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(54) Title: SUBSTITUTED SULFONAMIDE DERIVATIVES

(57) Abstract: The invention relates to substituted sulfonamide derivatives, processes for the preparation thereof, medicaments containing these compounds and the use of substituted sulfonamide derivatives for the preparation of medicaments.

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### Substituted sulfonamide derivatives

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The present invention relates to substituted sulfonamide derivatives, processes for the preparation thereof, medicaments containing these compounds and the use of substituted sulfonamide derivatives for the preparation of medicaments.

In contrast to the constitutive expression of the bradykinin 2 receptor (B2R), in most tissues the bradykinin 1 receptor (B1R) is not expressed or expressed only weakly. Nevertheless, expression of B1R can be induced on various cells. For example, in the course of inflammation reactions a rapid and pronounced induction of B1R takes place on neuronal cells, but also various peripheral cells, such as fibroblasts, endothelial cells, granulocytes, macrophages and lymphocytes. In the course of inflammation reactions, a switch from a B2R to a B1R dominance thus occurs on the cells involved. The cytokines interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF $\alpha$ ) are involved to a considerable degree in this upwards regulation of B1R (Passos et al. *J. Immunol.* 2004, 172, 1839-1847). After activation with specific ligands, B1R-expressing cells then themselves can secrete inflammation-promoting cytokines such as IL-6 and IL-8 (Hayashi et al., *Eur. Respir. J.* 2000, 16, 452-458). This leads to inwards migration of further inflammation cells, e.g. neutrophilic granulocytes (Pesquero et al., *PNAS* 2000, 97, 8140-8145). The bradykinin B1R system can contribute towards chronification of diseases via these mechanisms. This is demonstrated by a large number of animal studies (overviews in Leeb-Lundberg et al., *Pharmacol. Rev.* 2005, 57, 27-77 und Pesquero et al., *Biol. Chem.* 2006, 387, 119-126). On humans too, an enhanced expression of B1R, e.g. on enterocytes and macrophages in the affected tissue of patients with inflammatory intestinal diseases (Stadnicki et al., *Am. J. Physiol. Gastrointest. Liver Physiol.* 2005, 289, G361-366) or on T lymphocytes of patients with multiple sclerosis (Pratet et al., *Neurology.* 1999; 53, 2087-2092) or an activation of the bradykinin B2R-B1R system in the course of infections with *Staphylococcus aureus* (Bengtson et al., *Blood* 2006, 108, 2055-2063)

is found. Infections with *Staphylococcus aureus* are responsible for syndromes such as superficial infections of the skin up to septic shock.

On the basis of the pathophysiological relationships described, there is a great therapeutic potential for the use of B1R antagonists on acute and, in particular, chronically inflammatory diseases. These include diseases of the respiratory tract (bronchial asthma, allergies, COPD/chronic obstructive pulmonary disease, cystic fibrosis etc.), inflammatory intestinal diseases (ulcerative colitis, CD/Crohn's disease etc.), neurological diseases (multiple sclerosis, neurodegeneration etc.), inflammations of the skin (atopic dermatitis, psoriasis, bacterial infections etc.) and mucous membranes (Behcet's disease, pelvitis, prostatitis etc.), rheumatic diseases (rheumatoid arthritis, osteoarthritis etc.), septic shock and reperfusion syndrome (following cardiac infarction, stroke).

The bradykinin (receptor) system is moreover also involved in regulation of angiogenesis (potential as an angiogenesis inhibitor in cancer cases and macular degeneration on the eye), and B1R knockout mice are protected from induction of obesity by a particularly fat-rich diet (Pesquero et al., *Biol. Chem.* 2006, 387, 119-126). B1R antagonists are therefore also suitable for treatment of obesity.

B1R antagonists are suitable in particular for treatment of pain, in particular inflammation pain and neuropathic pain (Calixto et al., *Br. J. Pharmacol.* 2004, 1-16), and here in particular diabetic neuropathy (Gabra et al., *Biol. Chem.* 2006, 387, 127-143). They are furthermore suitable for treatment of migraine.

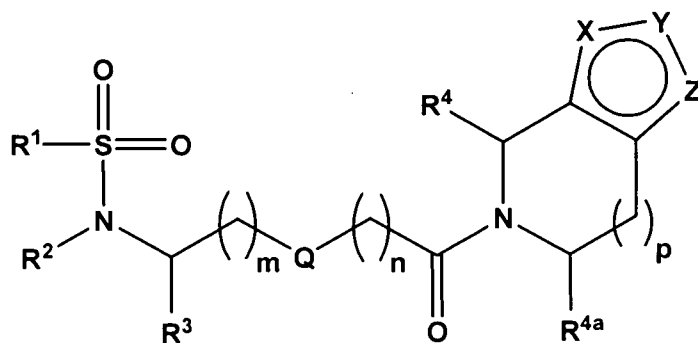
In the development of B1R modulators, however, there is the problem that the human and the rat B1R receptor differ so widely that many compounds which are good B1R modulators on the human-receptor have only a poor or no affinity for the rat receptor. This makes pharmacological studies on animals considerably difficult, since many studies are usually conducted on the rat. However, if no activity exists on the rat receptor, neither the action nor side effects can be investigated on the rat. This has already led to transgenic animals with human B1 receptors being produced for pharmacological studies on animals (Hess et al., *Biol. Chem.* 2006; 387(2):195-201).

Working with transgenic animals, however, is more expensive than working with the unmodified animals. Since in the development of medicaments, however, precisely long-term toxicity studies on the rat belong to the standard studies, but this is inappropriate in the event of an absence of activity on the receptor, an important established instrument for checking safety is lacking for the development of such compounds. There is therefore a need for novel B1R modulators, B1R modulators which bind both to the rat receptor and to the human receptor offering particular advantages.

One object of the present invention was therefore to provide novel compounds which are suitable in particular as pharmacological active compounds in medicaments, preferably in medicaments for treatment of disorders or diseases which are at least partly mediated by B1R receptors.

This object is achieved by the substituted sulfonamide derivatives according to the invention.

The invention therefore provides substituted sulfonamide derivatives of the general formula I



I

wherein

m and n independently of one another each represent 0, 1 or 2;

p represents 0, 1 or 2;

Q represents a single bond, -CH<sub>2</sub>- or -O-;

X represents N, NR<sup>5</sup>, O, S or CR<sup>8</sup>;

Y represents N, NR<sup>6</sup>, O, S or CR<sup>9</sup>;

Z represents N, NR<sup>7</sup>, O, S or CR<sup>10</sup>;

R<sup>1</sup> represents CH(aryl)<sub>2</sub>, aryl, heteroaryl or a CH(aryl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;

R<sup>2</sup> and R<sup>3</sup> are defined as described under (i) or (ii):

- (i) R<sup>2</sup> represents H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, bicyclic 8- to 12-membered carbocyclyl, CH(aryl)<sub>2</sub>, aryl or heteroaryl; or denotes a C<sub>3-8</sub>-cycloalkyl, bicyclic 8- to 12-membered carbocyclyl, CH(aryl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group;

R<sup>3</sup> represents H, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C(=O)-OR<sup>13</sup>, C<sub>1-6</sub>-alkyl, aryl or heteroaryl; or denotes an aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group, wherein R<sup>2</sup> and R<sup>3</sup> do not both simultaneously represent H, or

- (ii) R<sup>2</sup> and R<sup>3</sup> together with the -N-(CH)- group joining them form an unsubstituted or mono- or polysubstituted, e.g. di-, tri- or tetrasubstituted, heterocyclic ring, which can be fused with an aryl or heteroaryl radical,

wherein the heterocyclic ring is saturated or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero atom to which the radical R<sup>2</sup> is bonded, at least one, e.g. 1 or 2, further hetero atom(s) or hetero atom group(s) chosen from the group consisting of N, NR<sup>14</sup>, O, S, S=O or S(=O)<sub>2</sub>; wherein the radical R<sup>14</sup> denotes H, C<sub>1-6</sub>-alkyl, -C(=O)-R<sup>15</sup>, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or a C<sub>3-8</sub>-cycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group, and R<sup>15</sup> denotes C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-

cycloalkyl, aryl, heteroaryl or a C<sub>3-8</sub>-cycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group,

R<sup>4</sup> and R<sup>4a</sup> independently of one another each represent H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or a C<sub>3-8</sub>-cycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently of one another each represent H, C<sub>1-6</sub>-alkyl, aryl or heteroaryl;

R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>C-alkylene-NR<sup>11</sup>R<sup>12</sup>, C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group,

wherein preferably at least one of the radicals R<sup>4</sup>, R<sup>4a</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> does not represent H,

R<sup>11</sup> and R<sup>12</sup> are defined as described under (iii) or (iv):

(iii) R<sup>11</sup> and R<sup>12</sup> independently of one another each denote H, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;

or

(iv) R<sup>11</sup> and R<sup>12</sup> together with the nitrogen atom joining them form an unsubstituted or mono- or polysubstituted, e.g. di-, tri- or tetrasubstituted, heterocyclic ring, which can be fused with a saturated, at least monounsaturated or aromatic, unsubstituted or mono- or polysubstituted ring system,

wherein the heterocyclic ring is saturated, or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero

atom to which the radicals  $R^{11}$  and  $R^{12}$  are bonded, at least one, e.g. 1 or 2, further hetero atom(s) or hetero atom group(s) chosen from the group consisting of N,  $NR^{16}$ , O, S, S=O and  $S(=O)_2$ , the ring system is 4-, 5-, 6- or 7-membered, can contain at least one, e.g. 1 or 2, hetero atom(s) or hetero atom group(s) chosen from the group consisting of N,  $NR^{17}$ , O, S, S=O and  $S(=O)_2$ ,  $R^{16}$  represents a radical chosen from the group consisting of H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or  $C_{3-8}$ -cycloalkyl bonded via a  $C_{1-3}$ -alkylene group and  $R^{17}$  represents a radical chosen from the group consisting of H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or  $C_{3-8}$ -cycloalkyl bonded via a  $C_{1-3}$ -alkylene group;

$R^{13}$  represents H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group;

wherein the abovementioned radicals  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl,  $C_{1-3}$ -alkylene,  $C_{1-6}$ -alkylene,  $C_{2-6}$ -alkenylene,  $C_{2-6}$ -alkynylene,  $C_{3-8}$ -cycloalkyl, heterocycloalkyl, bicyclic 8- to 12-membered carbocyclyl, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals and the abovementioned radicals  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl,  $C_{1-3}$ -alkylene,  $C_{1-6}$ -alkylene,  $C_{2-6}$ -alkenylene and  $C_{2-6}$ -alkynylene can in each case be branched or unbranched;

optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

In the context of the present invention, the term "halogen" preferably represents the radicals F, Cl, Br and I, particularly preferably the radicals F, Cl and Br.

In the context of this invention, the expression "C<sub>1-6</sub>-alkyl" includes acyclic saturated hydrocarbon radicals having 1, 2, 3, 4, 5 or 6 C atoms, which can be branched- or straight-chain (unbranched) and unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals. The alkyl radicals can preferably be chosen from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl and hexyl. Particularly preferred alkyl radicals can be chosen from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl and tert-butyl.

In the context of this invention, the expression "C<sub>2-6</sub>-alkenyl" includes acyclic unsaturated hydrocarbon radicals having 2, 3, 4, 5 or 6 C atoms, which can be branched or straight-chain (unbranched) and unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals. In this context, the alkenyl radicals contain at least one C=C double bond. Alkenyl radicals can preferably be chosen from the group consisting of vinyl, prop-1-enyl, allyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, but-1,3-dienyl, 2-methylprop-1-enyl, but-2-en-2-yl, but-1-en-2-yl, pentenyl and hexenyl. Particularly preferred alkenyl radicals can be chosen from the group consisting of vinyl, prop-1-enyl, allyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, but-1,3-dienyl, 2-methylprop-1-enyl, but-2-en-2-yl and but-1-en-2-yl.

In the context of this invention, the expression "C<sub>3-8</sub>-cycloalkyl" denotes cyclic saturated hydrocarbons having 3, 4, 5, 6, 7 or 8 carbon atoms, which can be unsubstituted or substituted once or several times, for example by 2, 3, 4 or 5 identical or different radicals, on one or more ring members. C<sub>3-8</sub>-Cycloalkyl can preferably be chosen from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The expression "3- to 8-membered heterocycloalkyl" designates saturated heterocyclic rings which can contain as ring members, chosen independently of one another, 1, 2, 3, 4 or 5 identical or different hetero atoms, preferably from the group N, O or S. In the case where the heterocycloalkyl is bonded to a hetero atom, for example N, bonding

to the heterocycloalkyl is preferably via one of the carbon ring members of the heterocycloalkyl.

3- to 8-membered heterocycloalkyls can be, in particular, 4-, 5- or 6-membered. Examples of 3- to 8-membered heterocycloalkyls are azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydropyrany, dioxany and dioxolany, which can optionally be substituted as explained below.

In the context of this invention, the expression "aryl" denotes aromatic hydrocarbons, in particular phenyls and naphthyls. The aryl radicals can also be condensed with further saturated, (partially) unsaturated or aromatic ring systems. Each aryl radical can be unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, wherein the substituents on the aryl can be identical or different and can be in any desired and possible position of the aryl. Aryl can advantageously be chosen from the group consisting of phenyl, 1-naphthyl and 2-naphthyl, which can in each case be unsubstituted or substituted once or several times, for example by 2, 3, 4 or 5 radicals.

In the context of the present invention, the expression "heteroaryl" represents a 5-, 6- or 7-membered cyclic aromatic radical which contains at least 1, if appropriate also 2, 3, 4 or 5 hetero atoms, wherein the hetero atoms can be identical or different and the heteroaryl can be unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals. The substituents can be bonded in any desired and possible position of the heteroaryl. The heterocyclic ring can also be part of a bi- or polycyclic, in particular a mono-, bi- or tricyclic system, which can then be more than 7-membered in total, preferably up to 14-membered. Preferred hetero atoms are chosen from the group consisting of N, O and S. The heteroaryl radical can preferably be chosen from the group consisting of pyrroly, indoly, furyl (furanly), benzofuranly, thienyl (thiophenyl), benzothienyl, benzothiadiazoly, benzothiazoly, benzotriazolyl, benzodioxolany, benzodioxany, benzoxazolyl, benzoxadiazoly, imidazothiazoly, dibenzofuranly, dibenzothienyl, phthalaziny, pyrazoly, imidazolyl, thiazoly, oxazolyl, oxadiazoly, triazole, tetrazole, isoxazoyl, pyridiny (pyridyl), pyridaziny, pyrimidiny, pyraziny, pyranly, indazolyl, puriny, indoliziny, quinoliny, isoquinoliny, quinazoliny, quinoxaliny, carbazolyl, phenaziny, phenothiaziny and oxadiazoly, in particular from the group consisting of thienyl (thiophenyl), pyridiny

(pyridyl), pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl and quinolinyl, wherein bonding to the general structure I can be via any desired and possible ring member of the heteroaryl radical. The heteroaryl radical can be particularly preferably chosen from the group consisting of furyl, thienyl and pyridinyl.

In the context of the present invention, the expression "bicyclic 8- to 12-membered carbocyclyl" represents cyclic hydrocarbon compounds which comprise two condensed ring systems, wherein the two ring systems together contain 8-12 ring members and no hetero atoms. In this context the two ring systems can have different ring sizes and different degrees of saturation, i.e. the two rings can each in itself be either aromatic, saturated or partly unsaturated. In particular, bicyclic 8- to 12-membered carbocyclyls are understood as meaning compounds which comprise an aromatic ring system with a fused-on saturated ring system. In this context bonding to the general structure I can be via any desired and possible ring member of the carbocyclyl radical, but preferably via a ring member of an unsaturated ring. The bicyclic 8- to 12-membered carbocyclyl can be particularly preferably chosen from the group consisting of 2,3-dihydro-1*H*-indenyl or 1,2,3,4-tetrahydronaphthyl.

In the context of the present invention, the expression "C<sub>1-3</sub>-alkylene group" or "C<sub>1-6</sub>-alkylene group" includes acyclic saturated hydrocarbon radicals having 1, 2 or 3 or, respectively, having 1, 2, 3, 4, 5 or 6 C atoms, which can be branched- or straight-chain (unbranched) and unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals and which link a corresponding radical to the main general structure. The alkylene groups can preferably be chosen from the group consisting of -CH<sub>2</sub>-, -CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>3</sub>)-, -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)-, -CH(CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)-, -C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)-, -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, -CH(CH<sub>3</sub>)-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-CH(CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>-CH(CH<sub>3</sub>)-, -CH(CH<sub>2</sub>CH<sub>3</sub>)-CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-, -C(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)-CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)-, -C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)-, -C(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>- and -CH<sub>2</sub>-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>2</sub>-. The alkylene groups can

be particularly preferably chosen from the group consisting of  $-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ .

In the context of the present invention, the expression "C<sub>2-6</sub>-alkenylene group" includes acyclic hydrocarbon radicals having 2, 3, 4, 5 or 6 C atoms, which are unsaturated once or several times, for example 2, 3 or 4 times, and can be branched- or straight-chain (unbranched) and unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals and which link a corresponding radical to the main general structure. In this context the alkenylene groups contain at least one C=C double bond. The alkenylene groups can preferably be chosen from the group consisting of  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $-\text{C}(\text{CH}_3)=\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ ,  $-\text{C}(\text{CH}_3)=\text{CH}-\text{CH}_2-$ ,  $-\text{CH}=\text{C}(\text{CH}_3)-\text{CH}_2-$ ,  $-\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)-$ ,  $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}-$ ,  $-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{CH}=\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-$  and  $-\text{CH}=\text{CH}_2-\text{CH}-\text{CH}=\text{CH}_2-$ .

In the context of the invention, the expression "C<sub>2-6</sub>-alkynylene group" includes acyclic hydrocarbon radicals having 2, 3, 4, 5 or 6 C atoms, which are unsaturated once or several times, for example 2, 3 or 4 times, and can be branched- or straight-chain (unbranched) and unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals and which link a corresponding radical to the main general structure. In this context the alkynylene groups contain at least one C≡C triple bond. The alkynylene groups can preferably be chosen from the group consisting of  $-\text{C}\equiv\text{C}-$ ,  $-\text{C}\equiv\text{C}-\text{CH}_2-$ ,  $-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-$ ,  $-\text{C}\equiv\text{C}-\text{CH}(\text{CH}_3)-$ ,  $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-$ ,  $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-$ ,  $-\text{C}\equiv\text{C}-\text{C}(\text{CH}_3)_2-$ ,  $-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-$ ,  $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{CH}_2-$  and  $-\text{C}\equiv\text{C}-\text{CH}_2-\text{C}\equiv\text{C}-$ .

In the context of the present invention, the expression "aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group, a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group" means that the C<sub>1-3</sub>-alkylene groups, C<sub>1-6</sub>-alkylene groups, C<sub>2-6</sub>-alkenylene groups, C<sub>2-6</sub>-alkynylene groups and aryl or heteroaryl have the meanings defined above and the aryl or heteroaryl is bonded to the main general structure via a C<sub>1-3</sub>-alkylene group, C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group. There may be mentioned by way of example benzyl, phenethyl and phenylpropyl.

In the context of the present invention, the expression "C<sub>3-8</sub>-cycloalkyl and heterocyclyl bonded via a C<sub>1-3</sub>-alkylene group, C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group" means that the C<sub>1-3</sub>-alkylene group, C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group, C<sub>2-6</sub>-alkynylene group, C<sub>3-8</sub>-cycloalkyl and heterocyclyl have the meanings defined above and C<sub>3-8</sub>-cycloalkyl and heterocyclyl are bonded to the main general structure via a C<sub>1-3</sub>-alkylene group, C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group.

In connection with "alkyl", "alkenyl", "alkylene", "alkenylene", "alkynylene" and "cycloalkyl", in the context of this invention the term "substituted" is understood as meaning replacement of a hydrogen radical by F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl or benzyl, where radicals substituted several times are to be understood as meaning those radicals which are substituted several times, for example two or three times, either on different or on the same atoms, for example three times on the same C atom, as in the case of CF<sub>3</sub> or -CH<sub>2</sub>CF<sub>3</sub>, or at different places, as in the case of CH(Cl)-CH=CH-CHCl<sub>2</sub>. Substitution several times can be by identical or different substituents, such as, for example, in the case of CH(OH)-CH=CH-CHCl<sub>2</sub>.

With respect to "aryl" and "heteroaryl", in the context of this invention "substituted" is understood as meaning replacement once or several times, for example 2, 3, 4 or 5 times, of one or more hydrogen atoms of the corresponding ring system by F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NH-aryl<sup>1</sup>, N(aryl<sup>1</sup>)<sub>2</sub>, N(C<sub>1-6</sub>-alkyl)aryl<sup>1</sup>, pyrrolinyl, piperazinyl, morpholinyl, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkyl, O-C<sub>1-6</sub>-alkyl-OH, C(=O)C<sub>1-6</sub>-alkyl, NHSO<sub>2</sub>C<sub>1-6</sub>-alkyl, NHCO C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CH<sub>2</sub>SO<sub>2</sub>-phenyl, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl, OCF<sub>3</sub>, CF<sub>3</sub>, -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, -O-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, unsubstituted C<sub>1-6</sub>-alkyl, pyrrolidinyl, imidazolyl, piperidinyl, benzyloxy, phenoxy, phenyl, naphthyl, pyridinyl, -C<sub>1-3</sub>-alkylene-aryl<sup>1</sup>, benzyl, thienyl, furyl, wherein aryl<sup>1</sup> represents phenyl, furyl, thienyl or pyridinyl, on one or various atoms, wherein the abovementioned substituents – unless stated otherwise – can optionally be substituted in their turn by

the substituents mentioned. Substitution of aryl and heteroaryl several times can be by identical or different substituents. Preferred substituents for aryl and heteroaryl can be chosen from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, -O-C<sub>1-3</sub>-alkyl, unsubstituted C<sub>1-6</sub>-alkyl, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH, SH, phenyl, naphthyl, furyl, thienyl and pyridinyl, in particular from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, F, Cl, Br, CF<sub>3</sub>, CH<sub>3</sub> and OCH<sub>3</sub>.

In connection with "3- to 8-membered heterocycloalkyl", the term "substituted" is understood as meaning replacement of a hydrogen radical on one or more ring members by F, Cl, Br, I, -CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, pyrrolinyl, piperazinyl, morpholinyl, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl or benzyl. Replacement several times can be by identical or different substituents. A hydrogen bonded to an N ring member can be replaced by a C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or a C<sub>3-8</sub>-cycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group, wherein these alkyl, cycloalkyl, alkylene and aryl and heteroaryl groups can be unsubstituted or substituted as defined above. Examples of substituted 3- to 8-membered heterocycloalkyl groups are 1-methylpiperidin-4-yl, 1-phenylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 1-methylpyrrolidin-3-yl, 1-phenylpyrrolidin-3-yl, 1-benzylpyrrolidin-3-yl, 1-methylazetidin-3-yl, 1-phenylazetidin-3-yl or 1-benzylazetidin-3-yl.

In connection with the "heterocyclic ring", in the context of this invention the term "substituted" is understood as meaning replacement of a hydrogen radical bonded to a carbon ring atom by F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl or benzyl. If a heterocyclic radical is substituted several times, e.g. 1, 2, 3 or 4 times, the substituents can be on one and/or more carbon ring atoms. In preferred embodiments, one or more hydrogen radicals on one or more carbon ring atoms are exchanged for F, e.g. -(CF<sub>2</sub>)<sub>n</sub>.

