	Example 246	191	5330
Example 32	5.4	3280	Example 247	106	1080
Example 33	5.8	4100	Example 248	174	3060
Example 34	6.1	16100	Example 249	216	47
Example 35	6.1	1870	Example 250	673	746
Example 36	6.7	11500	Example 251	7.9	558
Example 37	7.1	1710	Example 252	82	210
Example 38	7.5	1550	Example 253	131	1770
Example 39	7.6	1540	Example 254	492	67
Example 40	9.0	848	Example 255	40	489
Example 41	9.5	8510	Example 256	6720	348
Example 42	9.6	7840	Example 257	6010	167
Example 43	9.5	925	Example 258	1.1	173
Example 44	10	4910	Example 259	354	>25000
Example 45	11	4160	Example 260	9.1	8730

Example 46	11	1600	Example 261	297	>25000
Example 47	12	1170	Example 262	97	106
Example 48	12	1380	Example 263	899	4460
Example 49	12	1510	Example 264	140	835
Example 50	13	1080	Example 265	49	462
Example 51	8.2	1487	Example 266	65	1210
Example 52	9.6	6357	Example 267	288	15300
Example 53	16	5030	Example 268	477	22900
Example 54	16	2587	Example 269	82	3550
Example 55	18	6680	Example 270	54	396
Example 56	18	1750	Example 271	673	>25000
Example 57	17	1660	Example 272	121	299
Example 58	20	6190	Example 273	213	432
Example 59	21	8280	Example 274	290	1170
Example 60	22	1481	Example 275	181	7040
Example 61	23	2267	Example 276	44	>25000
Example 62	24	363	Example 277	61	2010
Example 63	24	3950	Example 278	7.9	>25000
Example 64	19	68	Example 279	1.3	62
Example 65	26	>25000	Example 280	258	>25000
Example 66	34	2219	Example 281	31	>25000
Example 67	34	>25000	Example 282	146	>25000
Example 68	27	2170	Example 283	884	>25000
Example 69	58	708	Example 284	13	264
Example 70	61	4378	Example 285	9.0	224
Example 71	63	5550	Example 286	32	32
Example 72	70	1850	Example 287	516	>25000
Example 73	63	4615	Example 288	0.87	33
Example 74	72	18200	Example 289	1.6	214
Example 75	73	7976	Example 290	32	1440
Example 76	77	2432	Example 291	113	>25000
Example 77	80	2277	Example 292	71	661

Example 78	80	5480	Example 293	59	2370
Example 79	96	1300	Example 294	2.9	187
Example 80	97	7875	Example 295	1.3	116
Example 81	100	8734	Example 296	275	193
Example 82	118	6587	Example 297	367	28
Example 83	123	678	Example 298	24	4070
Example 84	133	5500	Example 299	273	359
Example 85	146	8300	Example 300	384	1820
Example 86	147	6942	Example 301	98	2700
Example 87	156	2205	Example 302	1.3	543
Example 88	168	9420	Example 303	45	1340
Example 89	191	2467	Example 304	12	1630
Example 90	194	2260	Example 305	350	2050
Example 91	200	2980	Example 306	23	2760
Example 92	204	2670	Example 307	76	2640
Example 93	216	>25000	Example 308	59	493
Example 94	218	1040	Example 309	367	1340
Example 95	223	1846	Example 310	26	466
Example 96	373	8045	Example 311	54	1170
Example 97	391	1430	Example 312	213	208
Example 98	477	582	Example 313	330	>25000
Example 99	552	5488	Example 314	103	204
Example 100	735	6114	Example 315	9.4	296
Example 101	812	457	Example 316	236	122
Example 102	0.46	>25000	Example 317	28	44
Example 103	4.8	6920	Example 318	13	18
Example 104	1.5	5250	Example 319	55	331
Example 105	2.4	3730	Example 320	52	472
Example 106	82	2935	Example 321	117	15
Example 107	1.8	2270	Example 322	0.61	382
Example 108	4.1	1480	Example 323	17	4690
Example 109	0.7	666	Example 324	5.7	1545