In connection with the "saturated or at least partly unsaturated ring system" which is fused with the heterocyclic ring formed by R<sup>11</sup> and R<sup>12</sup>, in the context of this invention the term "substituted" means replacement of a hydrogen radical bonded to a carbon ring atom by F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl or benzyl. If the ring system is substituted several times, the substituents can be on one and/or more carbon ring atoms. In connection with the "aromatic ring system", which is fused with the heterocyclic ring formed by R<sup>11</sup> and R<sup>12</sup>, in the context of this invention the term "substituted" is understood as meaning the corresponding substitution as defined for aryl and heteroaryl.

With respect to "bicyclic 8- to 12-membered carbocyclyl", in the context of this invention "substituted" is understood as meaning replacement once or several times of hydrogen atoms of the corresponding ring systems of the bicyclic carbocyclyl. In this context the substituents bonded to a saturated or partly unsaturated ring system of the carbocyclyl are chosen independently of one another from the group of substituents for cycloalkyl defined above, that is to say from F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl, or benzyl, wherein in the case of replacement several times several hydrogen atoms of one ring member and/or one hydrogen atom on several ring members are replaced. Substituents which are bonded to an aromatic ring system of the carbocyclyl are chosen independently of one another from the group of substituents for aryl or heteroaryl defined above, that is to say from F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NH-aryl<sup>1</sup>, N(aryl<sup>1</sup>)<sub>2</sub>, N(C<sub>1-6</sub>-alkyl)aryl<sup>1</sup>, pyrrolinyl, piperazinyl, morpholinyl, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkyl, O-C<sub>1-6</sub>-alkyl-OH, C(=O)C<sub>1-6</sub>-alkyl, NHSO<sub>2</sub>C<sub>1-6</sub>-alkyl, NHCOC<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CH<sub>2</sub>SO<sub>2</sub>-phenyl, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl, OCF<sub>3</sub>, CF<sub>3</sub>, -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, -O-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, unsubstituted C<sub>1-6</sub>-alkyl, pyrrolidinyl, imidazolyl, piperidinyl, benzyloxy, phenoxy, phenyl, naphthyl, pyridinyl, -C<sub>1-3</sub>-alkylene-aryl<sup>1</sup>, benzyl, thienyl, furyl, wherein aryl<sup>1</sup> represents phenyl, furyl, thienyl or pyridinyl. Preferred substituents for aromatic ring members of the bicyclic 8- to 12-membered carbocyclyl can be

chosen from the group consisting of  $-O-C_{1-3}$ -alkyl, unsubstituted  $C_{1-6}$ -alkyl, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ , OH, SH, phenyl, naphthyl, furyl, thienyl and pyridinyl, in particular from the group consisting of F, Cl, Br,  $CF_3$ ,  $CH_3$  and  $OCH_3$ .

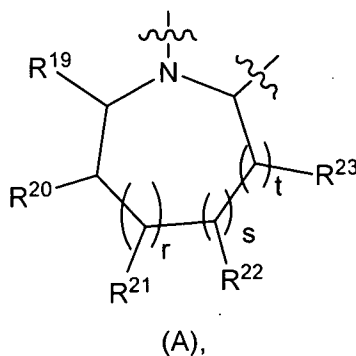
In the context of the present description, the symbol



used in formulae designates a linking of a corresponding radical to the particular main general structure.

The person skilled in the art understands that identical radicals which are used for definition of different substituents, such as, for example, the radicals  $R^{11}$  and  $R^{12}$  in the groups  $-(C=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $C(=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $NR^{11}R^{12}$ , can in each case be independent of one another.

In a preferred embodiment of the compounds according to the general formula I according to the invention, the radicals  $R^2$  and  $R^3$  together with the  $-N-(CH)-$  group joining them form a heterocyclic ring according to the general formula (A):



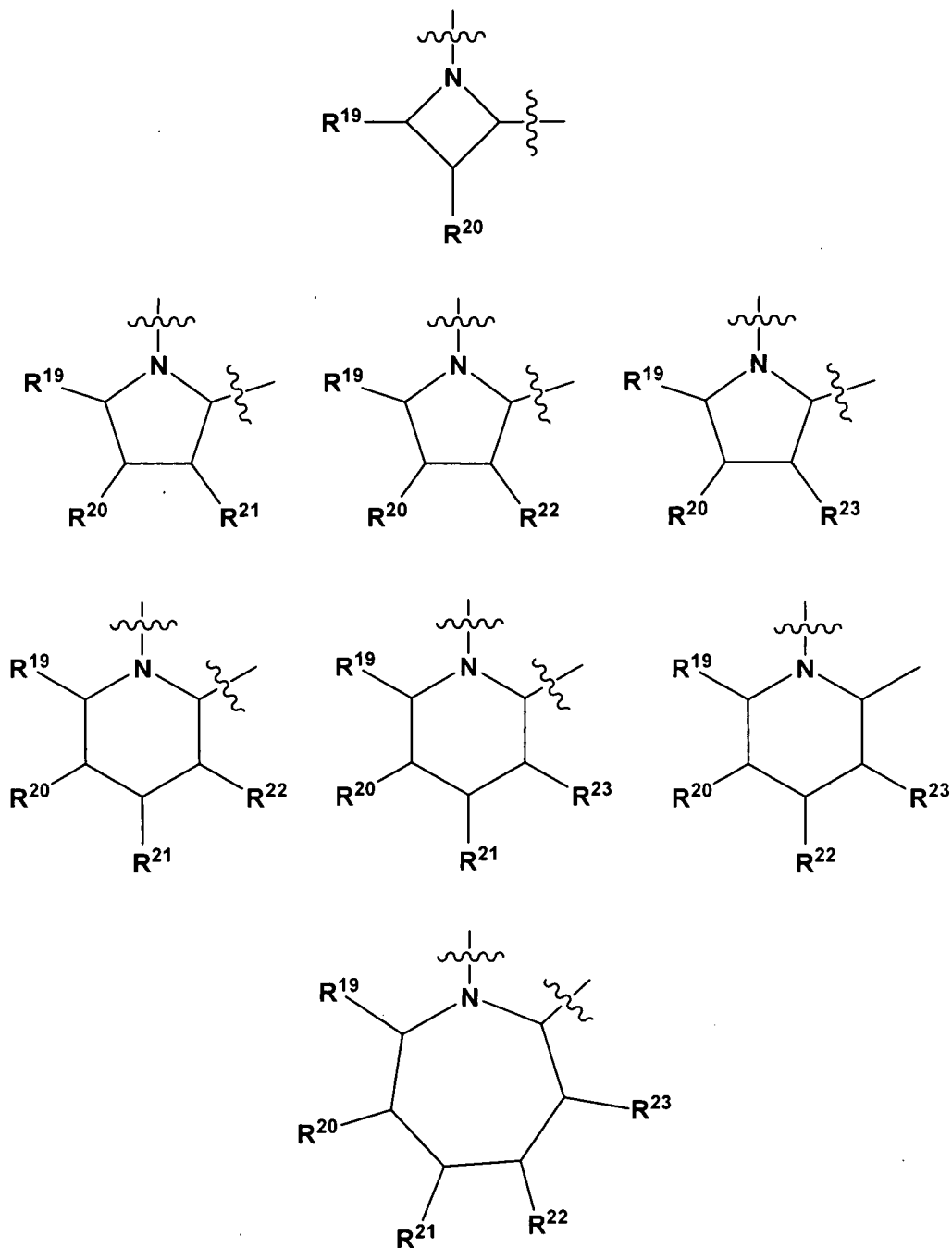
wherein

$r$ ,  $s$  and  $t$  independently of one another each represent 0 or 1; and

$R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$  and  $R^{23}$  independently of one another each represent H or two vicinal radicals from  $R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$  and  $R^{23}$  form a 5- or 6-membered fused-on aryl

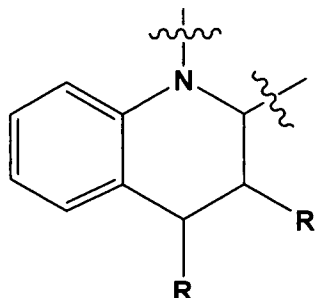
or heteroaryl radical, which can be unsubstituted or substituted once or several times by identical or different radicals.

The person skilled in the art understands that the part structure of the general formula (I) represented by the heterocyclic ring (A) can assume the following forms for the particular values 0 and 1 of the indices  $r$ ,  $s$  and  $t$ :



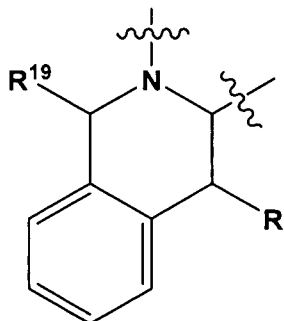
The person skilled in the art furthermore understands that if two vicinal (adjacent) radicals from R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup> and R<sup>23</sup> form a (fused-on) ring which is aromatic or is unsaturated on one or both of the carbon atoms linked with the vicinal radicals, this/these carbon atom(s) can no longer have a hydrogen radical.

For example, the following form thus results for a heterocyclic ring according to (A) in which one of the indices  $r$ ,  $s$  or  $t = 0$  and the other two are in each case  $= 1$  and the adjacent radicals  $R^{19}$  and  $R^{20}$  form a fused-on benzene ring:



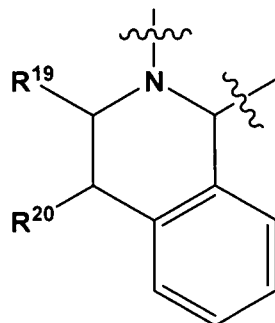
wherein  $R$  represents the corresponding radical from  $R^{21}$ ,  $R^{22}$  and  $R^{23}$ ,

the following form results for a heterocyclic ring according to (A) in which one of the indices  $r$ ,  $s$  or  $t = 0$  and the other two are in each case  $= 1$  and the adjacent radicals  $R^{20}$  and  $R^{21}$  or  $R^{22}$  form a fused-on benzene ring:

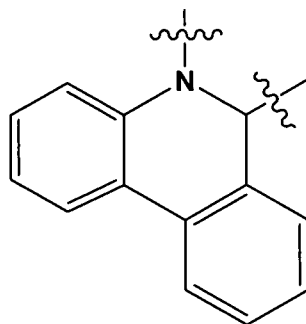


wherein  $R$  represents the corresponding radical from  $R^{22}$  or  $R^{23}$ ,

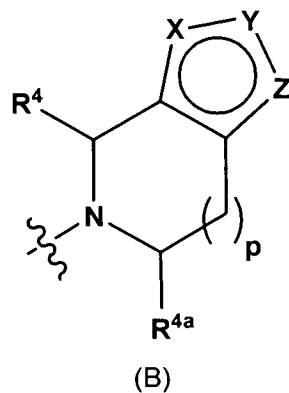
and the following form results for a heterocyclic ring (A) in which one of the indices  $r$ ,  $s$  or  $t = 0$  and the other two are in each case  $= 1$  and two adjacent radicals of  $R^{21}$ ,  $R^{22}$  and  $R^{23}$  form a fused-on benzene ring:



If the ring size of the heterocyclic radicals according to (A) described above allow, i.e. for compounds in which  $r + s + t = 2$  or  $3$ , in each case two pairs of adjacent radicals can also form a fused-on ring, for example:



In the compounds according to the invention, preferably at least one of the radicals  $R^4$ ,  $R^{4a}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  is not H, i.e. the following part structure (B)



contains at least one substituent which differs from H. For example, 1, 2 or 3, in particular 1 or 2 of the radicals R<sup>4</sup>, R<sup>4a</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> can differ from hydrogen.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention X, Y and Z are chosen such that one or none of these variables represents a substituted nitrogen atom (i.e. NR<sup>5</sup>, NR<sup>6</sup> or NR<sup>7</sup>).

In the context of this invention, the term "physiologically acceptable salt" is understood as meaning preferably salts of the compounds according to the invention with inorganic or organic acids, which are physiologically acceptable – in particular when used on humans and/or mammals. Examples of suitable acids are hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, maleic acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro-1λ<sup>6</sup>-benzo[d]isothiazol-3-one (saccharic acid), monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-liponic acid, acetylglycine, hippuric acid, phosphoric acid and/or aspartic acid. The salts of hydrochloric acid (hydrochlorides) and of citric acid (citrates) are particularly preferred. This term is furthermore also understood as meaning those compounds which are obtained by quaternization of a nitrogen atom present in the structure (e.g. pyridyl, N-methylpiperidyl). Such compounds can be obtained, for example, by alkylation with generation of the corresponding cation, with counter-ions such as, for example, Cl<sup>-</sup> and F<sup>-</sup>.

In a preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical R<sup>1</sup> represents CH(phenyl)<sub>2</sub>, phenyl, naphthyl, Indolyl, benzofuranyl, benzothiophenyl (benzothienyl), benzoxazolyl, benzoxadiazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinolinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothienyl), benzyl or 2-phenylethyl, preferably CH(aryl)<sub>2</sub>, phenyl, naphthyl, benzothiophenyl, benzoxadiazolyl, thiophenyl, pyridinyl,

imidazothiazolyl or dibenzofuranyl, particularly preferably phenyl or naphthyl, in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical  $R^1$  represents phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals chosen from the group consisting of methyl, methoxy,  $CF_3$ ,  $OCF_3$ ,  $F$ ,  $Cl$  and  $Br$ .

In a further preferred embodiment, the radical  $R^1$  in the sulfonamide derivatives according to the invention is chosen from the group consisting of 4-methoxy-2,3,6-trimethylphenyl, 4-methoxy-2,6-dimethylphenyl, 4-methoxy-2,3,5-trimethylphenyl, 2,4,6-trimethylphenyl, 2-chloro-6-methylphenyl, 2,4,6-trichlorophenyl, 2-chloro-6-(trifluoromethyl)phenyl, 2,6-dichloro-4-methoxyphenyl, 2,4-dichloro-6-methylphenyl, 2-methylnaphthyl, 2-chloronaphthyl, 2-fluoronaphthyl, 2-chloro-4-(trifluoromethoxy)phenyl, 4-chloro-2,5-dimethylphenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 1-naphthyl and 2-naphthyl.

In a further preferred embodiment, the radical  $R^1$  in the sulfonamide derivatives according to the invention is chosen from the group consisting of 4-methoxy-2,3,6-trimethylphenyl, 4-methoxy-2,6-dimethylphenyl, 2-chloro-6-methylphenyl, 4-chloro-2,5-dimethylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 1-naphthyl and 2-naphthyl, preferably from the group consisting of 4-methoxy-2,6-dimethylphenyl, 4-chloro-2,5-dimethylphenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 1-naphthyl and 2-naphthyl.

In a further preferred embodiment, the radical R<sup>1</sup> in the sulfonamide derivatives according to the invention is a 4-methoxy-2,6-dimethylphenyl radical.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical R<sup>2</sup> represents H, C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl, or a C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group, wherein the radicals C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene, C<sub>2-6</sub>-alkynylene and aryl are in each case unsubstituted or substituted once or several times, wherein aryl in particular is unsubstituted or substituted once or several times by identical or different radicals chosen independently of one another from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl-O-, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH and SH.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical R<sup>2</sup> represents H, C<sub>1-6</sub>-alkyl, cyclopropyl, CH(phenyl)<sub>2</sub>, phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinolinyl or a phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl bonded via a C<sub>1-6</sub>-alkylene group, wherein the phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl and quinolinyl is in each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub> and OH.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical R<sup>2</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or cyclopropyl.

In a further preferred embodiment of the present invention, in the substituted sulfonamide derivatives according to the invention the radical  $R^2$  represents H, methyl, ethyl or cyclopropyl.

Preferably,  $R^3$  in the sulfonamide derivatives according to the invention can represent H,  $-C(=O)-NR^{11}R^{12}$ ,  $-C(=O)-OR^{13}$ ,  $C_{1-6}$ -alkyl, aryl or heteroaryl; wherein the radicals  $C_{1-6}$ -alkyl, aryl and heteroaryl are in each case unsubstituted or substituted once or several times, wherein the aryl and heteroaryl in particular are unsubstituted or substituted once or several times by identical or different radicals chosen independently of one another from the group consisting of  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl-O-, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ , OH and SH.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^3$  represents H,  $-C(=O)-NR^{11}R^{12}$ ,  $-C(=O)-OR^{13}$ , phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl, wherein the phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl is each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$  and OH.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^3$  represents H or unsubstituted phenyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^2$  and  $R^3$  together with the  $-N-(CH)-$  group joining them form an unsubstituted or mono or polysubstituted, e.g. di-, tri- or tetrasubstituted, 4-, 5-, 6- or 7-membered, preferably 5-, 6- or 7-membered heterocyclic ring, which may contain an oxygen atom as a ring-member and which can be fused with one or two 6-membered aromatic ring(s) (benzo group).

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^2$  and  $R^3$  together with the  $-N-(CH-)$  group joining them form a 5- or 6-membered unsubstituted, mono- or disubstituted heterocyclic ring, which may contain an oxygen atom and which can be fused with a 6-membered aromatic ring (benzo group).

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^4$  and  $R^{4a}$  independently of one another each represent H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a  $C_{1-3}$ -alkylene group; wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^4$  and  $R^{4a}$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, phenyl, naphthyl, furyl, thienyl, pyridinyl, benzyl or phenethyl, wherein the phenyl, naphthyl, furyl, thienyl, pyridinyl or the aromatic part of benzyl and phenethyl is in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^4$  and  $R^{4a}$  independently of one another each represent H, methyl, ethyl, phenyl or pyridinyl, wherein the phenyl and pyridinyl is each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of methoxy, methyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$  and  $-OCF_3$ .

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>4a</sup> represents H or phenyl, in particular H.

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>4</sup> represents a radical chosen from the group consisting of H, methyl, ethyl, phenyl and pyridinyl, wherein the phenyl and pyridinyl is each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of methoxy, methyl, -F, -Cl, -Br, -I, -CF<sub>3</sub> and -OCF<sub>3</sub> and R<sup>4a</sup> represents H.

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or phenyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-NR<sup>11</sup>R<sup>12</sup>, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-6</sub>-alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl are unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)<sub>2</sub>-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)<sub>3</sub>-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)-(C=O)-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)<sub>2</sub>-(C=O)-NR<sup>11</sup>R<sup>12</sup>, -(CH<sub>2</sub>)<sub>3</sub>-(C=O)-NR<sup>11</sup>R<sup>12</sup>, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a -(CH<sub>2</sub>)-, -(CH<sub>2</sub>)<sub>2</sub>- or -(CH<sub>2</sub>)<sub>3</sub>- group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the

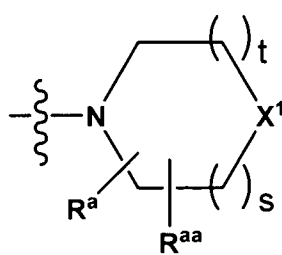
group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^8$ ,  $R^9$  and  $R^{10}$  independently of one another each represent  $H$ ,  $-CF_3$ ,  $-C(=O)-NR^{11}R^{12}$ ,  $-(CH_2)-NR^{11}R^{12}$ ,  $-(CH_2)_2-NR^{11}R^{12}$ ,  $-(CH_2)_3-NR^{11}R^{12}$ ,  $-(CH_2)-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_2-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_3-(C=O)-NR^{11}R^{12}$ , phenyl or pyridinyl or a phenyl or pyridinyl bonded via a  $-(CH_2)-$ ,  $-(CH_2)_2-$  or  $-(CH_2)_3-$  group, wherein the phenyl and pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of methoxy, methyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$  and  $-OCF_3$ .

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^{11}$  and  $R^{12}$  independently of one another each represent  $H$ , substituted or unsubstituted  $C_{1-6}$ -alkyl or  $C_{3-8}$ -cycloalkyl;

or

the group  $-NR^{11}R^{12}$  represents the heterocyclic ring of the type according to the general formula IIaa



IIaa

wherein

$X'$  represents  $O$ ,  $S$ ,  $NR^{18}$ ,  $CH_2$ ,  $C(H)(\text{halogen})$  or  $C(\text{halogen})_2$ , wherein halogen preferably denotes  $F$ ,  $Cl$  or  $Br$ ,  $R^{18}$  represents  $H$ ;  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl; aryl,

preferably phenyl or naphthyl; or heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl; or R<sup>18</sup> represents a C<sub>3-8</sub>-cycloalkyl bonded via a C<sub>1-3</sub>-alkylene group, an aryl, preferably phenyl or naphthyl, bonded via a C<sub>1-3</sub>-alkylene group; or a heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl, bonded via a C<sub>1-3</sub>-alkylene group;

and

R<sup>a</sup> and R<sup>aa</sup> independently of one another each represent H, methyl, ethyl, F, Cl or Br,

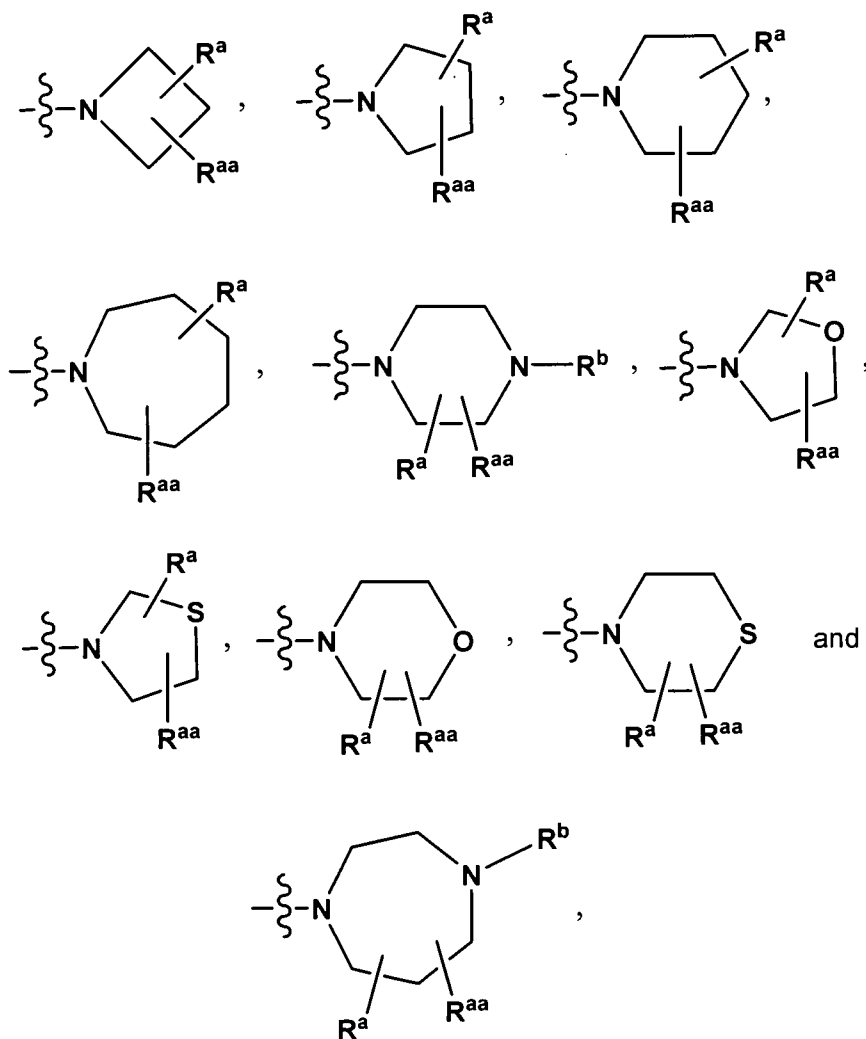
s and t independently of one another each represent 0, 1 or 2, with the proviso that s + t = 0, 1, 2 or 3,

wherein the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, C<sub>1-3</sub>-alkylene, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>11</sup> and R<sup>12</sup> independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl

or

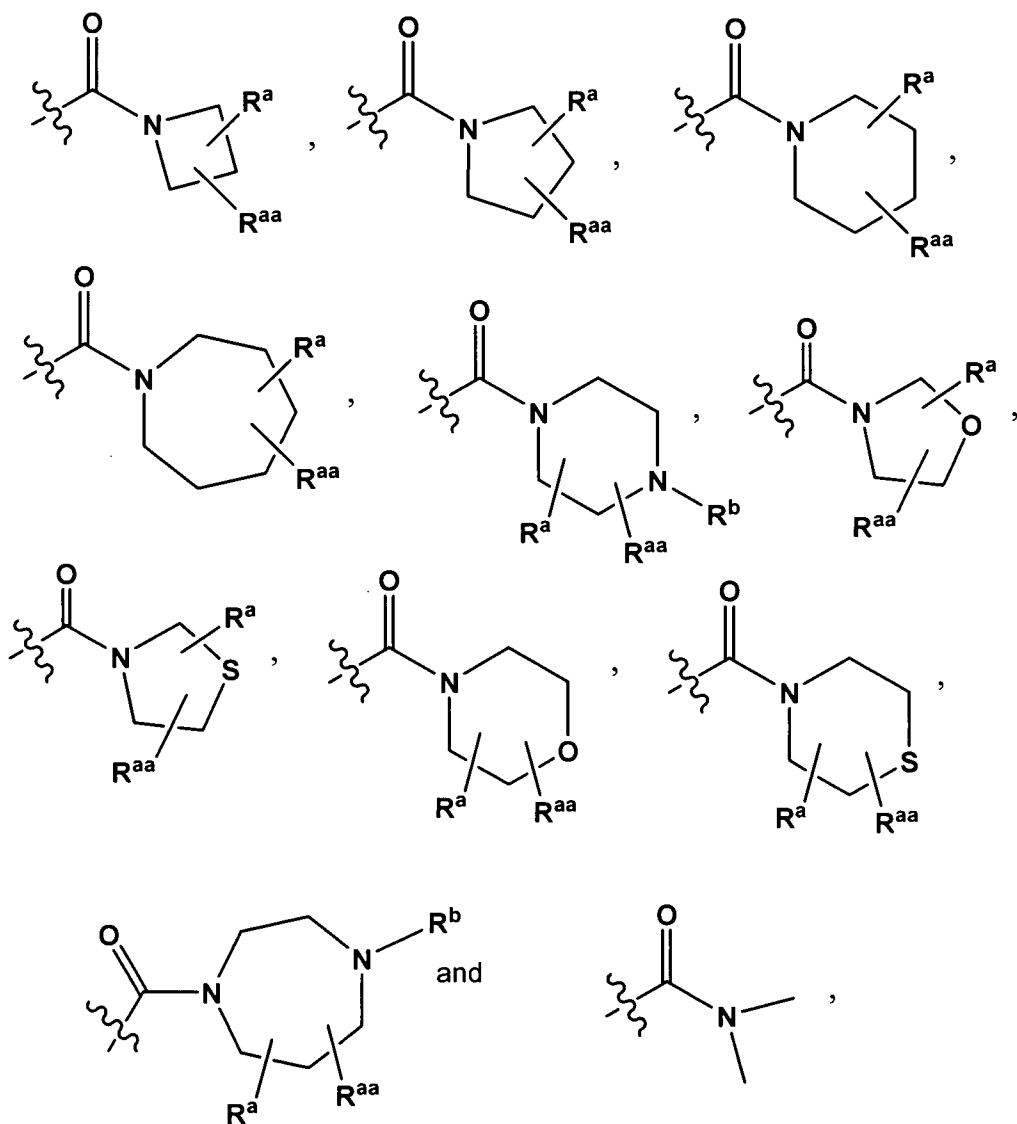
the group -NR<sup>11</sup>R<sup>12</sup> represents a heterocyclic ring chosen from the group consisting of



wherein  $R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br and  $R^b$  represents methyl, phenyl or pyridinyl, wherein the phenyl or pyridinyl can be bonded via a  $C_{1-6}$ -alkylene bridge and is unsubstituted or substituted once or several times, for example 2 times or 3 times, by identical or different substituents chosen independently of one another from the group consisting of methyl, methoxy, F and Cl.

In the  $-C_{1-6}$ -alkylene- $NR^{11}R^{12}$  group, the abovementioned  $-NR^{11}R^{12}$  radicals are in each case linked with the base structure via a  $-C_{1-6}$ -alkylene- bridge, in particular via a  $-(CH_2)-$ ,  $-(CH_2)_2-$  or  $-(CH_2)_3-$  group.

In the definitions mentioned, the  $-(C=O)-NR^{11}R^{12}$  group can preferably represent a radical which is chosen from the group consisting of

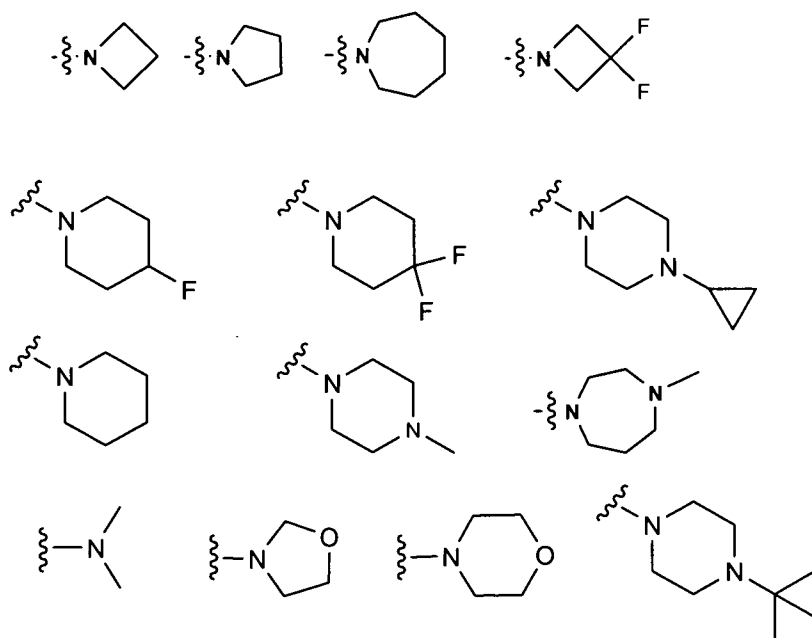


wherein  $R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br and  $R^b$  represents methyl, phenyl or pyridinyl, wherein the phenyl or pyridinyl can be bonded via a  $C_{1-6}$ -alkylene bridge and is unsubstituted or substituted once or several times, for example 2 times or 3 times, by identical or different substituents

chosen independently of one another from the group consisting of methyl, methoxy, F and Cl.

In the  $-C_{1-6}$ -alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup> definition mentioned, the abovementioned radicals are in each case linked with the base structure via a C<sub>1-6</sub>-alkylene bridge, in particular via a  $-(CH_2)-$ ,  $-(CH_2)_2-$  or  $-(CH_2)_3-$  group.

In the definitions mentioned herein, the  $-NR^{11}R^{12}$  group can represent in particular a radical which is chosen from the group consisting of



In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>13</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, benzyl or phenethyl.

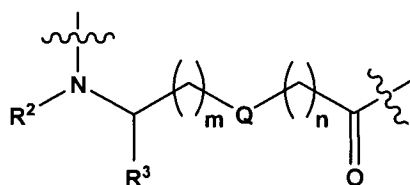
In a further preferred embodiment of the sulfonamide derivatives according to the invention, R<sup>14</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl,  $-C(=O)-R^{15}$ , phenyl, furyl, thiophenyl or pyridinyl or a phenyl, furyl, thiophenyl or pyridinyl bonded via a C<sub>1-3</sub>-alkylene group.

In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^{15}$  represents methyl, ethyl, phenyl, furyl, thiophenyl or pyridinyl or a phenyl, furyl, thiophenyl or pyridinyl bonded via a  $C_{1-3}$ -alkylene group.

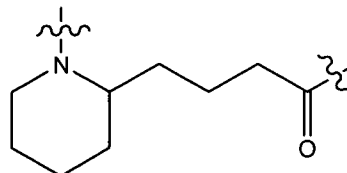
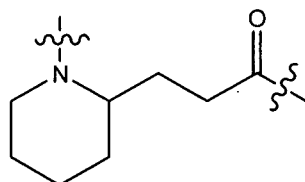
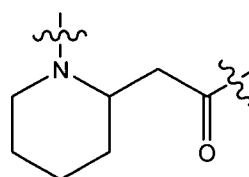
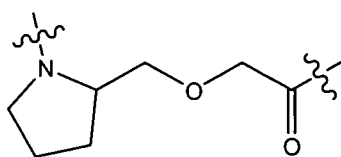
In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^{16}$  represents H, methyl, ethyl, phenyl, furyl, thiophenyl or pyridinyl or a phenyl, furyl, thiophenyl or pyridinyl bonded via a  $C_{1-3}$ -alkylene group.

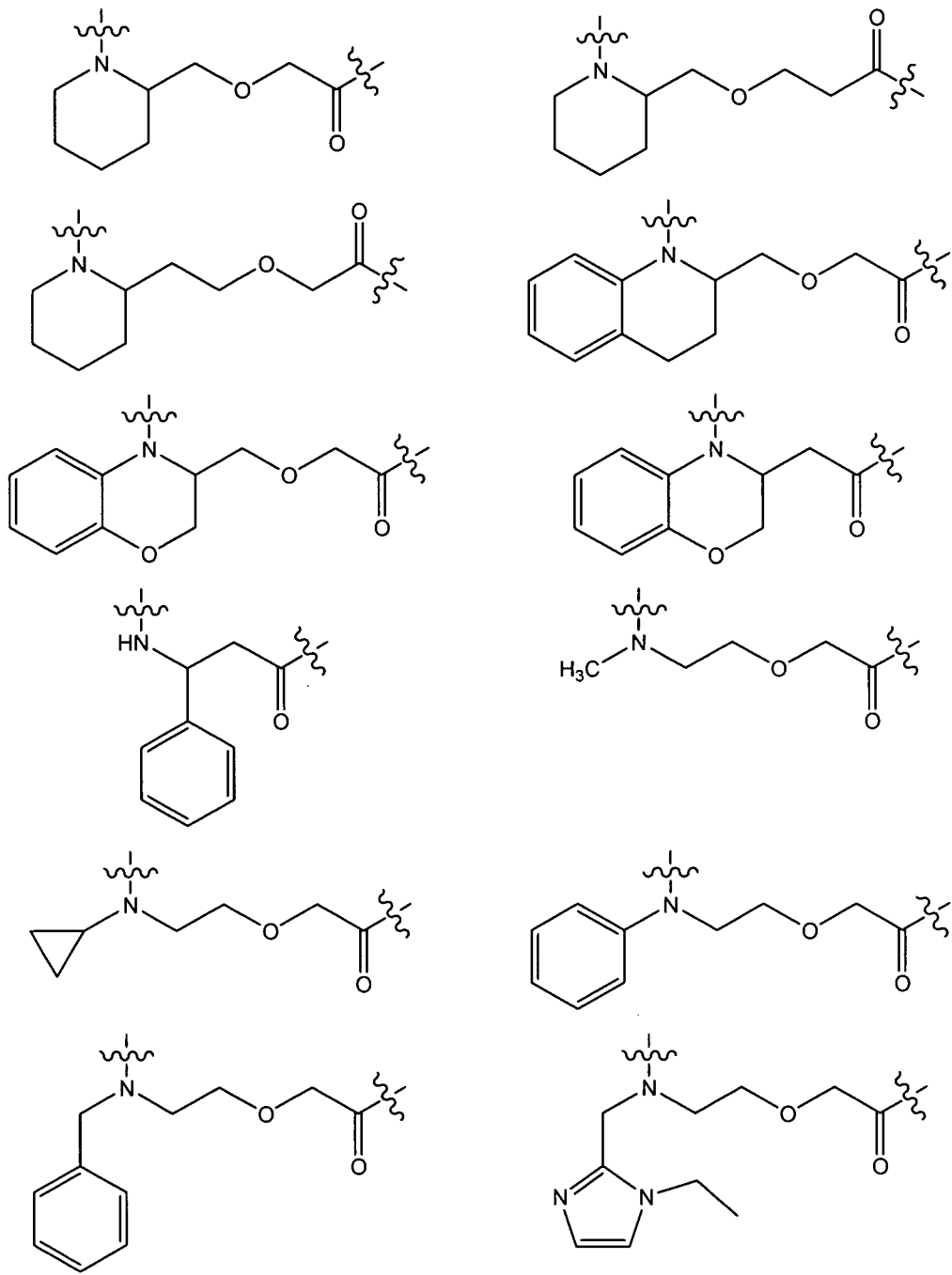
In a further preferred embodiment of the sulfonamide derivatives according to the invention,  $R^{17}$  represents H, methyl, ethyl, phenyl, furyl, thiophenyl or pyridinyl or a phenyl, furyl, thiophenyl or pyridinyl bonded via a  $C_{1-3}$ -alkylene group.

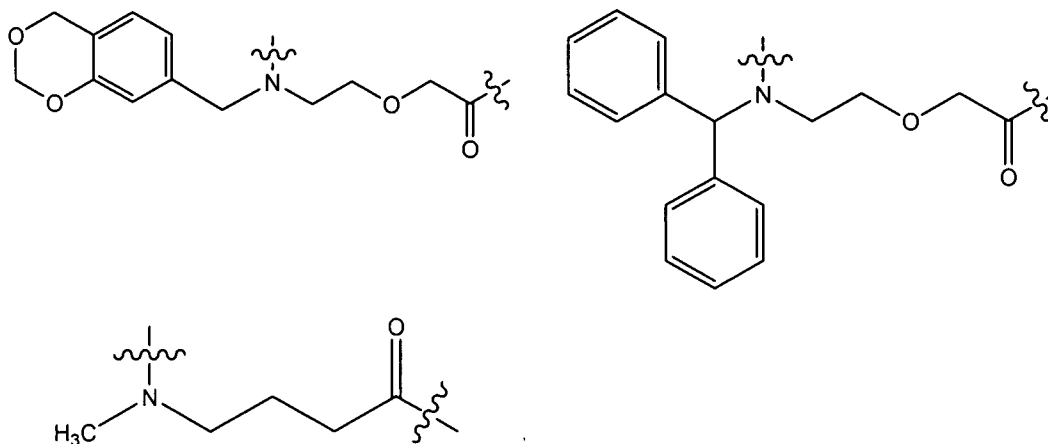
Preferred sulfonamide derivatives according to the invention are also compounds in which the following part structure



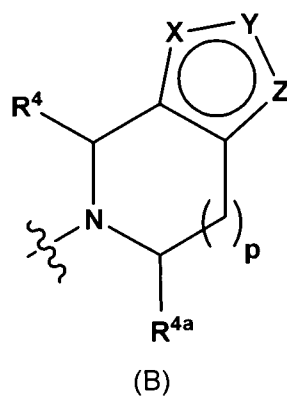
is selected from the group consisting of



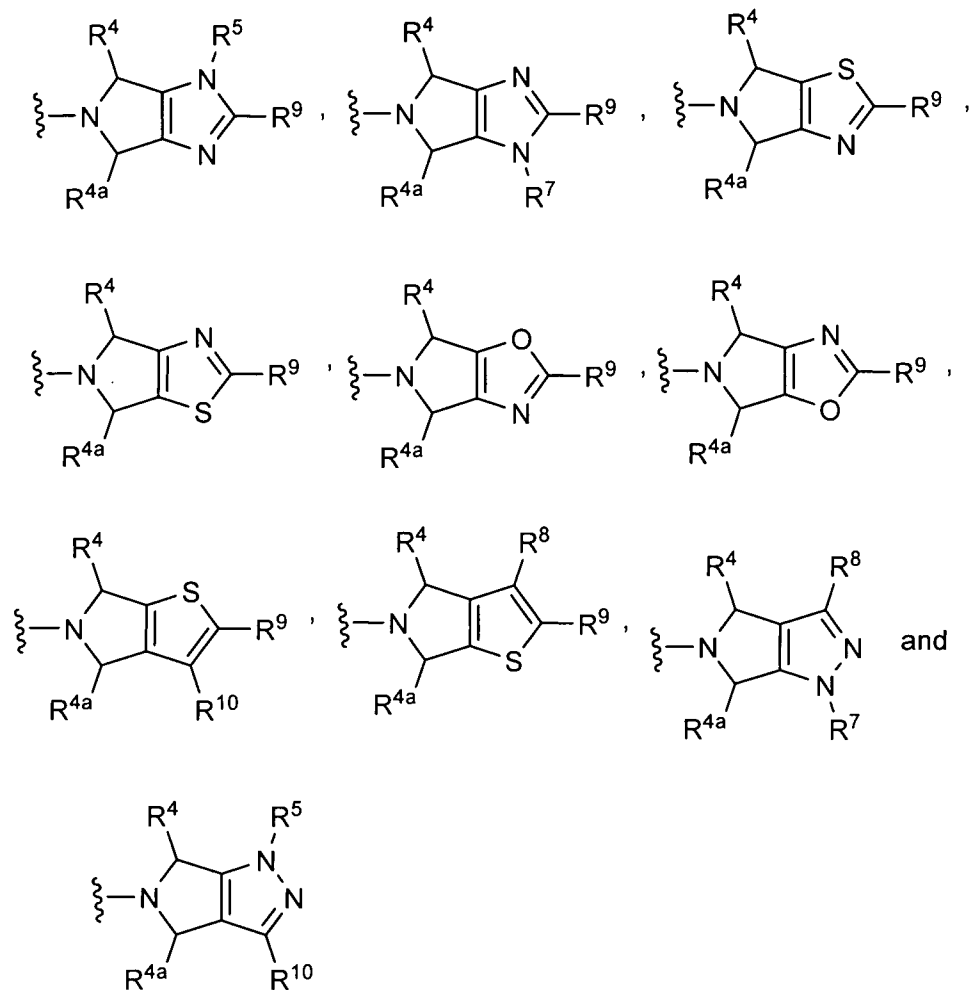




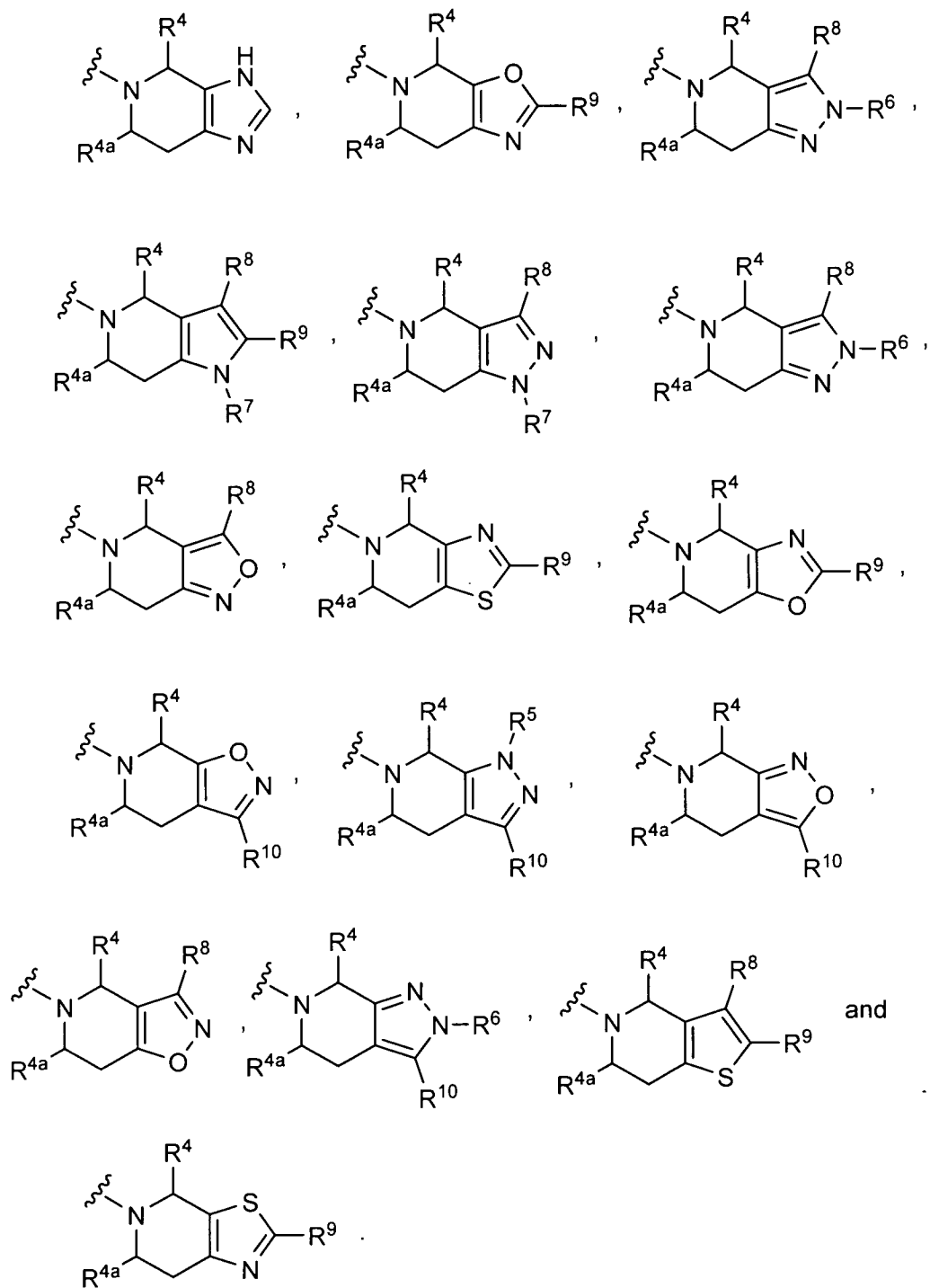
Preferred sulfonamide derivatives according to the invention are those in which  $p$  represents 0 and  $X$ ,  $Y$  and  $Z$  are chosen such that the following part structure



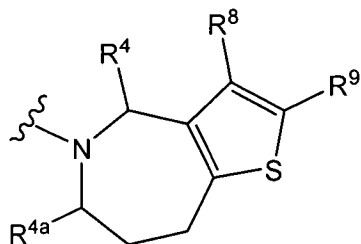
represents a radical which is chosen from the group B1 consisting of



Preferred sulfonamide derivatives according to the invention are furthermore those in which p represent 1 and X, Y and Z are chosen such that the part structure (B) represents a radical which is chosen from the group B2 consisting of



Preferred sulfonamide derivatives according to the invention are furthermore those in which  $p$  represents 2 and X, Y and Z are chosen such that the part structure (B) represents the following radical:



Preferred sulfonamide derivatives according to the invention are furthermore those in which preferably  $p = 1$  and

X represents  $CR^8$ ,

Y represents  $CR^9$  and

Z represents S,

or

X represents S,

Y represents  $CR^9$  and

Z represents N,

or

X represents  $CR^8$ ,

Y represents N and

Z represents O,

or

X represents CR<sup>8</sup>,  
Y represents CR<sup>9</sup> and  
Z represents NR<sup>7</sup>,

or

X represents S,  
Y represents CR<sup>9</sup> and  
Z represents CR<sup>10</sup>,

or

X represents N,  
Y represents CR<sup>9</sup> and  
Z represents NR<sup>7</sup>,

or

X represents O,  
Y represents CR<sup>9</sup> and  
Z represents N,

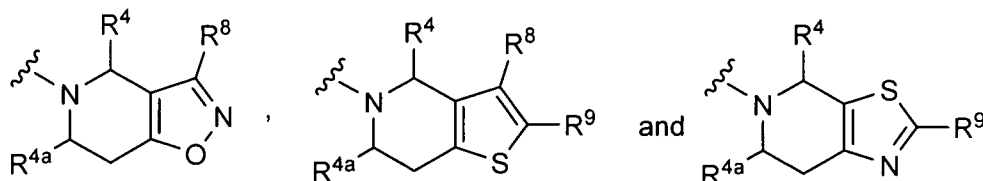
or

X represents NR<sup>5</sup>,  
Y represents N and  
Z represents CR<sup>10</sup>,

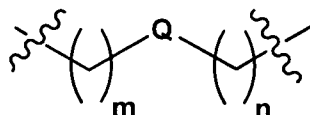
or

X represents CR<sup>8</sup>,  
Y represents N and  
Z represents NR<sup>7</sup>.