Example 110	16	307	Example 325	19	>14120
Example 111	1.3	71	Example 326	22	930
Example 112	8.3	57	Example 327	40	27
Example 113	0.35	15	Example 328	46	60
Example 114	1.4	532	Example 329	301	64
Example 115	2.0	204	Example 330	24	4420
Example 116	7.8	891	Example 331	82	8250
Example 117	10	359	Example 332	467	3540
Example 118	47	140	Example 333	519	1240
Example 119	17	404	Example 334	0.45	230
Example 120	17	363	Example 335	0.50	1300
Example 121	95	454	Example 336	6.2	1490
Example 122	79	496	Example 337	7.3	1210
Example 123	46	332	Example 338	168	139
Example 124	52	1150	Example 339	19	1480
Example 125	60	268	Example 340	30	255
Example 126	71	613	Example 341	1740	165
Example 127	95	2740	Example 342	>2390	100
Example 128	120	3440	Example 343	>2390	885
Example 129	121	1190	Example 344	7850	414
Example 130	166	6370	Example 345	>25000	734
Example 131	173	358	Example 346	1540	508
Example 132	898	79	Example 347	1800	417
Example 133	263	122	Example 348	3230	219
Example 134	319	612	Example 349	4720	200
Example 135	352	224	Example 350	5730	444
Example 136	365	1180	Example 351	6330	94
Example 137	556	192	Example 352	6700	958
Example 138	570	332	Example 353	6900	256
Example 139	731	152	Example 354	7410	223
Example 140	748	1310	Example 355	7500	477
Example 141	835	1600	Example 356	7710	948

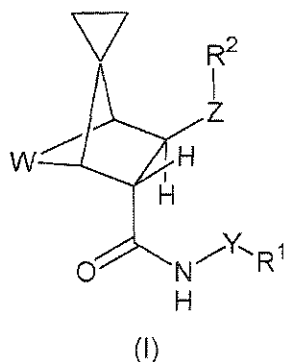
Example 142	1330	182	Example 357	7910	290
Example 143	2060	94	Example 358	7980	176
Example 144	2270	324	Example 359	8350	359
Example 145	3650	647	Example 360	8700	530
Example 146	4420	337	Example 361	8870	330
Example 147	7410	837	Example 362	9090	306
Example 148	7600	226	Example 363	9740	570
Example 149	8090	691	Example 364	9970	372
Example 150	8440	110	Example 365	9970	350
Example 151	9120	714	Example 366	10000	366
Example 152	9630	150	Example 367	10600	644
Example 153	9890	91	Example 368	11100	255
Example 154	10000	214	Example 369	>25000	204
Example 155	>25000	91	Example 370	>25000	180
Example 156	>25000	623	Example 371	>25000	271
Example 157	>25000	136	Example 372	>25000	389
Example 158	>25000	204	Example 373	>25000	478
Example 159	13	2370	Example 374	2620	237
Example 160	37	>25000	Example 375	9050	443
Example 161	47	7920	Example 376	10300	334
Example 162	61	1730	Example 377	>25000	417
Example 163	72	5680	Example 378	8610	74
Example 164	80	6820	Example 379	8810	6.6
Example 165	87	2600	Example 380	>25000	103
Example 166	88	4710	Example 381	3900	30
Example 167	103	3690	Example 382	6360	52
Example 168	71	862	Example 383	7680	29
Example 169	112	1790	Example 384	10300	72
Example 170	114	>25000	Example 385	>25000	27
Example 171	118	3220	Example 386	2910	254
Example 172	125	4610	Example 387	8270	26
Example 173	131	1820	Example 388	>25000	623