Particularly preferred sulfonamide derivatives according to the invention are furthermore those in which p represents 1 and X, Y and Z are chosen such that the part structure (B) represents a radical which is chosen from the group consisting of



In a further preferred embodiment of the sulfonamide derivatives according to the invention, m, n and Q in the part structure



are chosen such that this part structure is chosen from the group consisting of a single bond,  $-(CH_2)-$ ;  $-(CH_2)_2-$ ;  $-(CH_2)_3-$ ;  $-(CH_2)-O-(CH_2)-$ ;  $-(CH_2)_2-O-(CH_2)$ ;  $-(CH_2)-O-(CH_2)_2-$ ;  $-(CH_2)_2-O-(CH_2)_2$  and  $-(CH_2)-O-$ .

In a further preferred embodiment of the sulfonamide derivatives according to the invention, p represents 0 or 1, preferably 1.

Substituted sulfonamide derivatives of the general formula I according to the invention which are likewise preferred are those wherein

m and n independently of one another each represent 0, 1 or 2;  
p represents 0, 1 or 2;

Q represents a single bond,  $-CH_2-$  or  $-O-$ ;

X represents N, NR<sup>5</sup>, O, S or CR<sup>8</sup>;

Y represents N, NR<sup>6</sup>, O, S or CR<sup>9</sup>;

Z represents N, NR<sup>7</sup>, O, S or CR<sup>10</sup>;

R<sup>1</sup> represents CH(phenyl)<sub>2</sub>, phenyl, naphthyl, indolyl, benzofuranyl, benzothiophenyl (benzothienyl), benzoxazolyl, benzoxadiazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinoliny, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothienyl), benzyl or 2-phenylethyl, in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

R<sup>2</sup> represents H, C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl, or a C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group, wherein the radicals C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene, C<sub>2-6</sub>-alkynylene and aryl are in each case unsubstituted or substituted once or several times, wherein aryl in particular is unsubstituted or substituted once or several times by identical or different radicals which are chosen independently of one another from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl-O-, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH and SH;

R<sup>3</sup> represents H, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C(=O)-OR<sup>13</sup>, C<sub>1-6</sub>-alkyl, aryl or heteroaryl, wherein the radicals C<sub>1-6</sub>-alkyl, aryl and heteroaryl are in each case unsubstituted or substituted once or several times, wherein the aryl and heteroaryl in particular are unsubstituted or substituted once or several times by identical or different radicals chosen independently of one another from the group consisting of C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl-O-, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH and SH, wherein R<sup>2</sup> and R<sup>3</sup> do not both represent H; or

R<sup>2</sup> and R<sup>3</sup> together with the –N-(CH-)– group joining them form a 4-, 5-, 6- or 7-membered heterocyclic ring, which may contain an oxygen atom as a ring-member and can be fused with one or two 6-membered aromatic ring(s) (benzo group);

R<sup>4</sup> and R<sup>4a</sup> independently of one another each represent H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-3</sub>-alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of –O-C<sub>1-3</sub>-alkyl, C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently of one another each represent H, C<sub>1-4</sub>-alkyl or phenyl;

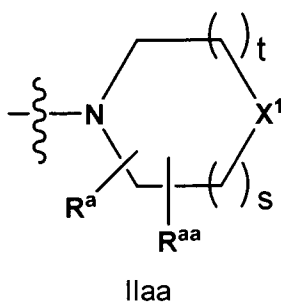
R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-NR<sup>11</sup>R<sup>12</sup>, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-6</sub>-alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of –O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

wherein preferably at least one of the radicals R<sup>4</sup>, R<sup>4a</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> does not represent H,

R<sup>11</sup> and R<sup>12</sup> independently of one another each represent H, substituted or unsubstituted C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl;

or

the group –NR<sup>11</sup>R<sup>12</sup> represents the heterocyclic ring of the type according to the general formula IIaa



wherein

$X^1$  represents O, S,  $NR^{18}$ ,  $CH_2$ ,  $C(H)(\text{halogen})$  or  $C(\text{halogen})_2$ , wherein halogen preferably denotes F, Cl or Br,  $R^{18}$  represents H;  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl; aryl, preferably phenyl or naphthyl; or heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl; or  $R^{18}$  represents a  $C_{3-8}$ -cycloalkyl bonded via a  $C_{1-3}$ -alkylene group, an aryl, preferably phenyl or naphthyl, bonded via a  $C_{1-3}$ -alkylene group; or a heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl, bonded via a  $C_{1-3}$ -alkylene group, wherein the abovementioned radicals  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl,  $C_{1-3}$ -alkylene, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl,

$R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br, and

s and t independently of one another each represent 0, 1 or 2, with the proviso that  $s + t = 0, 1, 2$  or 3,

$R^{13}$  represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, benzyl or phenethyl,

optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

Substituted sulfonamide derivatives of the general formula I according to the invention which are likewise preferred are those wherein

m and n independently of one another each represent 0, 1 or 2;

p represents 0, 1 or 2;

Q represents a single bond,  $-\text{CH}_2-$  or  $-\text{O}-$ ;

X represents N,  $\text{NR}^5$ , O, S or  $\text{CR}^8$ ;

Y represents N,  $\text{NR}^6$ , O, S or  $\text{CR}^9$ ;

Z represents N,  $\text{NR}^7$ , O, S or  $\text{CR}^{10}$ ;

$\text{R}^1$  represents phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals chosen from the group consisting of methyl, methoxy,  $\text{CF}_3$ ,  $\text{OCF}_3$ , F, Cl and Br;

$\text{R}^2$  represents H,  $\text{C}_{1-6}$ -alkyl, cyclopropyl,  $\text{CH}(\text{phenyl})_2$ , phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinolinyl or a phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl bonded via a  $\text{C}_{1-6}$ -alkylene group, wherein the phenyl, thienyl, pyridyl, pyrimidinyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl and quinolinyl is in each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{OCF}_3$  and OH;

$R^3$  represents H,  $-C(=O)-NR^{11}R^{12}$ ,  $-C(=O)-OR^{13}$ , phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl, wherein the phenyl naphthyl, thienyl, pyridyl, pyrimidyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl or quinolinyl is each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$  and OH, wherein  $R^2$  and  $R^3$  do not both simultaneously represent H; or

$R^2$  and  $R^3$  together with the  $-N-(CH)-$  group joining them form a 4-, 5-, 6- or 7-membered, preferably 5-, 6- or 7-membered heterocyclic ring, which may contain an oxygen atom and which can be fused with one or two 6-membered aromatic ring(s) (benzo group);

$R^4$  and  $R^{4a}$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, phenyl, naphthyl, furyl, thienyl, pyridinyl, benzyl or phenethyl, wherein the phenyl, naphthyl, furyl, thienyl, pyridinyl or the aromatic part of benzyl and phenethyl is in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl;

$R^5$ ,  $R^6$  and  $R^7$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or phenyl,

$R^8$ ,  $R^9$  and  $R^{10}$  independently of one another each represent H,  $-CF_3$ ,  $-C(=O)-NR^{11}R^{12}$ ,  $-(CH_2)-NR^{11}R^{12}$ ,  $-(CH_2)_2-NR^{11}R^{12}$ ,  $-(CH_2)_3-NR^{11}R^{12}$ ,  $-(CH_2)-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_2-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_3-(C=O)-NR^{11}R^{12}$ , phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a  $-(CH_2)-$ ,  $-(CH_2)_2-$  or  $-(CH_2)_3-$  group, wherein phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group

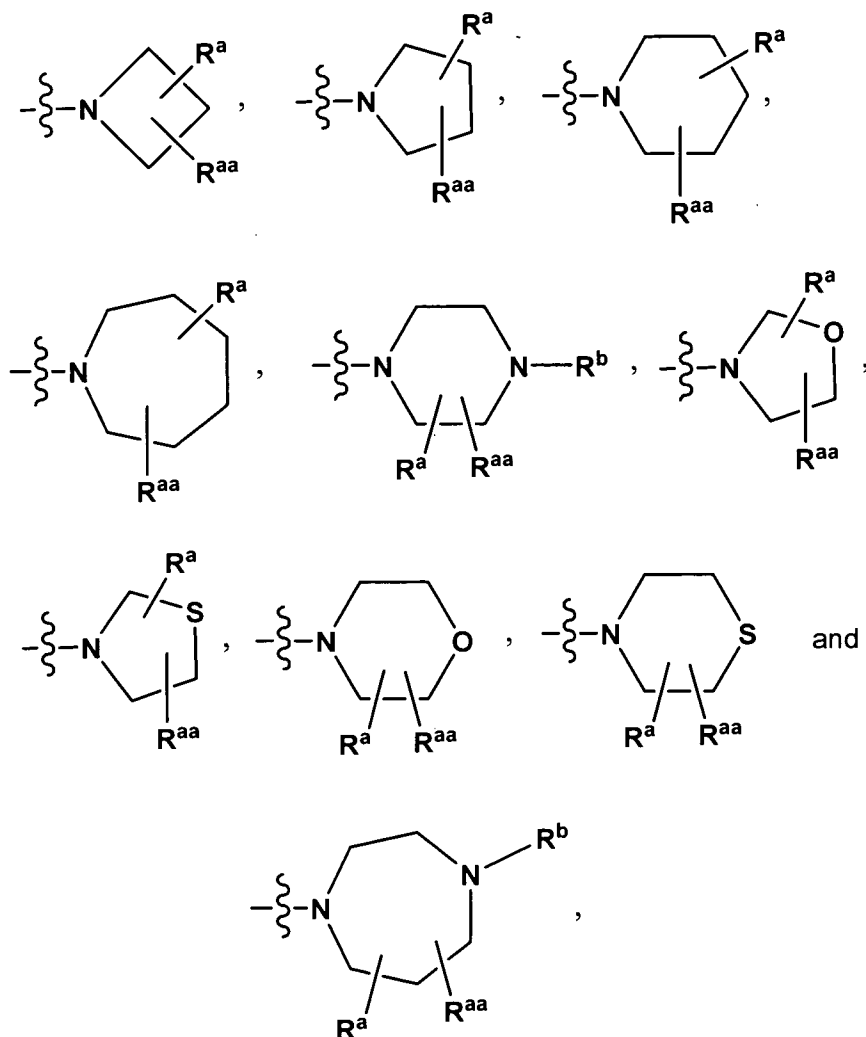
consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl;

wherein at least one of the radicals  $R^4$ ,  $R^{4a}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  does not represent H,

$R^{11}$  and  $R^{12}$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl

or

the group  $-NR^{11}R^{12}$  represents a heterocyclic ring chosen from the group consisting of



wherein  $R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br and  $R^b$  represents methyl, phenyl or pyridinyl, wherein the phenyl or pyridinyl can be bonded via a  $C_{1-6}$ -alkylene bridge and is unsubstituted or substituted once or several times, for example 2 times or 3 times, by identical or different substituents chosen independently of one another from the group consisting of methyl, methoxy, F and Cl.

$R^{13}$  represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, benzyl or phenethyl,

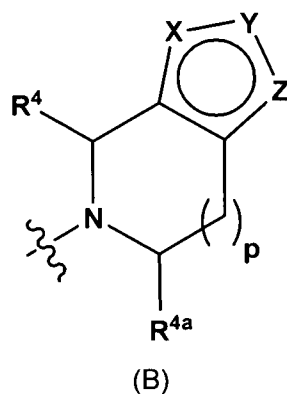
optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

Substituted sulfonamide derivatives of the general formula I according to the invention which are likewise preferred are those wherein

m and n independently of one another each represent 0, 1 or 2;

Q represents a single bond,  $-\text{CH}_2-$  or  $-\text{O}-$ ;

p and X, Y, Z are chosen such that the following part structure



represents a radical which is chosen from the abovementioned group B1 or B2,

$R^1$  represents phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals chosen from the group consisting of methyl, methoxy,  $\text{CF}_3$ ,  $\text{OCF}_3$ , F, Cl and Br;

$R^2$  represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or cyclopropyl;

$R^3$  represents H or phenyl, wherein the phenyl is each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$  and OH; wherein  $R^2$  and  $R^3$  do not both simultaneously represent H; or.

$R^2$  and  $R^3$  together with the  $-N-(CH_-)$  group joining them form a 4-, 5-, 6- or 7-membered, preferably 5-, 6- or 7-membered heterocyclic ring, which may contain an oxygen atom and which can be fused with one or two 6-membered aromatic ring(s) (benzo group);

$R^4$  and  $R^{4a}$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, phenyl, naphthyl, furyl, thienyl, pyridinyl, benzyl or phenethyl, wherein the phenyl, naphthyl, furyl, thienyl, pyridinyl or the aromatic part of benzyl and phenethyl is in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $C_{1-6}$ -alkyl, -F, -Cl, -Br, -I,  $-CF_3$ ,  $-OCF_3$ , -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

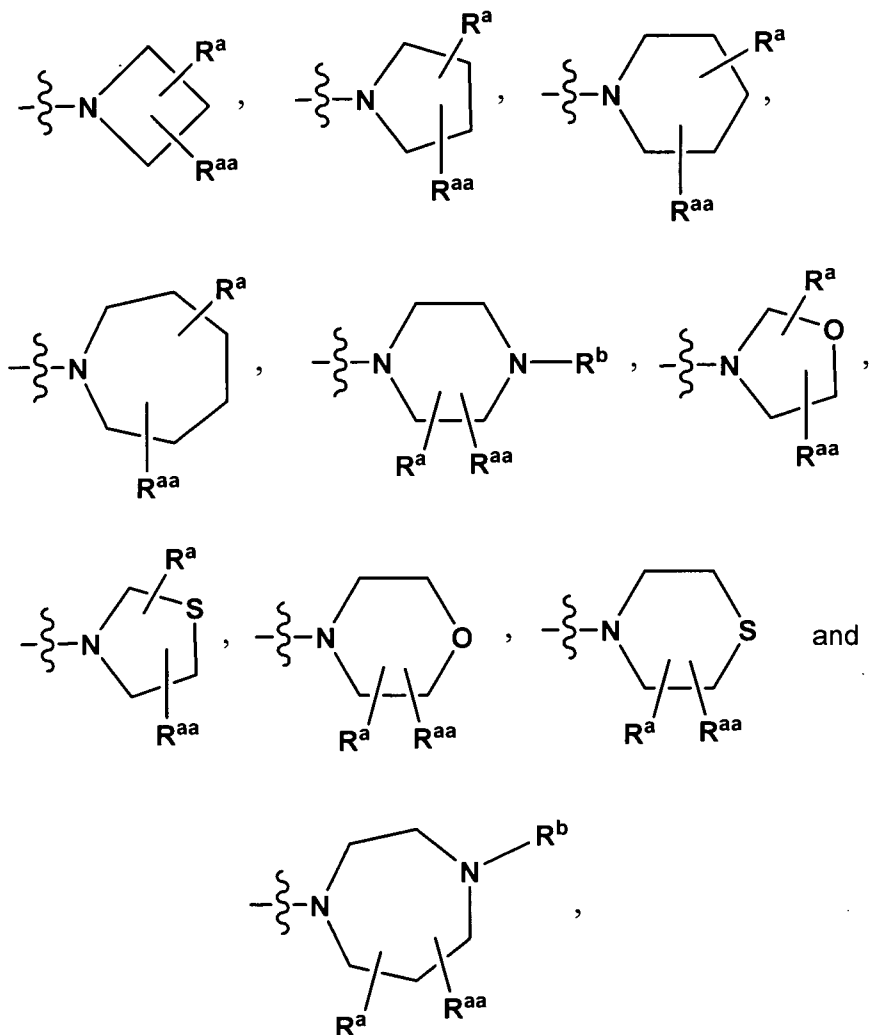
$R^5$ ,  $R^6$  and  $R^7$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl; tert-butyl and phenyl;

$R^8$ ,  $R^9$  and  $R^{10}$  independently of one another each represent H,  $-CF_3$ ,  $-C(=O)-NR^{11}R^{12}$ ,  $-(CH_2)-NR^{11}R^{12}$ ,  $-(CH_2)_2-NR^{11}R^{12}$ ,  $-(CH_2)_3-NR^{11}R^{12}$ ,  $-(CH_2)-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_2-(C=O)-NR^{11}R^{12}$ ,  $-(CH_2)_3-(C=O)-NR^{11}R^{12}$ , phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a  $-(CH_2)-$ ,  $-(CH_2)_2-$  or  $-(CH_2)_3-$  group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl, -F, -Cl, -Br, -I,  $-CF_3$ ,  $-OCF_3$ , -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

wherein at least one of the radicals  $R^4$ ,  $R^{4a}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  does not represent H,

$R^{11}$  and  $R^{12}$  independently of one another each represent H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, or

the group  $-NR^{11}R^{12}$  represents a heterocyclic ring chosen from the group consisting of



wherein  $R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br and  $R^b$  represents methyl, phenyl or pyridinyl, wherein the phenyl or pyridinyl can be bonded via a  $C_{1-6}$ -alkylene bridge and is unsubstituted or substituted once or

several times, for example 2 times or 3 times, by identical or different substituents chosen independently of one another from the group consisting of methyl, methoxy, F and Cl,

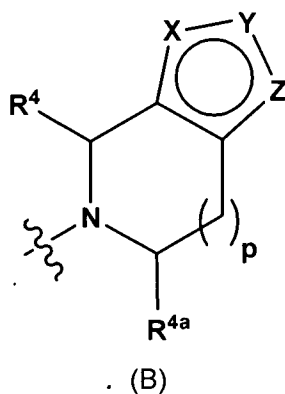
optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

Particularly preferred substituted sulfonamide derivatives of the general formula I according to the invention are those wherein

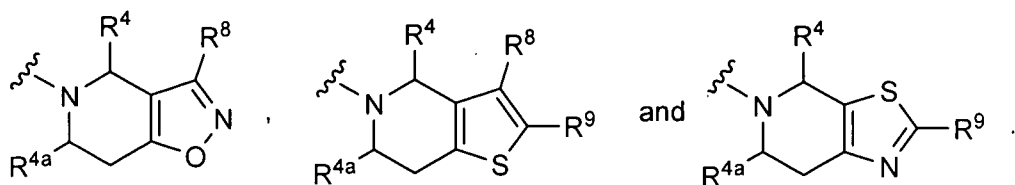
m and n independently of one another each represent 0, 1 or 2;  
p represents 1;

Q represents a single bond, -CH<sub>2</sub>- or -O-;

p and X, Y and Z are chosen such that the following part structure



represents a radical which is chosen from the group consisting of



R<sup>1</sup> represents phenyl or naphthyl, wherein the phenyl or naphthyl is unsubstituted or substituted once or several times, for example 2, 3, 4 or 5 times, by identical or different radicals chosen from the group consisting of methyl, methoxy, CF<sub>3</sub>, OCF<sub>3</sub>, F, Cl and Br;

R<sup>2</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl or cyclopropyl;

R<sup>3</sup> represents H or phenyl, wherein the phenyl is each case unsubstituted or substituted once or several times by identical or different radicals, wherein the radicals are chosen independently of one another from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, methoxy, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub> and OH; wherein R<sup>2</sup> and R<sup>3</sup> do not both simultaneously represent H; or.