Example 174	136	4810	Example 389	>25000	554
Example 175	155	7210	Example 390	>25000	576
Example 176	158	2230	Example 391	9710	3.8
Example 177	160	446	Example 392	10400	20
Example 178	115	4070	Example 393	1190	16
Example 179	200	1380	Example 394	1550	166
Example 180	252	888	Example 395	3800	13
Example 181	265	2050	Example 396	1040	872
Example 182	298	2020	Example 397	2.1	149
Example 183	303	8900	Example 398	1.8	7510
Example 184	315	>14505	Example 399	5.0	4770
Example 185	336	709	Example 400	1.4	7650
Example 186	463	8960	Example 401	4.4	516
Example 187	505	4270	Example 402	349	66
Example 188	529	1920	Example 403	158	21400
Example 189	697	3240	Example 404	96	10000
Example 190	963	1705	Example 405	80	7840
Example 191	140	826	Example 406	333	15200
Example 192	23	139	Example 407	11	9230
Example 193	463	355	Example 408	69	16300
Example 194	223	436	Example 409	129	9190
Example 195	28	647	Example 410	855	18200
Example 196	21	1080	Example 411	61	6520
Example 197	5.4	105	Example 412	8.9	1020
Example 198	92	462	Example 413	13	2110
Example 199	77	7.4	Example 414	14	773
Example 200	42	236	Example 415	9.1	354
Example 201	93	1440	Example 416	8.3	479
Example 202	33	75	Example 417	2.1	262
Example 203	24	200	Example 418	0.45	339
Example 204	3.4	2080	Example 419	57	2290
Example 205	7.3	4780	Example 420	0.13	1150

Example 206	31	2980	Example 421	13	1700
Example 207	6.5	7430	Example 422	11	99
Example 208	2.3	15			
Example 209	0.07	58			
Example 210	0.40	200			
Example 211	0.53	423			
Example 212	0.89	12			
Example 213	4.1	16			
Example 214	6.1	338			
Example 215	0.72	95			

Claims

1. A compound of the formula (I)



5 wherein

W represents $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$;

Y represents a bond or a $(\text{C}_1\text{-C}_4)$ alkandiyl group and **R**¹ represents

- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxy, $(\text{C}_1\text{-C}_2)$ alkyl-carbonyl, $(\text{C}_1\text{-C}_2)$ fluoroalkyl, $(\text{C}_1\text{-C}_2)$ fluoroalkoxy, nitro, cyano and phenyl, wherein the phenyl is unsubstituted or mono-substituted with halogen; or
- benzo[d][1,3]dioxolyl; or
- aryloxy; or
- 15 • a cyclohexyl- or a cyclohexenyl-group, which groups are independently unsubstituted or mono-substituted with $(\text{C}_1\text{-C}_4)$ alkyl; or
- $(\text{C}_1\text{-C}_2)$ alkyl-carbonyl; or
- $(\text{C}_1\text{-C}_4)$ alkoxy-carbonyl;

or **Y** represents together with **R**¹ a $(\text{C}_4\text{-C}_6)$ alkyl group or a amino- $(\text{C}_4\text{-C}_6)$ alkyl group;

20 **Z** represents $-\text{C}(\text{O})\text{NR}^3-$ or $-\text{CH}_2\text{NR}^4\text{C}(\text{O})-$,

wherein the asterisks indicate the bond which is linked to **R**²;

R² represents

- $(\text{C}_3\text{-C}_6)$ cycloalkyl, which is unsubstituted or mono-substituted with hydroxy, hydroxy-methyl, $\text{R}^5\text{R}^6\text{N-CH}_2-$, heterocyclyl-methyl or $-\text{CONH}_2$; or
- 25 • $(\text{C}_1\text{-C}_6)$ alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, $(\text{C}_1\text{-C}_4)$ alkylthio, $(\text{C}_1\text{-C}_4)$ alkoxy-carbonyl, hydroxy, cyano, $-\text{NR}^5\text{R}^6$, –

COOH, $-C(O)NR^7R^8$ or optionally mono-substituted (C_1-C_4) alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or