R<sup>2</sup> and R<sup>3</sup> together with the –N-(CH-)– group joining them form a 4-, 5-, 6- or 7-membered, preferably 5-, 6- or 7-membered heterocyclic ring, which can be fused with one or two 6-membered aromatic ring(s) (benzo group);

R<sup>4</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, phenyl, naphthyl, furyl, thienyl, pyridinyl, benzyl or phenethyl, wherein the phenyl, naphthyl, furyl, thienyl, pyridinyl or the aromatic part of benzyl and phenethyl is in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of –O-C<sub>1-3</sub>-alkyl, –C<sub>1-6</sub>-alkyl, –F, –Cl, –Br, –I, –CF<sub>3</sub>, –OCF<sub>3</sub>, –OH, –SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

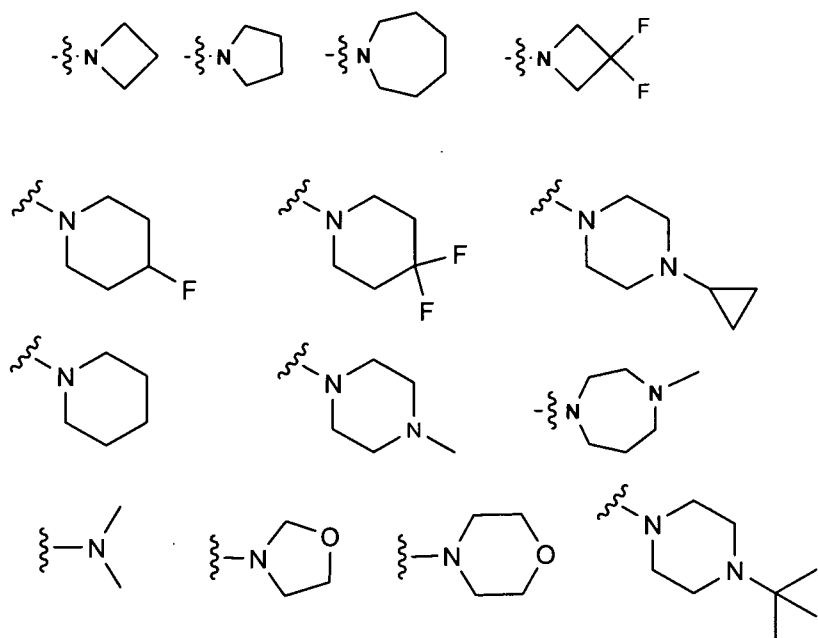
R<sup>4a</sup> represents H or phenyl, wherein the phenyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are

preferably chosen independently of one another from the group consisting of  $-\text{O}-\text{C}_{1-3}$ -alkyl,  $-\text{C}_{1-6}$ -alkyl,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OH}$ ,  $-\text{SH}$ , phenyl, naphthyl, furyl, thienyl and pyridinyl;

$\text{R}^8$  and  $\text{R}^9$  independently of one another each represent  $\text{H}$ ,  $-\text{C}(=\text{O})-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)_2-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)_3-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)-\text{C}(=\text{O})-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)_2-\text{C}(=\text{O})-\text{NR}^{11}\text{R}^{12}$ ,  $-(\text{CH}_2)_3-\text{C}(=\text{O})-\text{NR}^{11}\text{R}^{12}$ , phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a  $-(\text{CH}_2)-$ ,  $-(\text{CH}_2)_2-$  or  $-(\text{CH}_2)_3-$  group, wherein phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-\text{O}-\text{C}_{1-3}$ -alkyl,  $-\text{C}_{1-6}$ -alkyl,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OH}$ ,  $-\text{SH}$ , phenyl, naphthyl, furyl, thienyl and pyridinyl,

wherein at least one of the radicals  $\text{R}^4$ ,  $\text{R}^{4a}$ ,  $\text{R}^8$  and  $\text{R}^9$  does not represent  $\text{H}$ ;

the group  $-\text{NR}^{11}\text{R}^{12}$  represents a radical which is chosen from the group consisting of:



optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

Sulfonamide derivatives according to the invention which are very particularly preferred are chosen from the group consisting of

- 1 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 2 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 3 1-N-(3-oxo-1-phenyl-3-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 4 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 5 1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethanone
- 6 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 7 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-p-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 8 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-m-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 9 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 10 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-m-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 11 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-o-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one

- 12 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-*o*-tolyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)ethanone
- 13 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-*c*]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 14 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(piperidin-1-carbonyl)-6,7-dihydroisoxazolo[4,5-*c*]pyridin-5(4H)-yl)ethanone
- 15 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)ethanone
- 16 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-phenyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)propan-1-one
- 17 I-N-(3-oxo-1-phenyl-3-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-*c*]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 18 N-(2-(2-(4-ethyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide
- 19 1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethanone
- 20 N-((1R)-3-oxo-1-phenyl-3-(4-*p*-tolyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 21 N-((1R)-3-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)-3-oxo-1-phenylpropyl)naphthalene-2-sulfonamide
- 22 1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 23 1-(4-ethyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)-4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butan-1-one
- 24 1-(3-(4-chlorophenyl)-6,7-dihydroisoxazolo[4,5-*c*]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 25 1-(3-(4-fluorophenyl)-6,7-dihydroisoxazolo[4,5-*c*]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 26 I-N-(3-oxo-1-phenyl-3-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 27 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)ethanone

- 28 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 29 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(morpholinomethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 30 4-methoxy-N,2,6-trimethyl-N-(2-(2-(3-(morpholinomethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)benzenesulfonamide
- 31 1-(3-((dimethylamino)methyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 32 N-(2-(2-(3-((dimethylamino)methyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide
- 33 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(6-chloropyridin-3-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 34 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(3-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 35 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(3-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 36 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-(pyridin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 37 1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 38 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethan-1-one
- 39 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 40 1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 41 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propan-1-one
- 42 N-(3-oxo-1-phenyl-3-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide

- 43 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)butan-1-one
- 44 1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 45 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 46 N-(3-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-oxo-1-phenylpropyl)naphthalene-2-sulfonamide
- 47 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)butan-1-one
- 48 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethan-1-one
- 49 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 50 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethan-1-one
- 51 4-methoxy-N,2,6-trimethyl-N-(2-(2-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)benzenesulfonamide
- 52 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propan-1-one
- 53 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)butan-1-one
- 54 1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-2-[1-[[3-(trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]-ethanone
- 55 3-[1-[[4-chloro-2,5-dimethyl-phenyl]sulfonyl]-piperidin-2-yl]-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propan-1-one
- 56 N-[2-[2-[2-(azetidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-2-chloro-N-cyclopropyl-6-methyl-benzenesulfonic acid amide
- 57 2-chloro-N-cyclopropyl-N-[2-[2-[2-[(3,3-difluoro-azetidin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-6-methyl-benzenesulfonic acid amide

- 58 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-yl]-ethanone
- 59 2-[[[(2S)-1-[(2-chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 60 2-chloro-N-cyclopropyl-6-methyl-N-[2-[2-oxo-2-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethoxy]-ethyl]-benzenesulfonic acid amide
- 61 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 62 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(pyrrolidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 63 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-pyrrolidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 64 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-[(4-methyl-[1,4]diazepan-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 66 4-Methoxy-N,2,6-trimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 68 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-butan-1-one
- 69 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 71 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 73 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 74 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 75 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butan-1-one

- 76 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 78 N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 81 N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 82 N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 83 4-Methoxy-2,6-Dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide
- 84 4-Methoxy-2,6-Dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide
- 85 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 86 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 87 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one
- 88 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-4-[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one
- 91 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 92 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 93 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone
- 94 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone

- 95 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 96 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 97 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone
- 98 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone
- 99 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propan-1-one
- 100 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-propan-1-one
- 101 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 102 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 103 N-Methyl-N-[4-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-oxo-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide
- 104 N-Methyl-N-[4-Oxo-4-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide
- 105 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[4-(naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-ethanone
- 106 2-[4-(Naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 107 4-Methoxy-N,2,6-trimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 108 4-Methoxy-N,2,6-trimethyl-N-[2-[2-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide

- 109 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethanone
- 110 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-ethanone
- 111 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 112 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 113 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 114 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 115 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 116 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 117 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 118 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-4-[1-(naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 119 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 120 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-4-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 121 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 122 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-ethoxy]-ethyl]-benzenesulfonic acid amide
- 123 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide

- 124 N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 125 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]-1-(3-pyridin-4-yl-4,5,6,7-tetrahydro-isoxazolo[4,5-c]pyridin-5-yl)-ethanone
- 126 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-phenyl-3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone

optionally in the form of their physiologically acceptable salts.

The numbering of the individual embodiments of the compounds according to the invention used above is retained in the following explanations of the present invention, in particular in the description of the examples.

The compounds according to the invention have an antagonistic action on the human B1R receptor or the B1R receptor of the rat. In a preferred embodiment of the invention, the compounds according to the invention have an antagonistic action both on the human B1R receptor (hB1R) and on the B1R receptor of the rat (rB1R).

Compounds which show an inhibition of at least 15 %, 25 %, 50 %, 70 %, 80 % or 90 % on the human B1R receptor and/or on the B1R receptor of the rat in the FLIPR assay at a concentration of 10  $\mu$ m are particularly preferred. Compounds which show an inhibition on the human B1R receptor and on the B1R receptor of the rat of at least 70 %, in particular of at least 80 % and particularly preferably of at least 90 % at a concentration of 10  $\mu$ m are very particularly preferred.

The agonistic or antagonistic action of substances can be quantified on the bradykinin 1 receptor (B1R) of the human and rat species with ectopically expressing cell lines (CHO K1 cells) and with the aid of a  $Ca^{2+}$ -sensitive dyestuff (Fluo-4) in a fluorescent imaging plate reader (FLIPR). The figure in % activation is based on the  $Ca^{2+}$  signal after addition of Lys-Des-Arg<sup>9</sup>-bradykinin (0.5 nM) or Des-Arg<sup>9</sup>-bradykinin (100 nM).

Antagonists lead to a suppression of the  $\text{Ca}^{2+}$  inflow after addition of the agonist. % inhibition compared with the maximum achievable inhibition is stated.

The substances according to the invention act, for example, on the B1R relevant in connection with various diseases, so that they are suitable as a pharmaceutical active compound in medicaments. The invention therefore also provides medicaments containing at least one substituted sulfonamide derivative according to the invention and optionally suitable additives and/or auxiliary substances and/or optionally further active compounds.

The medicaments according to the invention optionally contain, in addition to at least one substituted sulfonamide derivative according to the invention, suitable additives and/or auxiliary substances, that is to say also carrier materials, fillers, solvents, diluents, dyestuffs and/or binders, and can be administered as liquid medicament forms in the form of injection solutions, drops or juices or as semi-solid medicament forms in the form of granules, tablets, pellets, patches, capsules, plasters/spray-on plasters or aerosols. The choice of auxiliary substances etc. and the amounts thereof to be employed depend on whether the medicament is to be administered orally, perorally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, nasally, buccally, rectally or topically, for example to the skin, the mucous membranes or into the eyes. Formulations in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration. Sulfonamide derivatives according to the invention in a depot, in dissolved form or in a plaster, optionally with the addition of agents which promote penetration through the skin, are suitable formulations for percutaneous administration. Formulation forms which can be used orally or percutaneously can release the substituted sulfonamide derivatives according to the invention in a delayed manner. The substituted sulfonamide derivatives according to the invention can also be used in parenteral long-term depot forms, such as e.g. implants or implanted pumps. In principle, other further active compounds known to the person skilled in the art can be added to the medicaments according to the invention.

The amount of active compound to be administered to patients varies as a function of the weight of the patient, of the mode of administration, the indication and the severity of the disease. 0.00005 to 50 mg/kg, preferably 0.01 to 5 mg/kg of at least one substituted sulfonamide derivative according to the invention are conventionally administered.

In a preferred form of the medicament, a substituted sulfonamide derivative according to the invention contained therein is present as the pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar mixture of the diastereomers and/or enantiomers.

B1R is involved in particular in the pain event. The substituted sulfonamide derivatives according to the invention can accordingly be used for the preparation of a medicament for treatment of pain, in particular acute, visceral, neuropathic, chronic or inflammatory pain.

The invention therefore also provides the use of a substituted sulfonamide derivative according to the invention for the preparation of a medicament for treatment of pain, in particular acute, visceral, neuropathic, chronic or inflammatory pain.

The invention also provide the use of a substituted sulfonamide derivative according to the invention for the preparation of a medicament for treatment of diabetes, diseases of the respiratory tract, for example bronchial asthma, allergies, COPD/chronic obstructive pulmonary disease or cystic fibrosis; inflammatory intestinal diseases, for example ulcerative colitis or CD/Crohn's disease; neurological diseases, for example multiple sclerosis or neurodegeneration; inflammations of the skin, for example atopic dermatitis, psoriasis or bacterial infections; rheumatic diseases, for example rheumatoid arthritis or osteoarthritis; septic shock; reperfusion syndrome, for example following cardiac infarction or stroke, obesity; and as an angiogenesis inhibitor.

In this context, in one of the above uses it may be preferable for a substituted sulfonamide derivative which is used to be present as the pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar mixture of the diastereomers and/or enantiomers.

The invention also provides a method for the treatment, in particular in one of the abovementioned indications, of a non-human mammal or a human requiring treatment thereof, by administration of a therapeutically active dose of a substituted sulfonamide derivative according to the invention, or of a medicament according to the invention.

The invention also provides a method for the treatment of pain, in particular of acute, visceral, neuropathic, chronic or inflammatory pain, of a non-human mammal or a human requiring treatment thereof, by administration of a therapeutically active dose of a substituted sulfonamide derivative according to the invention, or of a medicament according to the invention.

The invention also provides a process for the preparation of the substituted sulfonamide derivatives according to the invention as described in the following description, examples and claims. The general synthesis process for preparation of the compounds according to the invention is first described, the following abbreviations being used:

9-BBN = 9-borabicyclo[3,3,1]nonane

BOP = 1-benzotriazolylxy-tris-(dimethylamino)-phosphonium hexafluorophosphate

Bu = butyl

CDI = 1,1'-carbonyldiimidazole

DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene

DCC = dicyclohexylcarbodiimide

DCE = 1,2-dichloroethane

MC = methylene chloride

DIPEA = N,N-Diisopropylamine

DMAP = 4-dimethylaminopyridine

DMF = N,N-dimethylformamide

DMS = dimethyl sulfide

DMSO = dimethylsulfoxide

EDCI = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

Et = ethyl

HATU = N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridino-1-yl]methylenemethanaminium hexafluorophosphate N-oxide

HBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HOAt = 1-hydroxy-7-azabenzotriazole

HOBt = 1-hydroxybenzotriazole, where appropriate as the hydrate

Me = methyl

Ms = methanesulfonyl

PFPTFA = pentafluorophenyl trifluoroacetate

PFP = pentafluorophenol

PyBOP = benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxyl

TMSOTf = trimethylsilyl triflate

PTSA = p-toluenesulfonic acid

The protective group (PG) is a suitable nitrogen-protecting group, preferably ethyloxycarbonyl, *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl (Ac) or benzyl (Bn).

Preferred protecting groups for carboxylic acids are chosen in such a form that the protected hydroxy group forms a methyl carboxylic ester (-CO<sub>2</sub>Me), ethyl carboxylic ester (-CO<sub>2</sub>Et) or a *tert*-butoxy carboxylic ester (-CO<sub>2</sub>*tert*Bu).

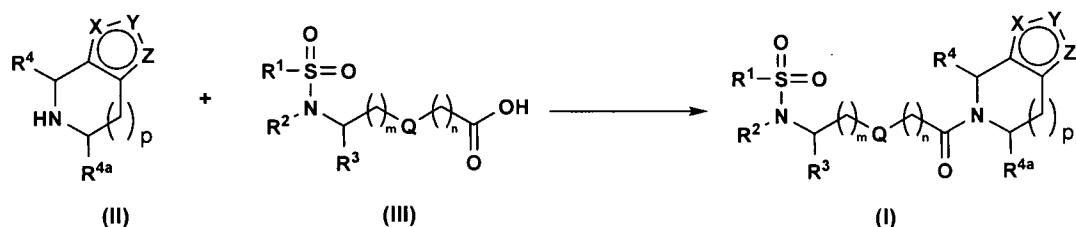
Preferred protecting groups for alcohols are silyl based protecting groups, such as trimethylsilyl (TMS), triethylsilyl (TES), *tert*-butyldimethylsilyl (TBDMS).

Protective groups can be introduced and split off by conventional literature methods known to the person skilled in the art, as described, for example, in (a) Philip J. Kocienski, *Protecting Groups*, 3<sup>rd</sup> edition, Georg Thieme Verlag, 2005 (ISBN 3-13-135603-0), particularly pages 187-314, 487-631, & 393-425 and (b) Peter G. M. Wuts, Theodora W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4<sup>th</sup> edition, Wiley-Interscience, 2007 (ISBN-13: 978-0-471-69754-1), particularly pages 16-366, .533-646 & 696-926.

It can be seen by the person skilled in the art that in some cases the sequence of the reaction steps can be modified where appropriate.

The separation of diastereomers and/or enantiomers is carried out by conventional methods known to the person skilled in the art, for example by recrystallization, chromatography or, in particular, HPLC chromatography or crystallization with an optionally chiral acid or base and separation of the salts or chiral HPLC chromatography (Fogassy et al., *Optical Resolution Methods*, *Org. Biomol. Chem* 2006, 4, 3011-3030).

The process for the preparation of the compounds of type (I) according to the invention is reproduced in the following Equation 1:



### Equation 1

The amines (II) are preferably reacted in an amide formation using carboxylic acids (III) in the presence of dehydrating agents, such as sodium sulfate or magnesium sulfate, phosphorus oxide or reagents such as, for example, CDI, DCC (optionally bonded to a polymer), TBTU, HATU, EDCI, PyBOP or PFPTFA, also in the

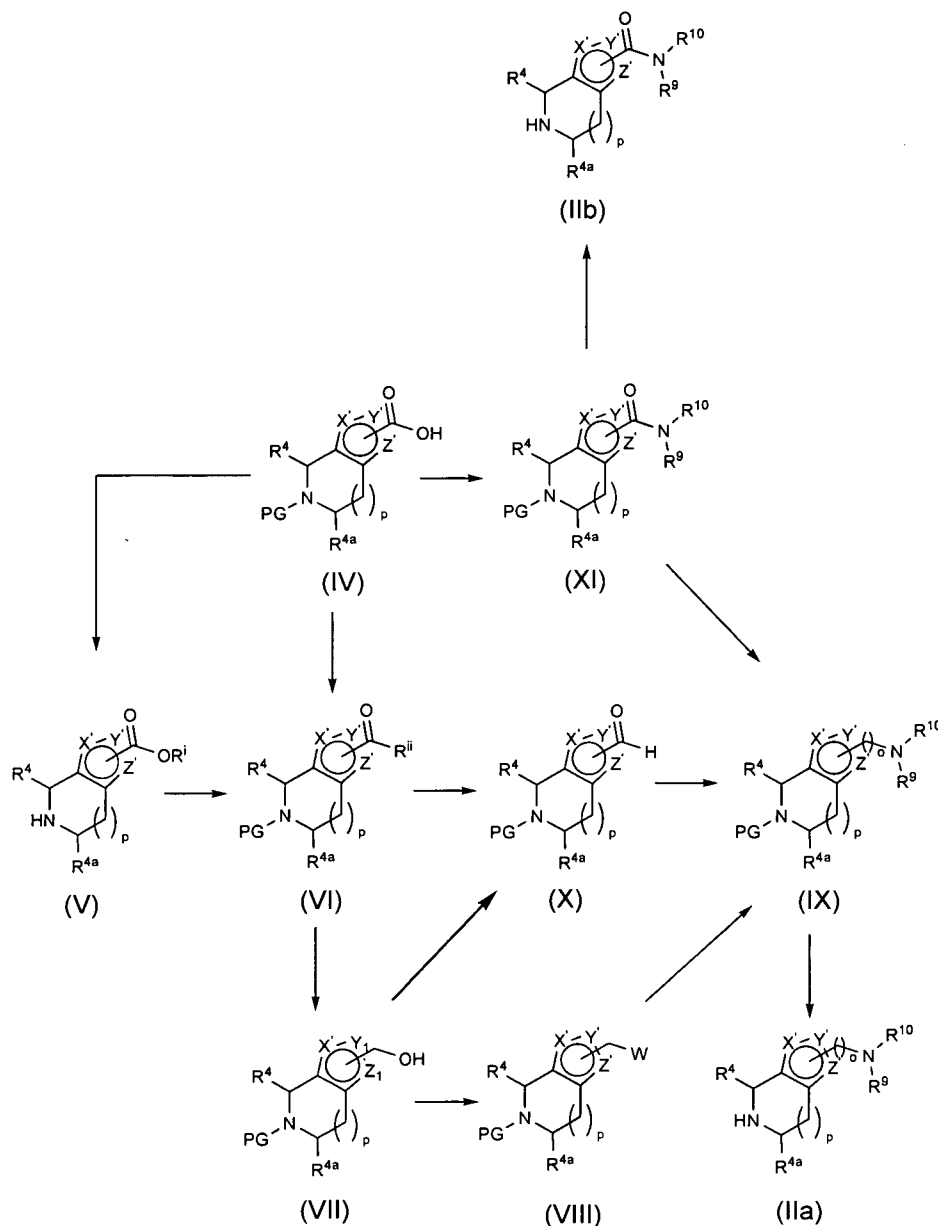
presence of HOAt or HOBt and an organic base, for example DIPEA, triethylamine or pyridine, in an organic solvent, such as THF, MC, diethyl ether, dioxane, DMF or acetonitrile, to give the compounds of the general formula (I) according to the invention. However, the amide bond can also be effected by conversion of the particular acid into the corresponding acid chloride or acid anhydride and subsequent reaction with the particular amine. The preparation of the acid chloride can be carried out by reaction with  $\text{SOCl}_2$ ,  $\text{PCl}_3$ ,  $\text{PCl}_5$  or 1-chloro-N,N,2-trimethyl-1-propenylamine, optionally in a solvent, such as THF, MC, diethyl ether, dioxane, DMF or acetonitrile.

#### 1. Amine units:

The amine units employed, compounds of the general formula (II), are commercially available, known from the literature, for example from EP1270557, WO2006105945 and W. T. Ashton et al., *Bioorg. Med. Chem. Lett.*, **15** (2005), 2253 – 2258, or can be prepared as described in the following.

**General process for the synthesis of the amine units**

**Synthesis of the amines of the general formula (IIa) and (IIb)**



**Equation 2**

PG = a suitable amine-protecting group, for example Boc, Cbz, Ac, Ethoxycarbonyl

W = halogen (Cl, Br, I), Oms or another suitable leaving group

R<sup>i</sup> = preferably Me, Et

R<sup>ii</sup> = preferably OMe, OEt, N(Me)OMe (Weinreb amide)

X' = Y' = Z' = O, S, N, C

o = 1 – 6

Compounds of the general formula (IV) can optionally be prepared from the corresponding unprotected amines by introduction of a suitable amine-protecting group by methods known to the person skilled in the art.

Compounds of the general formula (IV) are reacted in at least one solvent, preferably chosen from the group consisting of methanol, ethanol, propanol, isopropanol, dioxane, diethyl ether, THF, MC, DMF and DMSO, with an alcohol using at least an acid chloride or an acid anhydride or an acid, preferably from the group consisting of thionyl chloride, acetyl chloride, acetic anhydride, sulfuric acid and hydrochloric acid, at temperatures of from preferably 0 °C to 120 °C to give compounds having the general formula (V).

Compounds of the general formula (VI) are obtained from compounds of the general formula (V) by introduction of the corresponding amine-protecting group.

Compounds of the general formula (V) (optionally in the form of the corresponding hydrochloride) are reacted in at least one solvent, preferably chosen from the group consisting of water, methanol, ethanol, isopropanol, acetonitrile, MC, THF, dioxane, toluene, DMF and DMSO, with at least one suitable reagent, preferably chosen from the group consisting of di-*tert*-butyl dicarbonate, O-(*tert*-butoxycarbonyl)hydroxylamine, 1,2,2,2-tetrachloroethyl *tert*-butyl carbonate, O-*tert*-butyl S-pyridin-2-yl carbonothioate, *tert*-butyl carbonazidate, 1-(*tert*-butoxycarbonyl)benzotriazole, in the presence of an excess of base, preferably chosen from the group consisting of caesium carbonate, calcium carbonate, potassium carbonate, potassium bicarbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, triethylamine, diisopropylethylamine and pyridine, at temperatures of from preferably 0 °C to 80 °C to give compounds of the general formula (VI).

Alternatively, compounds of the general formula **(VI)** in which  $R^{ii} = N(Me)OMe$  (Weinreb amide) are obtained from carboxylic acids of the general formula **(IV)** by reaction with N,O-dimethylhydroxylamine hydrochloride in a suitable reaction medium, preferably diethyl ether, THF, acetonitrile, methanol, ethanol, DMF or MC or corresponding mixtures, optionally in the presence of a coupling reagent, preferably chosen from the group consisting of BOP, DCC (optionally bonded to a solid phase), EDCI, HATU, HBTU, HOAt, optionally in the presence of at least one inorganic base, preferably chosen from the group consisting of potassium carbonate and caesium carbonate, or an organic base, preferably chosen from the group consisting of triethylamine, pyridine, N-methylmorpholine, 4,4-dimethylaminopyridine and diisopropylethylamine, preferably at temperatures of from preferably -70 °C to 100 °C. However, the amide bond can also be effected by conversion of the acid into the corresponding acid chloride or acid anhydride and subsequent reaction with the particular amine. The acid chloride can be prepared by reaction with  $SOCl_2$ ,  $PCl_3$ ,  $PCl_5$  or 1-chloro-N,N,2-trimethyl-1-propenylamine, optionally in a solvent, such as THF, MC, diethyl ether, dioxane, DMF or acetonitrile, at a temperature of between -78 °C and 100 °C.

Compounds of the general formula **(VI)** are reacted in at least one solvent, preferably chosen from the group consisting of THF, diethyl ether, toluene or MC, with at least one reducing agent, preferably chosen from the group consisting of diisobutylaluminium hydride, lithium aluminium hydride, lithium tri-*tert*-butoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride, sodium borohydride, aluminium hydride, at temperatures of from preferably -78 °C to 50 °C to give compounds of the general formula **(VII)**.