- (C_1-C_6) alkyl, which is mono-substituted
 - ◇ with (C_3-C_6) cycloalkyl, which cycloalkyl is unsubstituted or mono-substituted with $-NR^5R^6$ or hydroxy;
 - ◇ with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with (C_1-C_4) alkyl, (C_1-C_2) alkyl-carbonyl or *tert*-butoxycarbonyl, and/or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen, (C_1-C_4) alkyl and (C_1-C_2) alkoxy- (C_1-C_2) alkyl; or
 - ◇ with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl, $-CH_2NHR^9$, $-SO_2NH_2$ and phenyl; or
- (C_3-C_5) fluoroalkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from halogen and (C_1-C_4) alkyl; or
- heterocyclyl, which is unsubstituted or mono-substituted at a nitrogen atom with (C_1-C_6) alkyl, benzyl or *tert*-butoxycarbonyl or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl; or
- an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl and phenyl; or
- a group selected from 1-carbamoyl-2-phenyl-ethyl, 1-methoxymethyl-2-phenyl-ethyl, 2-morpholino-2-phenyl-ethyl, 2-phenyl-vinyl, 2,2-dichloro-1-methyl-cyclopropyl;

R^3 represents hydrogen, (C_1-C_3) alkyl or 2-methoxy-ethyl; or

R^2 and R^3 form, together with the nitrogen that carries them, a ring of 5 to 7 members, which ring is substituted with amino- (C_1-C_4) alkyl;

R^4 represents hydrogen or methyl;

R^5 represents hydrogen, (C_1-C_3) alkyl or *tert*-butoxycarbonyl;

R^6 represents hydrogen or (C_1-C_3) alkyl;

R^7 and R^8 represent independently from each other hydrogen or methyl; or

R^7 and R^8 form, together with the nitrogen that carries them, a pyrrolidine or piperidine ring; and

R^9 represents hydrogen or *tert*-butoxycarbonyl;

5 or a salt of such a compound.

2. A compound of formula (I) according to claim 1, wherein

W represents $-CH_2CH_2-$ or $-CH=CH-$;

Y represents a bond;

10 R^1 represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_2) alkyl-carbonyl, and (C_1-C_2) fluoroalkyl;

Z represents $-C(O)NR^{3-*}$,

wherein the asterisk indicates the bond which is linked to R^2 ;

15 R^2 represents

- (C_3-C_6) cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or pyrrolidin-1-yl-methyl; or
- (C_1-C_6) alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C_1-C_4) alkylthio, hydroxy, cyano, $-NR^5R^6$, $-C(O)NH_2$ or optionally
20 mono-substituted (C_1-C_4) alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or
- (C_1-C_5) alkyl, which is mono-substituted
 - ◇ with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted
25 at a nitrogen atom with methyl or ethyl, or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from fluorine, methyl and methoxy-methyl; or
 - ◇ with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C_1-C_4) alkyl and
30 $-CH_2NH_2$; or

- (C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl; or
- heterocyclyl, which is unsubstituted or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl;

R³ represents hydrogen, (C₁-C₃)alkyl or 2-methoxy-ethyl;

5 **R**⁵ represents hydrogen, (C₁-C₃)alkyl or *tert*-butoxycarbonyl; and

R⁶ represents hydrogen or (C₁-C₃)alkyl;

or a salt of such a compound.

3. A compound of formula (I) according to any one of claims 1 or 2, wherein

Y represents a bond;

10 or a salt of such a compound.

4. A compound of formula (I) according to any one of claims 1 to 3, wherein

R¹ represents an aryl- or a heteroaryl-group, which groups are independently unsubstituted or mono-substituted, wherein the substituent is selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₂)alkyl-carbonyl and (C₁-
15 C₂)fluoroalkyl;

or a salt of such a compound.

5. A compound of formula (I) according to any one of claims 1 to 4, wherein

Z represents -C(O)NR³*, wherein the asterisk indicates the bond which is linked to R²;

or a salt of such a compound.

20 6. A compound of formula (I) according to any one of claims 1 to 5, wherein

R² represents

(C₃-C₆)cycloalkyl, which is unsubstituted or mono-substituted with hydroxy or pyrrolidin-1-yl-methyl; or

(C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl,

25 (C₁-C₄)alkylthio, hydroxy, cyano, -NR⁵R⁶, -C(O)NH₂ or optionally mono-substituted (C₁-C₄)alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl; or

(C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl, or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected

30 from fluorine, methyl and methoxy-methyl; or

(C₁-C₅)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl and -CH₂NH₂; or

(C₃-C₅)fluoroalkyl, which is mono-substituted with heterocyclyl; or

- 5 heterocyclyl, which is unsubstituted or mono-substituted at a carbon atom with pyrrolidin-1-yl-methyl;

or a salt of such a compound.