Compounds of the general formula **(VIII)** are obtained from compounds of the general formula **(VII)** by introduction of a suitable leaving group, such as, for example, halogen or mesylate.

Preferred compounds of the general formula **(VII)** are reacted in at least one solvent, preferably chosen from the group consisting of MC, dioxane, diethyl ether, THF, acetonitrile and DMF, with a sulfonyl chloride, preferably chosen from the group consisting of methylsulfonyl chloride, trifluoromethylsulfonyl chloride, tolylsulfonyl

chloride, and at least one base, preferably chosen from the group consisting of caesium carbonate, calcium carbonate, potassium carbonate, triethylamine, diisopropylethylamine and pyridine, at temperatures of from preferably 0 °C to 80 °C to give compounds of the general formula (VIII) (W = OMs).

Compounds of the general formula (VIII) are reacted in at least one solvent, preferably chosen from the group consisting of MC, dioxane, diethyl ether, THF, acetonitrile, toluene and DMF, with a suitable amine in the presence of an excess of a base, preferably chosen from the group consisting of caesium carbonate, calcium carbonate, potassium carbonate, potassium bicarbonate, sodium bicarbonate, triethylamine, diisopropylethylamine and pyridine, at temperatures of from preferably 0 °C to 80 °C to give compounds of the general formula (IX).

Alternatively, compounds of the general formula (IX) can be obtained from compounds of the general formula (X), which are in turn synthesized from compounds of the general formula (VI).

The liberation of the aldehyde function to give compounds of the general formula (X) is carried out by reaction of the compounds (VI) with a suitable reducing agent. In this context, diisobutylaluminium hydride, lithium aluminium hydride, lithium tri-*tert*-butoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride or bis(cyclopentadienyl)zirconium hydrido-chloride (Schwartz's reagent) in solvents, such as THF, diethyl ether, toluene or MC, can be employed. The reaction times can be between preferably 5 minutes and 7 hours, and the reaction temperature can vary between preferably -78 °C and 50 °C.

Additionally compounds of the general formula (X) can be obtained from compounds of the general formula (VII) by oxidation in the presence of a suitable oxidising agent, such as TEMPO / NaOCl, manganese(IV) oxide, pyridinium dichromate, pyridinium chlorochromate, (COCl)<sub>2</sub> / DMSO / triethylamine or Dess-Martin periodinone, where necessary in the presence of acetic acid or sodium acetate, in a suitable solvent such as dichloromethane, chloroform, diethylether or mixtures thereof, at temperatures of preferably -78 °C to 200 °C.

In the reductive amination, compounds of the general formula **(X)** are reacted with an amine and the imine formed is then reduced to give the amine **(IX)** ( $o = 1$ ). Suitable reducing agents are, for example,  $\text{NaBH}_4$ ,  $\text{NaBH}(\text{OAc})_3$ ,  $\text{NaCNBH}_3$ ,  $\text{NH}_4\text{CNBH}_3$ , polymer-bonded cyanoborohydride, borane-pyridine complex or triethylsilane. The reaction can be carried out in solvents, such as, for example, methanol, ethanol, MC, DCE, acetonitrile, THF, toluene, water, DMSO, DMF, 1-methyl-2-pyrrolidin-2-one or mixtures of the solvents. Auxiliary reagents, such as, for example, HCl (gaseous or as an aqueous solution), acetic acid, TFA,  $\text{ZnCl}_2$ , 1,3-dimethyl-2-imidazolidine,  $\text{MgSO}_4$ ,  $\text{Na}_2\text{SO}_4$  or a molecular sieve, are often also used. However, the imine formed can also be converted into the amine by catalytic hydrogenation on catalysts, such as, for example,  $\text{PtO}_2$  or Pd/C, in solvents, such as, for example, methanol or ethanol.

In the case where  $o = 2 - 6$ , compounds of the general formula **(X)** are reacted with methoxy-methyl-triphenylphosphine in a suitable organic solvent, preferably THF, in the presence of a suitable base, preferably potassium *tert*-butylate, at temperatures of between preferably  $-10$  and  $40$  °C to give the correspondingly lengthened aldehydes. Where appropriate, this step is repeated often in a corresponding manner, before the aldehydes are reacted in a reductive amination, as described above, to give compounds of the general formula **(IX)** ( $o = 2 - 6$ ).

Alternatively, compounds of the general formula **(IX)** can be obtained from compounds of the general formula **(XI)**, which are in turn synthesized from compounds of the general formula **(IV)**.

Compounds of the general formula **(IV)** are reacted with amines in a reaction medium such as diethyl ether, THF, acetonitrile, methanol, ethanol, DMF, MC or corresponding mixtures, optionally in the presence of at least one coupling reagent, such as BOP, DCC (optionally bonded to a solid phase), HATU, HBTU, HOAt and EDCI, optionally in the presence of at least one inorganic base, such as potassium carbonate or caesium carbonate, or an organic base, such as triethylamine, pyridine, N-methylmorpholine, 4,4-dimethylaminopyridine and diisopropylethylamine, at temperatures of from preferably  $-70$  °C to  $100$  °C to give compounds of the general formula **(XI)**.

Alternatively, the carboxylic acid can be converted into the corresponding acid chloride or acid anhydride and reacted with the corresponding amine.

Compounds of the general formula **(XI)** are reduced to give compounds of the general formula **(IX)**. Suitable reducing agents are, for example, NaBH<sub>4</sub>, LiBH<sub>4</sub>, L-Selectride, superhydride, NaBH(Oac)<sub>3</sub>, NaCNBH<sub>3</sub>, polymer-bonded cyanoborohydride, NH<sub>4</sub>CNBH<sub>3</sub>, Bu<sub>4</sub>NBH<sub>4</sub>, sodium (dimethylamino)trihydroborate, 9-BBN, diborane, borane-THF complex, borane-diethyl ether complex, borane-DMS complex, borane-diethylaniline complex, borane-dimethylamine complex, borane-ethylphenylpropylamine complex, borane-diisopropylamine complex, borane-pyridine complex, lithium aluminium hydride, alane, diisobutylaluminium hydride, lithium tri-*tert*-butoxyaluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride, diphenylsilane, methylphenylsilane, optionally in the present of BF<sub>3</sub> etherate, chlorotrimethylsilane, titanium tetrachloride, Meerwein's salt, zinc chloride, RhH(CO)(PPh<sub>3</sub>)<sub>3</sub> or Cp<sub>2</sub>TiF<sub>2</sub>. The reaction can be carried out in solvents, such as, for example, methanol, ethanol, MC, DCE, dodecane, acetonitrile, THF, diethyl ether, dioxane, toluene, 1,2-dimethoxyethane or mixtures of the solvents, and at a temperature of from -78 to 100 °C. The reaction time can be between 30 minutes and 70 hours.

Compounds of the general formula **(IIa)** are obtained from compounds of the general formula **(IX)** by splitting of the corresponding amine-protecting group by methods known to the person skilled in the art.

Compounds of the general formula **(IIb)** are obtained from compounds of the general formula **(XI)** by splitting of the corresponding amine-protecting group by methods known to the person skilled in the art.

Preferred protective groups can be split off as follows:

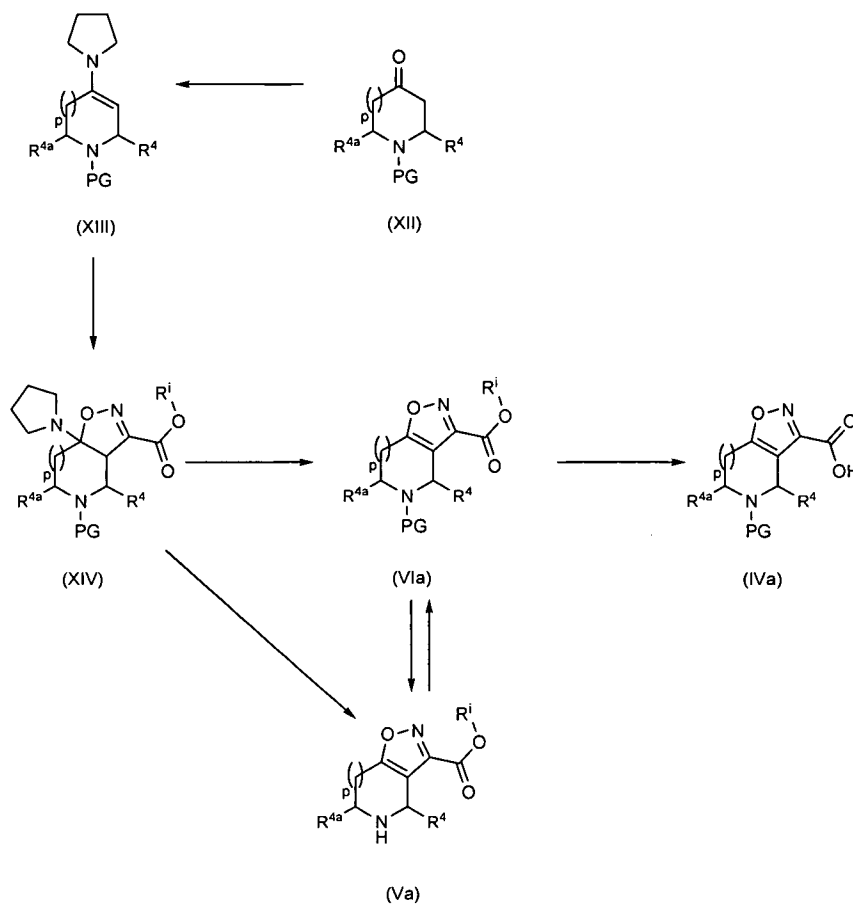
BOC protective groups can be split off in at least one solvent, preferably chosen from the group consisting of acetonitrile, diethyl ether, THF, methanol, ethanol, MC, dioxane and DMF, with an acid, preferably chosen from the group consisting of

trifluoroacetic acid, hydrochloric acid, methanesulfonic acid and sulfuric acid, at temperatures of from preferably 0 °C to 110 °C.

Cbz protective groups can be split off under acidic conditions. This acidic splitting off can be carried out, for example, by reaction with an HBr/glacial acetic acid mixture, a mixture of TFA in dioxane / water or HCl in methanol or ethanol. However, reagents such as, for example, Me<sub>3</sub>Sil, in solvents, such as, for example, MC, chloroform or acetonitrile, BF<sub>3</sub> etherate with the addition of ethanethiol or Me<sub>2</sub>S in solvents, such as, for example, MC, a mixture of aluminium chloride / anisole in a mixture of MC and nitromethane or triethylsilane/PdCl<sub>2</sub> in methanol, with the addition of triethylamine, are also suitable. A further method is the hydrogenolytic splitting off of the protective group under increased pressure or normal pressure with the aid of catalysts, such as, for example, Pd on charcoal, Pd(OH)<sub>2</sub>, PdCl<sub>2</sub>, Raney nickel or PtO<sub>2</sub>, in solvents, such as, for example, methanol, ethanol, 2-propanol, THF, acetic acid, ethyl acetate, chloroform, optionally with the addition of HCl, formic acid or TFA.

Educts of the general formula **(IVa)**, **(Va)** and **(VIa)**

These are commercially available, known from the literature (for example: EP1270557; WO2006/105945; Venkatesan, A. M. et al., Journal of Medicinal Chemistry, 2006, 49, 15, 4623-4637; Kikuchi, C. et al., Bioorganic & Medicinal Chemistry Letters, 2002, 12, 18, 2549-2552; Haginoya, N. et al., Heterocycles, 2004, 63, 7, 1555-1562) or can be prepared as described in the following (Equation 3).



### Equation 3

PG = a suitable amine-protecting group, for example Boc, Cbz, Ac

R<sup>i</sup> = preferably Me, Et

Commercial compounds / compounds known from the literature of the general formula (XII) are reacted in a solvent, such as toluene or benzene, with pyrrolidine in the presence of a catalytic amount of acid, preferably in the presence of p-toluenesulphonic acid, under reflux using a water separator to give compounds of the general formula (XIII).

Compounds of the general formula (XIII) are reacted with a chlorohydroxyiminoacetic acid ester in a reaction medium, such as acetonitrile, MC, chloroform, DMF, dimethylacetamide, DMSO and corresponding mixtures, in the presence of at least

one base, such as triethylamine, pyridine, 4,4-dimethylaminopyridine, N-methylmorpholine and diisopropylethylamine, at a temperature of preferably 0 – 30 °C to give compounds of the general formula **(XIV)**.

Compounds of the general formula **(XIV)** are reacted (depending on the amine-protecting group chosen) in a solvent, such as acetonitrile, MC, chloroform, DMF, dimethylacetamide, DMSO, water, methanol, ethanol and corresponding mixtures, in the presence of a suitable acid, preferably TFA or sulfuric acid, to give compounds of the general formula **(Va)** or **(VIa)**.

Compounds of the general formula **(Va)** can be reacted by splitting off of the protective group (PG – amine-protecting group) by processes known to the person skilled in the art to give compounds of the general formula **(VIa)**.

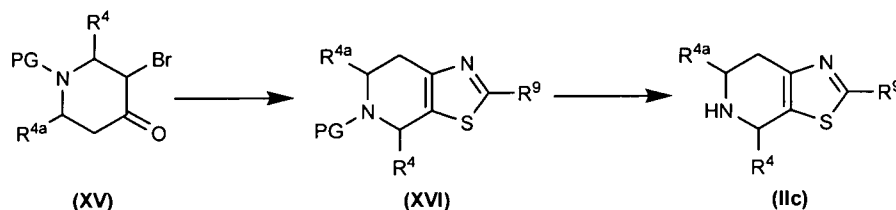
The preferred acetyl protective groups can be split off, for example, in a solvent, such as methanol, ethanol, isopropanol, THF, water and corresponding mixtures, in the presence of an inorganic acid, such as HCl and/or sulfuric acid, under reflux.

Compounds of the general formula **(VIa)** can be reacted by introduction of a protective group (PG – amine-protecting group) by processes known to the person skilled in the art to give compounds of the general formula **(Va)**.

The preferred Boc protective group can be introduced in a reaction medium, such as dioxane, ethanol, methanol, isopropanol, water, MC and corresponding mixtures, in the presence of an organic base, preferably triethylamine, diisopropylamine, pyridine, 4,4-dimethylaminopyridine and N-methylmorpholine, DIPEA, with di-*tert*-butyl dicarbonate at 0 °C and subsequently at preferably 20 – 30 °C.

Compounds of the general formula **(VIa)** can be reacted by splitting off of the protective group (acid-protecting group) by processes known to the person skilled in the art to give compounds of the general formula **(IVa)**.

The hydrolysis of compounds of the general formula **(VIa)** can be carried out in a suitable solvent, such as THF, methanol, ethanol, isopropanol, water and corresponding mixtures, with an inorganic base, preferably lithium hydroxide, potassium hydroxide or sodium hydroxide, at a temperature of preferably 0 – 150 °C.

Synthesis of the amines of the general formula (IIc)**Equation 4**

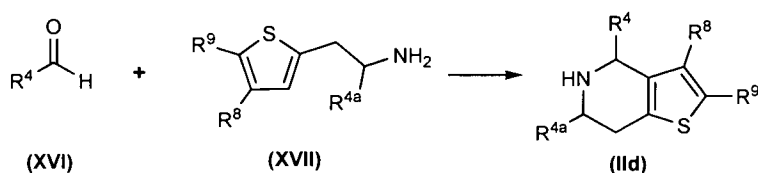
Compounds of the general formula (XV) known from the literature (US6265418, US6599895) are reacted in at least one solvent, preferably chosen from the group consisting of methanol, ethanol, propanol, *iso*-propanol, dioxane, diethyl ether, THF, water and DMF, with a thioamide of the general formula  $R^9CSNH_2$ , wherein  $R^9$  has the meaning given above, in the presence of an excess of a base, preferably chosen from the group consisting of caesium carbonate, calcium carbonate, potassium carbonate, triethylamine, diisopropylethylamine and pyridine, at temperatures of from preferably 0 °C to 120 °C to give compounds of the general formula (XVI), it being possible for the thioamides  $R^9CSNH_2$  employed to be obtained from the corresponding nitriles in at least one solvent, preferably chosen from the group consisting of methanol, ethanol, propanol, *iso*-propanol, dioxane, diethyl ether and THF, in the presence of an excess of ammonia and in the presence of an excess of hydrogen sulphide at temperatures of from preferably 0 °C to 80 °C.

Compounds of the general formula (XVI) can be reacted by splitting off of the protective group (amine-protective group) by known processes to give compounds of the general formula (IIc).

In the case of the protective group (PG) = *tert*-butyloxycarbonyl (Boc), the compounds of the general formula (XVI) are reacted in at least one solvent, preferably chosen from the group consisting of methanol, ethanol, MC, diethyl ether, THF, acetonitrile, dioxane, DMF and DMSO, with an acid, preferably chosen from the group consisting of trifluoroacetic acid, sulfuric acid and hydrochloric acid, at temperatures of from preferably 0 °C to 80 °C to give compounds having the general formula (IIb).

In the case of the protective group (PG) = ethyloxycarbonyl, the compounds of the general formula (XVI) are reacted in at least one solvent, preferably chosen from the group consisting of methanol, ethanol, isopropanol, ethylene glycol, water, THF, dioxane, DMF and DMSO, with at least one base, preferably chosen from the group consisting of sodium hydroxide, potassium hydroxide, potassium carbonate, barium hydroxide, lithium propanethiolate, hydrazine, methyllithium and potassium trimethylsilanolate, at temperatures of from preferably 0 °C to 120 °C to give compounds having the general formula (IIb).

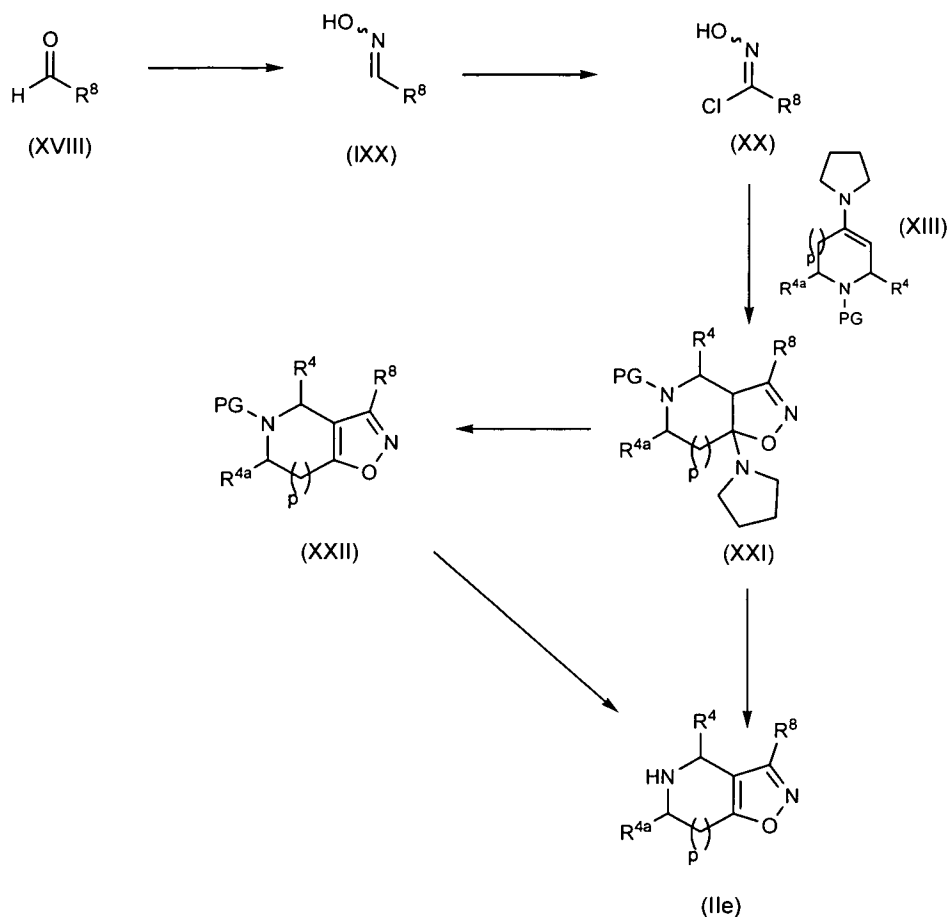
#### Synthesis of the amines of the general formula (IIc)



#### Equation 5

The educts employed, compounds of the general formula (XVII) and (XVI), are commercially available or can be prepared by methods known from the literature.

Compounds having the general formula (IIc) are obtained by reaction of compounds having the general formula (XVII) with compounds having the general formula (XVI) in solvents, such as ethanol, methanol, diethyl ether, MC, ethyl acetate, pyridine, benzene, toluene or a mixture of these solvents, optionally with the addition of triethylamine, sodium hydroxide, trifluoroacetic acid, and optionally with removal of the water formed during the reaction, for example by azeotropic distillation or by addition of a molecular sieve. The reaction times can be between preferably 1 – 75 hours and the reaction temperature can vary between preferably 20 °C and 110 °C. However, the cyclization to give compounds of the general formula (IIc) can also be achieved by reaction of compounds having the general formula (XVII) with the corresponding carboxylic acid and subsequent reduction of the cyclic imine primarily formed with reducing agents, such as, for example, sodium borohydride.

Synthesis of the amines of the general formula (Ile)**Equation 6**

$PG$  = a suitable amine-protecting group, for example Boc or Ac

If compounds of the general formula **(XVIII)** are not commercially available, these can be prepared from the corresponding carboxylic acids in the presence of a suitable reducing agent, or from the corresponding alcohols in the presence of a suitable oxidizing agent.

If compounds of the general formula **(IXX)** are not commercially available, these can be prepared from compounds of the general formula **(XVIII)** in the presence of hydroxylamine or hydroxylamine hydrochloride in a suitable reaction medium, such as,

for example, methanol, ethanol, DMF, acetonitrile, DMSO or water and corresponding mixtures, optionally in the presence of a base, such as, for example, triethylamine, diisopropylethylamine, sodium acetate or sodium hydroxide, or in the presence of an ion exchanger (for example Amberlite) at preferred temperatures of between preferably 0 °C and 150 °C.

Compounds of the general formula **(IXX)** can be reacted in the presence of N-chlorosuccinimide or alternative suitable reagents in a suitable reaction medium, such as, for example, DMF, acetonitrile, DMSO or chloroform and corresponding mixtures, at preferred temperatures of between preferably 0 °C and 150 °C to give compounds of the general formula **(XX)**.

Compounds of the general formula **(XIII)** (see Equation 3) are reacted with compounds of the general formula **(XX)** in a reaction medium, such as acetonitrile, MC, chloroform, DMF, dimethylacetamide, DMSO and corresponding mixtures, in the presence of at least one base, such as triethylamine, pyridine, 4,4-dimethylaminopyridine, N-methylmorpholine and diisopropylethylamine, at a temperature of preferably 0 – 30 °C to give compounds of the general formula **(XXI)**.

Compounds of the general formula **(XXI)** are reacted, depending on the amine-protecting group chosen, in a solvent, such as acetonitrile, MC, chloroform, DMF, dimethylacetamide, DMSO, water, ethanol, methanol and corresponding mixtures, in the presence of a suitable acid, preferably TFA or sulfuric acid, under reflux to give compounds of the general formula **(XXII)** or **(Ile)**.