7. A compound of formula (I) according to any one of claims 1 to 5, wherein

- 10 **R**² represents (C₁-C₆)alkyl, which is unsubstituted or mono-substituted with fluorine, trifluoromethyl, (C₁-C₄)alkylthio, hydroxy, cyano, -NR⁵R⁶, -C(O)NR⁷R⁸ or optionally mono-substituted (C₁-C₄)alkoxy, wherein the substituent is selected from hydroxy and heterocyclyl;

or a salt of such a compound.

8. A compound of formula (I) according to any one of claims 1 to 5, wherein

- 15 **R**² represents (C₁-C₅)alkyl, which is mono-substituted with heterocyclyl, which heterocyclyl is unsubstituted or mono-substituted at a nitrogen atom with methyl or ethyl, or mono- or di-substituted at one or two of the carbon atoms with substituents independently selected from fluorine, methyl and methoxy-methyl;

or a salt of such a compound.

- 20 9. A compound of formula (I) according to any one of claims 1 to 5, wherein

R² represents (C₁-C₄)alkyl, which is mono-substituted with an aryl- or heteroaryl-group, which groups are independently unsubstituted, mono- or di-substituted, wherein the substituents are independently selected from the group consisting of (C₁-C₄)alkyl and -CH₂NH₂;

- 25 or a salt of such a compound.

10. A compound of formula (I) according to claim 1, selected from the group consisting of:

(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(5-amino-pentyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- 30 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