Compounds of the general formula **(XXII)** can be reacted by splitting off of the protective group (PG – amine-protecting group) by processes known to the person skilled in the art to give compounds of the general formula **(Ile)**.

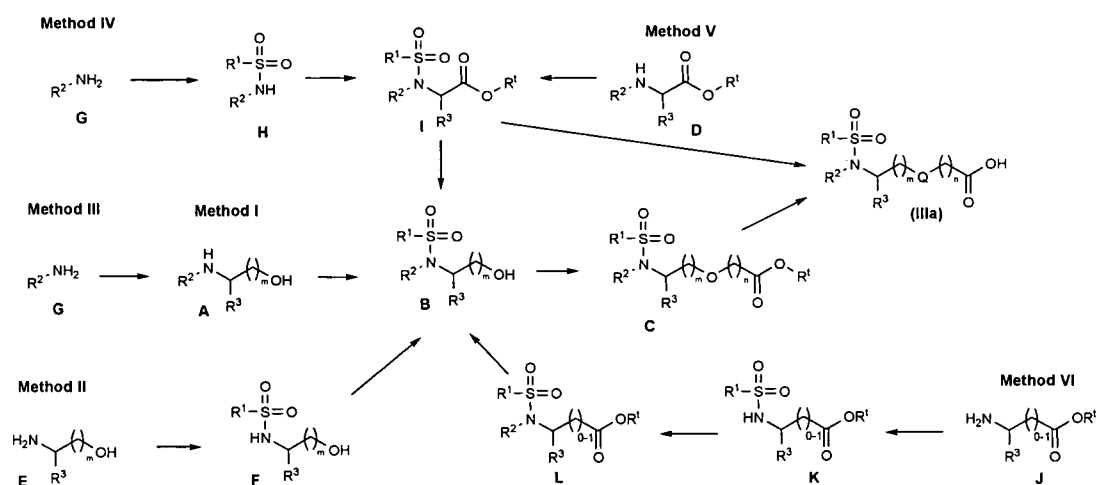
The preferred acetyl protective group can be split off, for example, in a solvent, such as methanol, ethanol, isopropanol, THF, water and corresponding mixtures, in the presence of an inorganic acid, such as HCl and/or sulfuric acid, under reflux.

## 2. Acid units:

The acid units employed, compounds of the general formula (III), are known from the literature (e.g. from  $\beta$ -Amino Acids – Tetrahedron Report Number 617: M. Liu, M. P. Sibi, *Tetrahedron*, **58**, (2002), 7991 – 8053) or can be prepared as described in the following.

$\beta$ -Amino acids can be converted into the acid units of the general formula (III), optionally using suitable protective groups, by introduction of a sulfonyl radical analogously to the processes described in the following.

### General synthesis process for the preparation of the acyclic acid units (IIIa)



### Equation 7

$R^t$  = preferably Me, Et, *tert*-Bu (or H – if appropriate)

In **Method I**, the racemic (R and S configuration) or enantiomerically pure (R or S configuration) amino alcohols **A** are reacted in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for

example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino alcohols **B**.

The sulfonylated amino alcohols **B** are reacted in an alkylation reaction with halogenated ester derivatives using tetrabutylammonium chloride or bromide or tetrabutylammonium hydrogen sulfate in a phase transfer reaction using an organic solvent, such as THF, toluene, benzene or xylene, and an inorganic base, such as potassium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, or in the presence of an organic or inorganic base, conventional inorganic bases are metal alcoholates, such as sodium methanolate, sodium ethanolate, potassium *tert*-butylate, lithium bases or sodium bases, such as lithium diisopropylamide, butyllithium, *tert*-butyllithium, sodium methylate, or metal hydrides, such as potassium hydride, lithium hydride, sodium hydride, conventional organic bases are diisopropylethylamine, triethylamine, in an organic solvent, such as MC, THF or diethyl ether, at 0 °C to the reflux temperature, to give the products of the general structure **C**.

In **Method II**, the racemic (R and S configuration) or enantiomerically pure (R or S configuration) amino alcohols **E** are reacted in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino alcohols **F**. The sulfonylated amino alcohols **F** are then reacted in an alkylation reaction with alkyl halides ( $RX, X = I, Br, Cl$ ), mesylates or alternative alkylating reagents, optionally in the presence of an organic or inorganic base, for example sodium hydroxide, potassium carbonate, caesium carbonate, DBU or DIPEA, preferably in an organic solvent, for example dimethylformamide, acetone, THF, acetonitrile, dioxane or these solvents as mixtures, at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino alcohols **B**. These are converted to the ester derivatives **C** as described in Method I.

In **Methods I-III**, the ester derivatives **C** are reacted in an ester cleavage using organic acids, such as trifluoroacetic acid, or aqueous inorganic acids, such as hydrochloric acid, or using aqueous inorganic bases, such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, in organic solvents, such as methanol, dioxane, MC, THF, diethyl ether or these solvents as mixtures, at 0 °C to room temperature, to give the acid stages of the general formula (**IIIa**).

In **Method III**, commercial amines or amines accessible to the person skilled in the art are alkylated with 2-bromoethanol or derivatives in organic solvents, such as ethanol, methanol, ether, THF or MC, at a temperature of from 0 °C to the reflux temperature for up to 20 hours. The further process proceeds analogously to the other methods.

In **Method IV**, the amines are reacted in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated derivatives **H**.

The sulfonylated amines are then reacted in an alkylation reaction with methyl 2-bromoacetate or derivatives **H**, optionally in the presence of an organic or inorganic base, for example sodium hydride, potassium carbonate, caesium carbonate, DBU or DIPEA, preferably in an organic solvent, for example dimethylformamide, acetone, THF, acetonitrile, dioxane or these solvents as mixtures, to give the sulfonylated amino esters **I**.

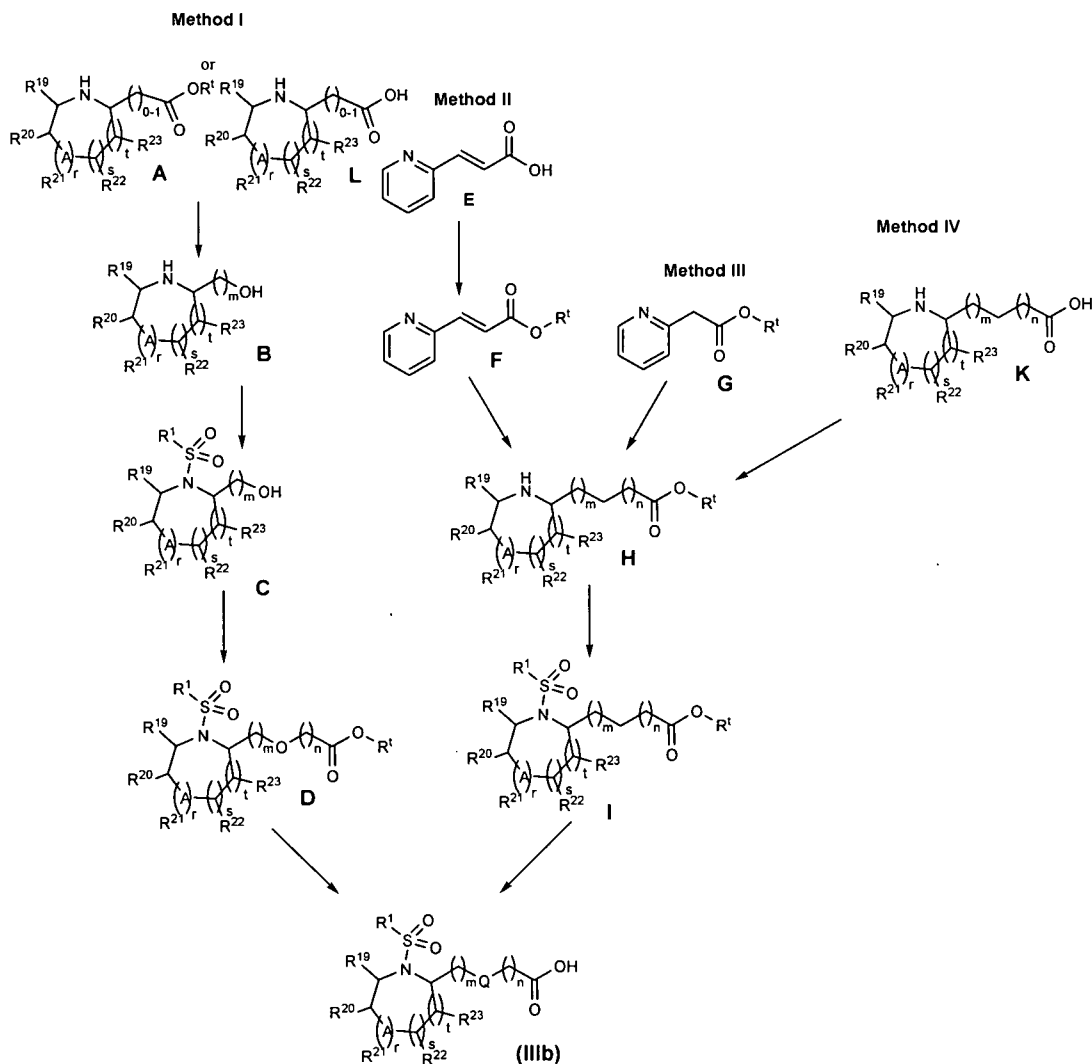
The sulfonylated amino esters **I** are reacted in a reduction reaction to give a sulfonylated amino alcohol **B** using metal hydrides as reducing agents, such as, for example,  $LiAlH_4$ ,  $BH_3 \cdot DMS$  or  $NaBH_4$ , in an organic solvent, such as THF or diethyl ether. The further process of **Method IV** corresponds to the other methods.

In **Method V**, the amino acids or amino esters **D** are reacted in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ),

optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino acids/esters **I**. The derivatives **I** are reacted in an ester cleavage using organic acids, such as trifluoroacetic acid, or aqueous inorganic acids, such as hydrochloric acid, or using aqueous inorganic bases, such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, in organic solvents, such as methanol, dioxane, MC, THF, diethyl ether or these solvents as mixtures, at 0 °C to room temperature, to give the acid stages of the general formula **(IIIa)**.

In **Method VI**, the amino acid or amino ester derivatives **J** are reacted in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino acids/esters **K**. The sulfonylated amino acids/esters **K** are reacted with an alcohol under Mitsunobu conditions, employing for example DEAD (Diethylazodicarboxylate), DIAD (Diisopropylazodicarboxylate) or fluorinated equivalents in the presence of triphenylphosphine (or a fluorinated equivalent or  $PPh_3$  on solid support) in a suitable organic solvent, such as THF or fluorinated solvents, to give compounds of the general formula **L**. The sulfonylated derivatives **L** are reacted in a reduction reaction to give a sulfonylated amino alcohol **B** using metal hydrides as reducing agents, such as, for example,  $LiAlH_4$ ,  $BH_3 \cdot x DMS$  or  $NaBH_4$ , in an organic solvent, such as THF or diethyl ether. The further process of **Method IV** corresponds to the other methods.

### General synthesis process for the preparation of the cyclic acid units (IIIb)



#### Equation 8

$R^t$  = preferably Me, Et, *tert*-Bu or H

A = N, O, S

In **Method I**, the racemic (R and S configuration) or enantiomerically pure (R or S configuration) amino acid esters **A** or amino acids **L** are reacted by a reduction to give an amino alcohol **B** using metal hydrides as reducing agents, such as, for example,  $\text{LiAlH}_4$ ,  $\text{BF}_3$  etherate,  $\text{BH}_3 \times \text{DMS}$  or  $\text{NaBH}_4$ , in an organic solvent, such as THF or

diethyl ether, at temperatures of from 0 °C to the reflux temperature. The amino alcohols **B** are reacted further in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, dimethylaminopyridine, diethylamine or DBU, preferably in an organic solvent, for example acetone, acetonitrile, MC or THF, and at a temperature of from 0 °C to the reflux temperature, to give the sulfonylated amino alcohols **C**.

The sulfonylated amino alcohols **C** are reacted in an alkylation reaction with halogenated ester derivatives (or carboxylic acids) using tetrabutylammonium chloride or bromide or tetrabutylammonium hydrogen sulfate in a phase transfer reaction using an organic solvent, such as THF, toluene, benzene or xylene, and an inorganic base, such as potassium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, or in the presence of an organic or inorganic base, conventional inorganic bases are metal alcoholates, such as sodium methanolate, sodium ethanolate, potassium *tert*-butylate, lithium bases or sodium bases, such as lithium diisopropylamide, butyllithium, *tert*-butyllithium, sodium methylate, or metal hydrides, such as potassium hydride, lithium hydride, sodium hydride, conventional organic bases are diisopropylethylamine, triethylamine, in an organic solvent, such as MC, THF or diethyl ether, at 0 °C to the reflux temperature, to give the products of the general structure **D**.

In **Method II**, 3-(pyridin-2-yl)acrylic acid **E** is esterified using dehydrating reagents, for example inorganic acids, such as  $H_2SO_4$  or phosphorus oxides, or organic reagents, such as thionyl chloride, in organic solvents, such as THF, diethyl ether, methanol, ethanol or MC, to give stage **F**, at temperatures of from room temperature to the reflux temperature.

In **Methods II and III**, the ester stages **F** and **G** are hydrogenated in a hydrogenation under conditions known to the person skilled in the art in organic solvents, such as THF, chloroform, and in the presence of catalysts, such as platinum oxides, with hydrogen under normal pressure or increased pressure to give the intermediates **H**.

In **Methods II-III**, stage **H** is reacted further in a sulfonylation with sulfonyl chlorides, bromides or pentafluorophenolate  $R^1SO_2X$  ( $X = Cl, Br, OPFP$ ), optionally in the presence of an organic or inorganic base, for example potassium carbonate, sodium bicarbonate, diisopropylethylamine, triethylamine, pyridine, diethylamine or DBU, preferably in an organic solvent, for example acetonitrile, MC or THF, at 0 °C to the reflux temperature, to give the sulfonylated amino esters **I**.

In **Methods I-III**, the ester derivatives **D** and **I** (provided  $R^t$  is not H – If  $R^t$  is H, then **D** and **I** are equivalent to (IIIb) and do not need to be deprotected) are reacted in an ester cleavage using organic acids, such as trifluoroacetic acid, or aqueous inorganic acids, such as hydrochloric acid, or using aqueous inorganic bases, such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, in organic solvents, such as methanol, dioxane, MC, THF, diethyl ether or these solvents as mixtures, at 0 °C to room temperature, to give the acid stages of the general formula (IIIb).

In **Method IV**, the racemic (R and S configuration) or enantiomerically pure (R or S configuration) amino acids **K** are esterified using dehydrating reagents, for example inorganic acids, such as  $H_2SO_4$  or phosphorus oxides, or organic reagents, such as thionyl chloride, in organic solvents, such as THF, diethyl ether, methanol, ethanol or MC, to give the amino esters **H**. The further course of the general process corresponds to **Methods II-III**.

It is obvious to a person skilled in the art that in each case where either an amine or an alcohol is depicted it may be replaced by a suitably protected derivative, where appropriate. It should be noted that the protecting group has to be removed by a suitable standard deprotection procedure known to the person skilled in the art prior to those steps where modification of the functional group in question is desired (i.e. prior to conversion to yield the compounds of the general formula C, D and I).

## Pharmacological studies

### 1 Functional investigation on the bradykinin 1 receptor (B1R)

The agonistic or antagonistic action of substances can be determined on the bradykinin 1 receptor (B1R) of the human and rat species with the following assay. In accordance with this assay, the  $\text{Ca}^{2+}$  inflow through the channel is quantified with the aid of a  $\text{Ca}^{2+}$ -sensitive dyestuff (type Fluo-4, Molecular Probes Europe BV, Leiden, Holland) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA).

### 2 Method:

Chinese hamster ovary cells (CHO K1 cells) transfected stably with the human B1R gene (hB1R cells) or the B1R gene of the rat (rB1R cells) are used. For functional studies, these cells are plated out on black 96-well plates with a clear base (BD Biosciences, Heidelberg, Germany or Greiner, Frickenhausen, Germany) in a density of 20,000 – 35,000 cells/well. The cells are left overnight at 37 °C and 5 %  $\text{CO}_2$  in culture medium (hB1R cells: Nutrient Mixture Ham's F12, Gibco Invitrogen GmbH, Karlsruhe, Germany or DMEM, Sigma-Aldrich, Taufkirchen, Germany; rB1R cells: D-MEM/F12, Gibco Invitrogen GmbH, Karlsruhe, Germany) with 10 vol.% FBS (foetal bovine serum, Gibco Invitrogen GmbH, Karlsruhe, Germany or PAN Biotech GmbH, Aidenbach, Germany).

On the following day, the cells are loaded for 60 min at 37 °C with 2.13  $\mu\text{M}$  Fluo-4 (Molecular Probes Europe BV, Leiden, Holland) in HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany ) with 2.5 mM probenecid (Sigma-Aldrich, Taufkirchen, Germany) and 10 mM HEPES (Sigma-Aldrich, Taufkirchen, Germany). The plates are then washed 2 x with HBSS buffer, and HBSS buffer which additionally contains 0.1 % BSA (bovine serum albumin; Sigma-Aldrich, Taufkirchen, Germany), 5.6 mM glucose and 0.05 % gelatine (Merck

KgaA, Darmstadt, Germany) is added. After a further incubation of 20 minutes at room temperature, the plates are inserted into the FLIPR for the  $\text{Ca}^{2+}$  measurement.

Alternatively, the plates are washed with buffer A (15 mM HEPES, 80 mM NaCl, 5 mM KCl, 1.2 mM  $\text{CaCl}_2$ , 0.7 mM  $\text{MgSO}_4$ , 2 g/l glucose, 2.5 mM probenecid), buffer A is added and the plates are loaded with 2.5  $\mu\text{M}$  Fluo-4 and 0.025 % Pluronic F127 (Sigma-Aldrich, Taufkirchen, Germany). Thereafter, the cells are washed 2 x with buffer A and incubated for 30 minutes with buffer A, which additionally contains 0.05 % BSA and 0.05 % gelatine, at room temperature and thereafter inserted into the FLIPR for the  $\text{Ca}^{2+}$  measurement.

The  $\text{Ca}^{2+}$ -dependent fluorescence is measured here before and after addition of substances ( $\lambda_{\text{ex}} = 488 \text{ nm}$ ,  $\lambda_{\text{em}} = 540 \text{ nm}$ ). Quantification is by measurement of the highest fluorescence intensity (FC, fluorescence counts) over time.

### 3 FLIPR assay:

The FLIPR protocol consists of 2 additions of substance. Test substances (10  $\mu\text{M}$ ) are first pipetted on to the cells and the  $\text{Ca}^{2+}$  inflow is compared with the control (hB1R: Lys-Des-Arg<sup>9</sup>-bradykinin  $\geq 50 \text{ nM}$ ; rB1R: Des-Arg<sup>9</sup>-bradykinin 10  $\mu\text{M}$ ). This gives the figure in % activation based on the  $\text{Ca}^{2+}$  signal after addition of Lys-Des-Arg<sup>9</sup>-bradykinin ( $\geq 50 \text{ nM}$ ) or Des-Arg<sup>9</sup>-bradykinin (10  $\mu\text{M}$ ).

After incubation for 10-20 minutes, Lys-Des-Arg<sup>9</sup>-bradykinin (hB1R) or Des-Arg<sup>9</sup>-bradykinin (rB1R) in the concentration of the  $\text{EC}_{80}$  is applied and the inflow of  $\text{Ca}^{2+}$  is likewise determined.

Antagonists lead to a suppression of the  $\text{Ca}^{2+}$  inflow. % inhibition compared with the maximum achievable inhibition is calculated.

For determination of the  $\text{IC}_{50}$  value, the substances are added in various concentrations. Duplicate or triplicate determinations ( $n = 2$  or  $n = 3$ ) are carried out, and these are repeated in at least one further independent experiment ( $N \geq 2$ ).

The following examples serve to explain the invention in more detail, but do not limit the general inventive idea.

## Examples

The chemicals and solvents employed were obtained commercially from the conventional suppliers (Acros, Aldrich, Fluka, Lancaster, Maybridge, TCI, Fluorochem, Tyger, ABCR, Fulcrum, FrontierScientific etc.) or were synthesised by the methods known to the person skilled in the art. The yields of the compounds prepared are not optimized.

Commercially available materials, for example  $\text{Al}_2\text{O}_3$  or silica gel [for example from E. Merck, Darmstadt, Germany], were used as the stationary phase for column chromatography. Thin-layer chromatography investigations were carried out with commercially available HPTLC pre-coated plates (for example silica gel 60 F 254 from E. Merck, Darmstadt).

The mixing ratios of solvents, eluants or for chromatographic investigations are always given in volume/volume unless indicated otherwise.

Unless indicated otherwise, analysis was carried out by mass spectroscopy (ESI-MS).

The number of equivalents of reagents, as well as the solvent amount, the reaction temperature and the reaction time may vary slightly for reactions which have been carried out by an analogous method. Work-up and purification (mainly column chromatography) were adjusted in order to compensate for the characteristics of each compound synthesised by an analogous method.

Analytical method for individual compounds:

The analytical studies were carried out by mass spectroscopy. Equipment and Methods for HPLC-MS Analytics:

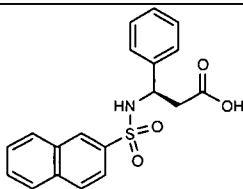
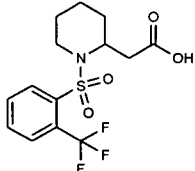
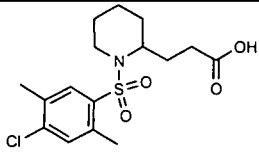
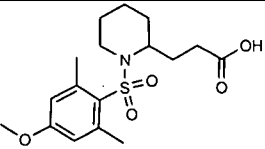
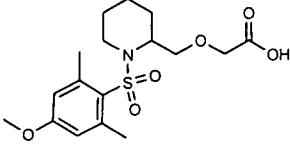
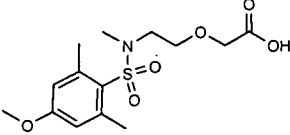
HPLC: Waters Alliance 2795 with PDA Waters 2998; MS: Micromass Quattro MicroTM API ; Column: Waters Atlantis® T3 , 3  $\mu\text{m}$ , 100 Å , 2.1 x 30 mm; temp.: 40 °C, Eluent A: water + 0.1% formic acid; Eluent B: acetonitrile + 0.1% formic acid; Gradient: 0% B to 100% B in 8.8 min, 100% B for 0.4 min, 100% B

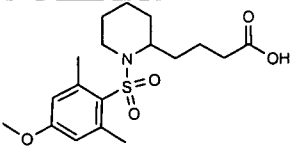
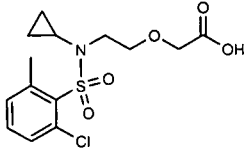
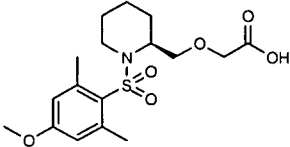
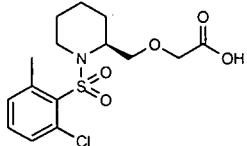
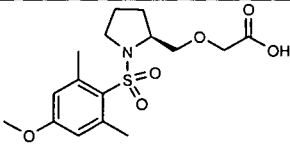
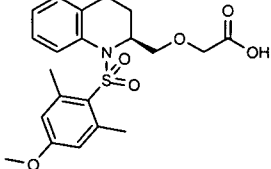
to 0% B in 0.01 min, 0% B for 0.8 min; Flow: 1.0 mL/min; Ionisation: ES+, 25 V;  
Make up: 100 µL/min 70% methanol + 0.2% formic acid; UV: 200 – 400 nm.