(5*R*^{*})-*N*⁵-(4-Bromophenyl)-(6*R*^{*})-*N*⁶-(piperidin-4-yl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-iso-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-*N,N*-dimethyl-amino-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-((3-aminomethyl-phenyl)-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-piperidiny-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-(*N,N*-diethyl-amino)-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3-hydroxy-propyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-carbamoyl-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-pyrrolidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-ethoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidinyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2,2-trifluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-fluoro-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-methyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-tetrahydrofuranyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-ethylsulfanyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(*N,N*-diethyl-amino)-pent-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-*tert*-butoxycarbonyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-hydroxy-prop-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-imidazolidin-2-on-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-hydroxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyano-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-pyrazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-aminomethyl-phenyl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-ethyl-*N*⁶-(2-diethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-imidazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-([1,4]-dioxan-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-hydroxy-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-(2-dimethylamino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-*tert*-butoxycarbonyl-amino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methyl-*tert*-butoxycarbonyl-amino)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyrrolidin-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-1*H*-[1,2,4]-triazol-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(furan-3-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-dimethyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1-ethyl-pyrrolidin-2-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-1*H*-[1,2,4]-triazol-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(*N*-*tert*-butoxycarbonyl-amino)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-1-hydroxy-4-methyl-pent-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(methoxy-carbonyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-5-methyl-1*H*-pyrazol-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶,*N*⁶-bis-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-diethyl-amino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-(3-methyl-butyl)-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-pyridin-2-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-*N*-*tert*-butoxycarbonyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-phenyl-1*H*-pyrazol-5-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(hexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-phenyl-2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-diethyl-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-pyrrolidin-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-morpholino-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(1-piperidin-1-yl-propan-1-on-2-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-benzyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-methyl-*N*⁶-hexyl-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3,3-dimethyl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-methyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-morpholino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(5-methyl-1*H*-pyrazol-4-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-*tert*-butoxycarbonyl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-{[(3-*N*-*tert*-butoxycarbonyl-aminomethyl)-phenyl]-methyl}-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-propyl-*N*⁶-(cyclopropylmethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclohexyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-piperidin-4-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-1-carbamoyl-2-phenyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2*S*)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(4-*N*-*tert*-butoxycarbonyl-aminomethyl-phenyl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(*N*-*tert*-butoxycarbonyl-azetidin-3-yl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(*N*-*tert*-butoxycarbonyl-piperidin-3-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(1*S*)-2-methoxy-1-benzyl-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(5-methyl-3-phenyl-isoxazol-4-yl)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-carbamoyl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methoxy-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(tetrahydrofuran-2-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-[(2-imidazolidin-2-on-1-yl)-ethyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(cyclopropyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-hydroxy-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(1*H*-imidazol-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(5-(dimethyl-amino)-pentyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-(4-methyl-piperazin-1-yl)-propyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-(4,5-dimethyl-1*H*-imidazol-2-yl)-ethyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromopyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Methoxyphenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-Pentyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-[(4-Methyl-phenyl)-methyl]-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Methoxycarbonyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(Cyclohexyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Methyl-cyclohex-1-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Oxo-hexyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-Nitro-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Chloro-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(5-Cyano-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(1-(4-Bromophenyl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Trifluoromethoxyphenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Phenoxy-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(3-Methyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-Butyl-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Methyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(2-Methyl-benzothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Phenyl-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Oxo-pentyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-(1*H*-Imidazol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(2-Chloro-pyrimidin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-*tert*-Butyl-isoxazol-3-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Methyl-benzo[*d*]isothiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(1*H*-Indol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(6-Fluoro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Ethyl-butyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-(4-Chlorophenyl)-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Benzo[2,1,3]oxadiazol-4-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-*tert*-Butyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Phenyl-[1,2,4]thiadiazol-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(6-Chloro-benzothiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(3-(2-Methyl-1*H*-indol-1-yl)-propyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(1-Methyl-1*H*-benzoimidazol-2-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-(1*H*-Indol-1-yl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(2-Methoxy-phenyl)-ethyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(3,5-dimethyl-pyrazol-1-yl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(5-phenyl-isoxazole-4-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-(2-oxo-pyrrolidin-1-yl)-butyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-chloro-phenyl)-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-methoxy-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(*N,N*-dimethyl-aminocarbonyl)-propionyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2,2-dichloro-1-methyl-cyclopropylcarbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-methoxycarbonyl-butanoyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-(pentanoylamino-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2,5-dimethyl-thiazol-4-yl)-acetyl-amino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(1-phenyl-1*H*-pyrazole-5-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-aminocarbonyl-propionyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-methyl-pyridine-3-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(isobutyrylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(*N*-ethyl-piperidine-4-carbonyl)-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;

- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-pyridin-3-yl-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[*N*-(3-methoxy-propionyl)-*N*-methyl-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[2-chloro-3-fluoro-phenyl-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(4-pyrrolidin-1-yl-butanoylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[1,5-dimethyl-1*H*-pyrazole-3-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[cyclopentyl-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(2-methyl-thiazol-4-yl)-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 15 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-(*N,N*-dimethyl-amino)-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[*N*-(2-(2-chloro-phenyl)-acetyl)-*N*-methyl-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[*N*-(1,5-dimethyl-1*H*-pyrazole-3-carbonyl)-*N*-methyl-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(2-cyclopropyl-acetylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(1-methyl-1*H*-benzoimidazol-2-yl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-1*H*-indol-3-yl-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(butanoylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-(4-fluoro-phenyl)-propionylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[(3-phenyl-acryloylamino)-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl)-(6*R**)-6-[[5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carbonyl]-amino]-methyl]-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5-carboxamide;

- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-phenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(5-Methyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Acetyl-thiophen-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(5-Acetyl-furan-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Trifluoromethyl-phenyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(2-Acetyl-oxazol-5-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(4,5-Dimethyl-1*H*-imidazol-2-yl)-ethyl)-(6*R**)-*N*⁶-(4-bromophenyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Iodophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(5-(iso-Butyl)-isoxazol-3-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Bromo-thiophen-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide; and
- 25 (5*R**)-*N*⁵-(2-Fluoro-4-bromophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- or a salt of such a compound.

11. A compound of formula (I) according to claim 1, selected from the group consisting of:
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-dimethylamino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(4-amino-4-oxobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-pyrrolidino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(2-amino-2-oxoethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-ethyl-piperazin-1-yl)-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-piperidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(azetidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-morpholino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-1,4-diazepan-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-methyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-4-oxobutyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(2-(2-(pyrrolidin-1-yl)ethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-((3*R*,6*S*)-6-(pyrrolidin-1-ylmethyl)tetrahydro-2*H*-pyran-3-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(4-acetyl-piperazin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*R*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-((3*S*)-fluoropyrrolidino)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(5-pyrrolidino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(pyrrolidin-1-yl-methyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl)-(6*R**)-*N*⁶-(3-methylamino-3-oxopropyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-Acetyl-thiazol-5-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(2,6-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,3-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Fluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(3,5-Difluoro-4-methoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Chloro-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Fluoro-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Trifluoromethoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Isopropoxy-phenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(4-Bromo-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Acetyl-oxazol-4-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-pyrrolidin-1-yl-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethylenespiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylenespiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromo-pyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Acetyl-oxazol-2-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(isobutyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromo-phenyl-methyl)-(6*R**)-*N*⁶-(3-(1*H*-benzoimidazol-2-yl)-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Methoxy-pyrid-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(2-Bromo-pyrazin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Trifluoromethyl-pyridin-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(2-Methyl-pyridin-5-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(Benzo[d]oxazol-6-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Methyl-isoxazol-3-yl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(4-Methyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Trifluoromethyl-1,3,4-thiadiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(2-Bromo-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(2-fluoro-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(3-amino-3-oxopropyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(4-diethylamino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-ethoxy-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(3-pyrrolidino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*^{*})-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*^{*})-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(2-dimethylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(3-dimethylamino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*^{*})-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-diethylamino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(2-fluoroethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(4-diethylamino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-(4-methylpiperazin-1-yl)-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(2-dimethylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-((2-imidazolidin-2-on)-1-yl-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(2-methoxy-ethyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R**)-*N*⁶-(3-dimethylamino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromopyrid-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(5-Bromopyrid-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Chloropyrid-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromothiazol-5-yl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-hydroxyl-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Methoxyphenyl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(5-Bromo-pyridin-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-methylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromo-3-chlorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Chloro-pyridin-5-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(3-amino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Acetyl-thiazol-2-yl-methyl)-(6*R*^{*})-*N*⁶-(piperidin-4-yl-methyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(2-methylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(5-amino-pentyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*^{*})-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*^{*})-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(2-methylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(piperidin-4-yl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-amino-propyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Bromophenyl-methyl)-(6*R*^{*})-*N*⁶-(3-(aminomethyl)phenyl-methyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(4-(aminomethyl)phenyl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(2,2-dimethyl-3-amino-propyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Bromophenyl-methyl)-(6*R**)-*N*⁶-(piperidin-4-yl-methyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromo-thiazol-5-yl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Methyl-pyridin-2-yl)-(6*R*)-*N*⁶-(3-amino-3-oxopropyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,6-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-
- 20 ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(4-Bromo-3-fluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-
- 30 spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶,*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-2-fluorophenyl-methyl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,3-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-2,5-difluorophenyl-methyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(isobutyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-*tert*-butoxycarbonyl-amino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-*tert*-butoxycarbonyl-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(5-amino-pentyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-amino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶,*N*⁶-(3-(aminomethyl)pentane-1,5-diyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-4-yl-methyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-Aminobutyl)-(6*R*^{*})-*N*⁶-(4-bromophenyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(5-Aminopentyl)-(6*R*^{*})-*N*⁶-(4-bromophenyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*^{*})-*N*⁵-(2-(Cyclohexen-1-yl)ethyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*^{*})-*N*⁵-(4-*tert*-Butyl-cyclohexyl)-(6*R*^{*})-*N*⁶-(4-pyrrolidino-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-(Pyridin-2-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(4-Trifluoromethyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,4,6-Trifluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,4-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-[(2-Acetyl-thiazol-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Chloro-2-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(4-Methyl-oxazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(5-Acetyl-thiazol-2-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Acetylphenyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R**)-*N*⁵-(2-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Bromo-4-fluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(2,3,5-Trifluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R**)-*N*⁵-(3,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(3-Difluoromethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-[(2-Methoxypyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(3-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Acetylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-
- 10 (4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Fluoro-5-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Fluoro-3-trifluoromethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-[(2,6-Dichloropyridin-4-yl)methyl]-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,5-Dimethylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4,5-Dimethyl-thiazol-2-yl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-
- 20 ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Methoxy-5-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-3,6-difluorophenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R**)-*N*⁵-(2-Isopropoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-Chloro-6-fluoro-3-methylphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3-Chloro-4-methoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-
- 30 ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(3,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2,4-Dimethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R**)-*N*⁵-(2-(3,4-Dimethoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(4-Methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R**)-*N*⁵-(2-(4-Bromophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(3,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(4-Methylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R**)-*N*⁵-(2-(4-Fluorophenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R**)-*N*⁵-(2-(3-Bromo-4-methoxyphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(2-(2,4-Dimethylphenyl)ethyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R**)-*N*⁵-(4-Ethoxyphenyl-methyl)-(6*R**)-*N*⁶-(4-pyrrolidino-butyl)-(4*S**,7*R**)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-dimethylamino-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(pyridin-2-yl)ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(2-(4-aminosulfonyl-phenyl)-ethyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-(2,4-Dichlorophenyl)ethyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(2-(4-Chlorophenyl)ethyl)-(6*R*)-*N*⁶-(*N*-isopentyl-piperidin-4-yl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3,5-difluorophenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(4-Bromo-thiazol-2-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromo-3-trifluoromethylphenyl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*^{*})-*N*⁵-[(4-Acetyl-thiazol-2-yl)methyl]-(6*R*^{*})-*N*⁶-(2-methylamino-ethyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2,5-dimethylpyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(pyrrolidin-1-yl)pentyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(3-fluoro-4-(pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(2-(methoxymethyl)pyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(4-(3,3-difluoropyrrolidin-1-yl)butyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(2-Bromo-3-fluoro-pyridin-5-yl)-(6*R*)-*N*⁶-(4-pyrrolidino-butyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-hydroxyethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-hydroxypropyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxybutyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-methyl-3-hydroxyprop-2-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(2-hydroxyethoxy)ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(4-hydroxy-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 30 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(1-hydroxy-cyclohexyl)methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*trans*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;

- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(*cis*-4-(hydroxymethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(pyrrolidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 5 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(2-(*N*-methylamino)-ethyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(3-(*N*-methylamino)-propyl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(piperidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 10 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(pyrrolidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-2-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 15 (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-[(piperidin-3-yl)-methyl]-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(5-Bromothiazol-2-yl)-(6*R*)-*N*⁶-(azetidin-3-yl)-(4*S*,7*R*)-[4,7-ethylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*cis*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 20 (5*R*)-*N*⁵-(4-Bromophenyl)-(6*R*)-*N*⁶-(*trans*-4-(aminomethyl)-cyclohexyl)-(4*S*,7*R*)-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide; and
- (5*R*^{*})-*N*⁵-(2-Trifluoromethyl-pyridin-5-yl)-(6*R*^{*})-*N*⁶-(4-pyrrolidin-1-yl-butyl)-(4*S*^{*},7*R*^{*})-[4,7-ethenylene-spiro[2.4]heptane]-5,6-dicarboxamide;
- 25 or a salt of such a compound.

12. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as medicament.

13. A pharmaceutical composition containing, as active principle, a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.
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14. Use of a compound of formula (I) according to claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a disease selected from inflammatory diseases, obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders,

neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.

15. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a disease selected from inflammatory diseases,
5 obstructive airway diseases, allergic conditions, HIV-mediated retroviral infections, cardiovascular disorders, neuroinflammation, neurological disorders, pain, prion-mediated diseases and amyloid-mediated disorders; and for the modulation of immune responses.