The person skilled in the art will understand that the acid and amine structural units employed within the scope of the syntheses of individual substances can also be used analogously in parallel synthesis according to the methods described.

**I. Individual substances****1. Acid units**

The following acid units were synthesized and employed for synthesis of the compounds according to the invention:

| Acid | Structure                                                                           | Name                                                                           |
|------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| AC1  |    | (R)-3-(Naphthalene-2-sulfonamido)-3-phenylpropanoic acid                       |
| AC2  |   | 2-(1-(2-(Trifluoromethyl)phenylsulfonyl)piperidin-2-yl)acetic acid             |
| AC3  |  | 3-(1-(4-Chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)propanoic acid        |
| AC4  |  | 3-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)propanoic acid       |
| AC5  |  | 2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid |
| AC6  |  | 2-(2-(4-Methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetic acid            |

|      |                                                                                     |                                                                                                      |
|------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| AC7  |    | 4-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid                              |
| AC27 |    | 2-(2-(2-Chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetic acid                            |
| AC28 |    | (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid                   |
| AC29 |   | (S)-2-((1-(2-Chloro-6-methylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid                        |
| AC30 |  | (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetic acid                  |
| AC31 |  | (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methoxy)acetic acid |

**Synthesis of (3R)-(naphthalene-2-sulfonamido)-3-phenylpropionic acid (AC1)****Stage 1. (3R)-(Naphthalene-2-sulfonamido)-3-phenylpropionic acid tert-butyl ester**

Triethylamine (1.8 ml, 13.55 mmol) and catalytic amounts of DMAP were added to a solution of (3R)-3-amino-3-phenylpropionic acid tert-butyl ester (1 g, 4.52 mmol) in methylene chloride (MC, 10 ml). 2-Naphthalenesulfonic acid chloride (1 g, 4.52 mmol), dissolved in MC (7 ml), was added, while cooling with ice. After stirring for 10 minutes, while cooling with ice, the mixture was slowly warmed to room temperature and stirred overnight. NaHCO<sub>3</sub> solution was added to the reaction mixture and the mixture was stirred. After separation of the phases, the aqueous phase was extracted with methylene chloride. This organic phase was washed with sat. NaCl solution, dried with MgSO<sub>4</sub>, filtered and concentrated to dryness in vacuo. Purification was carried out by chromatography on silica gel (hexane / tert-butyl methyl ether 3/1). The yield was 1.6 g (86 %).

**Stage 2. (3R)-(Naphthalene-2-sulfonamido)-3-phenylpropionic acid (AC1)**

(3R)-(Naphthalene-2-sulfonamido)-3-phenylpropionic acid tert-butyl ester (1.6 g, 3.88 mmol) was dissolved in MC (40 ml), trifluoroacetic acid (5 ml, 64.9 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then concentrated and the residue was codistilled twice with toluene. The yield was 1.3 g (100 %).

**Synthesis of 2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)acetic acid (AC2)****Stage 1. 2-(Piperidinyl-2-yl)acetic acid hydrochloride**

PtO<sub>2</sub> (0.8 g, moistened with methanol) was added to a solution of 2-(pyridin-2-yl)acetic acid hydrochloride (20 g) in methanol (200 ml) and the mixture was stirred under a hydrogen atmosphere for 2 hours. The reaction was monitored by means of thin layer chromatography and the mixture was filtered over Celite when the conversion was complete. The filtrate was concentrated in vacuo. The yield was 20.5 g (quantitative).

**Stage 2. 2-(Piperidin-2-yl)acetic acid methyl ester hydrochloride**

2-(Piperidin-2-yl)acetic acid hydrochloride (20.5 g) was dissolved in methanol (200 ml) and the solution was cooled to 0 °C. Thionyl chloride (16.3 g) was added dropwise at this temperature in the course of 10-15 minutes. The reaction mixture was then stirred under reflux at 65 °C for 2 hours and the reaction was observed by means of thin layer chromatography. When the reaction was complete, the mixture was concentrated in vacuo. The yield was 22 g (quantitative).

**Stage 3. 1-(3-(Trifluoromethyl)phenylsulfonyl)piperidin-2-yl)acetic acid methyl ester**

2-(Piperidin-2-yl)acetic acid methyl ester hydrochloride (1.7 g) was dissolved in MC (65 ml) and K<sub>2</sub>CO<sub>3</sub> (2.66 g) was added. A solution of 3-(trifluoromethyl)benzene-1-sulfonyl chloride (2.14 g) in methylene chloride (20 ml) was added dropwise to this mixture in the course of 10 minutes. The mixture was stirred at room temperature for 8 hours and the reaction was monitored by means of thin layer chromatography. When the reaction had ended, the mixture was filtered and the filtrate was washed with water (100 ml). After separation of the phases, the organic phase was concentrated in vacuo. Purification was carried out by chromatography on silica gel (20 % ethyl acetate in hexane). The yield was 2.89 g (90 %).

**Stage 4. 2-(1-(3-(Trifluoromethyl)phenylsulfonyl)piperidin-2-yl)acetic acid (AC2)**

KOH (8.12 g) was added to a solution of 1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)acetic acid methyl ester (26 g) in methanol (260 ml) and the mixture was stirred at room temperature for 6 hours. The reaction was observed by means of thin layer chromatography. When the reaction had ended, the reaction mixture was concentrated in vacuo and the residue obtained was taken up in water (200 ml). This solution was cooled to 0 °C, adjusted to pH = 2 with concentrated HCl and extracted with methylene chloride (2 x 200 ml). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to dryness in vacuo. The yield was 23.32 g (93 %).

### **Synthesis of 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid (AC3)**

#### **Stage 1. 3-(2-Pyridyl)acrylic acid ethyl ester**

(Ethoxycarbonylmethyl)-triphenylphosphonium salt (341.5 g) was added to a solution of picolinaldehyde (31.1 ml) in toluene (350 ml) at room temperature and the mixture was stirred for a further 90 minutes. The reaction was observed by means of thin layer chromatography. When the reaction had ended, the toluene was distilled off, the residue was taken up in hexane (200 ml) and the mixture was stirred vigorously for 15 minutes. The solid which had precipitated out was filtered off and washed thoroughly with hexane and the filtrate was concentrated in vacuo. Purification of the crude product was carried out by means of chromatography on silica gel (hexane). The yield was 50 g (86 %).

#### **Stage 2. 3-(Piperidin-2-yl)propionic acid ethyl ester hydrochloride**

3-(2-Pyridyl)acrylic acid ethyl ester (16.88 g) was dissolved in methanol (160 ml), PtO<sub>2</sub> (0.717 g, moistened with methanol) was added and the mixture was stirred under a hydrogen atmosphere at 80 PSI for 3 hours. The reaction was monitored by means of thin layer chromatography. When the reaction had ended, the mixture was filtered over Celite. The filtrate was concentrated in vacuo. The yield was 17 g (97 %).

#### **Stage 3. 3-(1-(4-Chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid ethyl ester**

Triethylamine (30 g) was added dropwise to a solution of 3-(piperidin-2-yl)propionic acid ethyl ester hydrochloride (30 g) in methylene chloride (210 ml) at 0 °C and the mixture was then stirred at room temperature for 10 minutes. Chloro-2,5-dimethylbenzene-1-sulfonyl chloride (32.3 g) was then added slowly and the mixture was stirred for 2 hours. The reaction was observed by means of thin layer chromatography. Because of incomplete conversion, the mixture was stirred for a further 17 hours before the reaction was ended by addition of water (200 ml). The phases were separated and the aqueous phase was extracted with MC (150 ml). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo.

Purification of the crude product was carried out by chromatography on silica gel (5 % ethyl acetate in hexane). The yield was 47.23 g (90 %).

**Stage 4. 3-(1-(4-Chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid (AC3)**

KOH (10.5 g) was added to a solution of 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid ethyl ester (33 g) in methanol/water (230 ml/100 ml) and the mixture was stirred at room temperature for 15 hours. The reaction was observed by means of thin layer chromatography. When the reaction was complete, the methanol was distilled off and the aqueous phase was extracted with ethyl acetate (2 x 75 ml). The aqueous phase was then adjusted to pH = 4 with HCl, while cooling with ice, and extracted with MC. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The yield was 30.6 g (100 %).

**Synthesis of 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid (AC4)**

The synthesis of this carboxylic acid was carried out analogously to acid unit AC3.

**Synthesis of 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC5)**

**Stage 1. 4-Methoxy-2,6-dimethylbenzene-1-sulfonyl chloride**

3,5-Dimethylanisole (102.5 g, 753 mmol) was dissolved in MC (1,000 ml) and the solution was cooled to 0 °C. Chlorosulfonic acid (251 ml, 3,763 mmol, in 250 ml of MC) was slowly added dropwise to this solution. After 10 minutes, the reaction mixture was poured on to ice (1,000 ml) and extracted with MC (1 x 250 ml). The combined organic phases were washed with water (1,000 ml) and NaCl solution (1,000 ml), dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification of the crude product was carried out by chromatography on silica gel (heptane/MC, 5:1). The yield was 63.50 g (36 %).

**Stage 2. (1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methanol**

K<sub>2</sub>CO<sub>3</sub> (20.40 g, 147.6 mmol) and 4-methoxy-2,6-dimethylbenzene-1-sulfonyl chloride (19.05 g, 81.2 mmol) were added in succession to a suspension of piperidin-2-ylmethanol (8.50 g, 73.8 mmol) in acetone (350 ml). The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated in vacuo. The crude product was employed in the next stage without further purification. The yield was 27.25 g (quantitative).

**Stage 3. tert-Butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetate**

*n*-Bu<sub>4</sub>NCl (7.52 g, 27.1 mmol) was added to a solution of (1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methanol (27.2 g, max. 73.8 mmol) in toluene/MC (150 ml/150 ml) and the mixture was cooled to 0 °C. A 35 % strength aqueous NaOH solution (300 ml) was then added. Bromoacetic acid *tert*-butyl ester (17.8 ml, 122 mmol) was then added dropwise to the reaction mixture and the mixture was stirred at room temperature for 3 hours. The organic phase was separated off, washed with water (3 x 300 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification was carried out by chromatography on silica gel (heptane/ethyl acetate 3:1). The yield was 26.8 g (85 % over 2 stages).

**Stage 4. 2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC5)**

A 6 M aqueous NaOH solution (200 ml, 1,200 mmol) was added to a solution of *tert*-butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetate (26.8 g, 62.7 mmol) in THF (200 ml) and methanol (200 ml) and the reaction was stirred at room temperature for 1 hour. The organic solvents were then distilled off and 6 M aqueous HCl (210 ml) was added to the residue at 0 °C. The aqueous phase was extracted with methylene chloride (200 ml) and ethyl acetate (200 ml). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue obtained was codistilled twice with diisopropyl ether. The yield was 21.92 g (94%).

**Synthesis of 2-(2-(4-methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetic acid (AC6)****Stage 1. N-(2-Hydroxyethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide**

Triethylamine (213 ml, 1,512.5 mmol) was added to a solution of 2-(methylamino)ethanol (53.5 ml, 665.5 mmol) in MC (1,250 ml) and the mixture was cooled to 0 °C. A solution of 4-methoxy-2,6-dimethylbenzene-1-sulfonyl chloride (142 g, 605 mmol) [see AC5, Stage 1] in MC (750 ml) was then slowly added dropwise. The reaction mixture was stirred at room temperature for 2 hours. The organic phase was then washed with aqueous 0.5 M HCl (800 ml) and water (2 x 1,000 ml). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Purification was carried out by chromatography on silica gel (heptane/ethyl acetate 1:1). The yield was 116.3 g (70 %).

**Stage 2. tert.-Butyl 2-(2-(4-methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetate**

*n*-Bu<sub>4</sub>NCl (39 g, 140.1 mmol) was added to a solution of N-(2-hydroxyethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide (116 g, 424.4 mmol) in toluene (750 ml) and the mixture was cooled to 0 °C. Aqueous 35 % strength NaOH solution (1,000 ml) was then added. Bromoacetic acid *tert*-butyl ester (93 ml, 636.6 mmol) was then added dropwise to the reaction mixture and the mixture was stirred at room temperature for 2 hours. The organic phase was separated off, washed with water (3 x 750 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification was carried out by chromatography on silica gel (heptane/ethyl acetate 4:1). The yield was 124.6 g (76 %).

**Stage 3. 2-(2-(4-Methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetic acid (AC6)**

*tert*-Butyl 2-(2-(4-methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetate (124.5 g, 321.3 mmol) was dissolved in THF (1,150 ml) and MeOH (1,900 ml), and an aqueous 6 M NaOH solution (1,300 ml) was added. The reaction mixture was stirred at room temperature for 1 hour and the organic solvents were then distilled off. The residue was taken up in aqueous 6 M HCl (2,000 ml) at 0 °C and the mixture was extracted

with methylene chloride (2 x 1,000 ml). The combined organic phases were dried, filtered and concentrated to dryness in vacuo. The yield was 103.5 g (97 %).

### **Synthesis of 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid (AC7)**

#### **Stage 1. Methyl 4-(piperidin-2-yl)butanoic acid methyl ester hydrochloride**

Hydrogen chloride in methanol 1.25 mol/l (58 ml, 72.43 mmol) was added to 4-piperidin-2-ylbutanoic acid hydrochloride (1.5 g, 7.243 mmol) and the mixture was refluxed for 6 hours, cooled to room temperature and stirred for 3 days. A thin layer chromatography control still showed educt, and the mixture was topped up with hydrogen chloride in methanol (4 ml) and refluxed for 3 hours. The reaction mixture was concentrated in vacuo and the residue was taken up in ethanol/ether 1/1 (5 ml). The solution was slowly added dropwise to ice-cooled ether (300 ml), the suspension formed was stirred in an ice-bath for 1 hour and the solid was filtered off with suction, washed with ether and dried in vacuo. The yield was 1.21 g (75 %).

#### **Stage 2. Methyl 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid methyl ester**

Methyl 4-(piperidin-2-yl)butanoic acid methyl ester hydrochloride (1.26 g, 5.683 mmol) was dissolved in methylene chloride (25 ml) and triethylamine (4 ml, 28.417 mmol) and a solution of 4-methoxy-2,6-dimethylbenzenesulfonic acid chloride (2.67 g, 11.37 mmol) [see AC5, stage 1) in methylene chloride (10 ml) was added. The mixture was stirred at room temperature overnight. 1 mol/l HCl solution (10 ml) was added to the reaction mixture, phase separation, extraction of the aqueous phase with methylene chloride (2 x 20 ml). The combined organic phases were washed with sat. sodium chloride solution (20 ml), dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) with hexane / methylene chloride / ether (400 / 100 / 50). The yield was 1.65 g (75 %).

**Stage 3. 4-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid (AC7)**

Methyl 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid methyl ester (1.65 g, 4.3 mmol) was dissolved in water (10 ml) and methanol (35 ml), and lithium hydroxide was added (0.3 g, 12.9 mmol). The mixture was stirred at room temperature for 3 days, the methanol was then distilled off in vacuo and ethyl acetate (50 ml) and HCl solution (1 mol/l, 10 ml) were added to the residue. The phases were then separated, extraction was carried out with ethyl acetate (2 x 50 ml) and the combined organic phases were dried over sodium sulfate and concentrated in vacuo. The yield was 1.56 g (98 %).

**Synthesis of 2-(2-(2-chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetic acid (AC27)****Step (i): 2-(Cyclopropylamino)ethanol**

Cyclopropylamine (5 g, 1 eq.) was dissolved in ethanol (60 ml) and 2-bromo ethanol (0.5 eq.) was added. The resulting reaction mixture was heated to 60°C for 16 h. The reaction mixture was evaporated under reduced pressure and used directly in the next step without further purification.

Yield: 70%

**Step (ii): 2-Chloro-N-cyclopropyl-N-(2-hydroxyethyl)-6-methylbenzenesulfonamide**

To 2-(cyclopropylamino)ethanol (2 eq.) was added triethylamine (2.5 eq.) and the mixture was cooled to 0°C. To this cold reaction mixture was added 2-chloro-6-methylbenzene sulfonyl chloride (1 eq.) and the mixture was allowed to stir at 25°C for 2 h. It was diluted with dichloromethane and the organic layer was washed with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was purified by column chromatography (10% ethyl acetate in hexane).

Yield: 50%

**Step (iii): tert-Butyl 2-(2-(2-chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetate**

To a cold solution of 2-chloro-N-cyclopropyl-N-(2-hydroxyethyl)-6-methylbenzenesulfonamide (1 eq.) in dichloromethane (15 ml) was added tetrabutylammonium chloride (0.1 eq.) and 35% sodium hydroxide solution (15 ml) at 0°C. tert-Butyl 2-bromoacetate (1.2 eq.) was added dropwise to this cold reaction mixture maintaining the same temperature. After addition was complete, the reaction mixture was allowed to stir at room temperature for 16 h (monitored by TLC). It was diluted with dichloromethane and the organic layer was washed with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was purified by column chromatography (20% ethyl acetate in hexane). Yield: 70%

**Step (iv): 2-(2-(2-Chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetic acid (AC27)**

To a dichloromethane (10ml/mmol) solution of tert-butyl 2-(2-(2-chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetate (1 eq.) was added trifluoroacetic acid (13 eq.) at 0°C and the resulting reaction mixture was allowed to stir at ambient temperature for 2 h. The solvent was evaporated off and the residue dried under vacuum to remove traces of trifluoroacetic acid. The crude product was used in the next step without further purification.

Yield: quantitative

**Synthesis of (S)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC28)****Step (i): (S)-Piperidin-2-ylmethanol**

(S)-Piperidine-2-carboxylic acid (2 g, 15.5 mmol) was placed in tetrahydrofuran (20 ml); boron trifluoride etherate (2.1 ml, 117.1 mmol) was added, followed by boron dimethylsulfide in tetrahydrofuran (dropwise, 3 ml, 30.9 mmol). The reaction mixture was then refluxed for 16 h. Quenching was carried out with ice-cold methanol (10 ml); hydrogen chloride solution (conc. aq., 3 ml) was added dropwise, and refluxing was carried out for 30 min. After cooling, the mixture was rendered alkaline with dilute

sodium hydroxide solution (4%) and extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The crude product was used in the next stage without being purified further.

Yield: 44%

**Step (ii): (S)-1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methanol**

(S)-Piperidin-2-ylmethanol (1.1 eq.) was dissolved in dichloromethane (4 ml/mmol) and cooled, and triethylamine (2.5 eq.) was added. A solution of 4-methoxy-2,6-dimethylbenzenesulfonyl chloride (1 eq.) in dichloromethane (2 ml/mmol) was added dropwise at 0°C, and then stirring was carried out for 90 min at room temperature. Hydrogen chloride solution (eq., 0.5 mol/l, 2 ml/mmol) was added, stirring was carried out for 15 min, and the phases were separated. The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The crude product was used in the next stage without being purified further.

Yield: 20%

**Step (iii): (S)-tert-Butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetate**

Tetra-n-butylammonium chloride (0.33 eq.) and sodium hydroxide solution (5 ml/mmol, 35%) were added at 0°C to a cooled solution of (S)-1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methanol (1 eq.) in toluene (5 ml/mmol). tert-Butyl 2-bromoacetate (1.5 eq.) was then added slowly at 0°C. After stirring for 90 min at room temperature, the phases were separated, and the organic phase was washed with water until pH neutral, dried over sodium sulfate and concentrated *in vacuo*. The crude product was used in the next stage without being purified further.

Yield: 64%

**Step (iv): (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC28)**

(S)-tert-butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetate (1 eq.) was dissolved in dichloromethane (10 ml/mmol) and cooled, and trifluoroacetic acid (13 eq.) was added slowly at 0°C. After stirring for 2 h at room

temperature, the reaction mixture was concentrated *in vacuo* and dried. The crude product was used in the next stage without being purified further.

Yield: quantitative

**Synthesis of (S)-2-((1-(2-chloro-6-methylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC29)**

Synthesis of this acid unit was carried out in analogy to (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC28) employing 2-chloro-6-methylbenzene-1-sulfonyl chloride in step (ii).

**Synthesis of (S)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetic acid (AC30)**

**Step 1: (S)-Pyrrolidin-2-ylmethanol**

A solution of (S)-pyrrolidine-2-carboxylic acid (3 g, 26.0575 mmol) in tetrahydrofuran (290 ml) was cooled to 0°C and LiAlH<sub>4</sub> (3.4 g, 91.2012 mmol) was added very slowly. The reaction was then refluxed for 2 h. TLC revealed complete consumption of the starting material. The reaction mixture was cooled to room temperature and excess LiAlH<sub>4</sub> was quenched with saturated sodium sulfate solution, diluted with ethyl acetate and filtered through a bed of Celite. The filtrate was dried over sodium sulfate, concentrated and used in next step without further purification.

Yield: 83%

**Step 2: (S)-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methanol**

To a solution of (S)-pyrrolidin-2-ylmethanol (2.2 g, 8.54 mmol) in dichloromethane (20 ml) was added triethylamine (2.9 ml, 21.36 mmol) and the mixture was cooled to 0°C. Then a solution of 4-methoxy-2,6-dimethyl-benzenesulfonyl chloride (2 g, 8.547 m.mole) in dichloromethane (10 ml) was added and the mixture was allowed to stir at room temperature for 2 h. TLC showed complete consumption of the starting material. The reaction mixture was diluted in dichloromethane and was washed with water and brine. The organic layer was dried over sodium sulfate, concentrated and purified by column chromatography.

Yield: 55%

**Step 3: (S)-tert-Butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetate**

To a solution of (S)-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methanol (2.7 g, 9.0303 mmol) in dichloromethane (45 ml) was added 35% aq NaOH solution (45 ml) followed by addition of tetra-n-butylammonium chloride (290 mg, 0.09308 mmol). The reaction mixture was allowed to stir for 15 min at room temperature. Then it was cooled to 0°C and tert-butyl 2-bromoacetate (1.7 ml, 10.83 mmol) was added and the mixture stirred for 2 h at room temperature. After completion of the reaction the organic layer was separated and washed with water and brine. The organic layer was dried over sodium sulfate and purified by column chromatography.

Yield: 81%

**Step 4: (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetic acid (AC30)**

To a solution of (S)-tert-butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetate (1 eq.) in dichloromethane (10 ml/mmol) was added trifluoroacetic acid (2 ml/mmol) at 0°C and the resulting reaction mixture was allowed to stir at 25°C for 2 h. The solvent was evaporated off and it was dried under vacuum to remove traces of trifluoroacetic acid. The crude product was used directly for the next step.

Yield: quantitative

**Synthesis of (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methoxy)acetic acid [AC31]**

**Step (i): (S)-tert-Butyl 2-(hydroxymethyl)-3,4-dihydroquinoline-1(2H)-carboxylate**  
(S)-1-(tert-Butoxycarbonyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (5 g, 18.03 mmol) was dissolved in tetrahydrofuran (40 ml) and the mixture was cooled. Boron hydride-tetrahydrofuran complex (27 ml, 1 mol/l in tetrahydrofuran) was cautiously added dropwise at 0°C and the mixture was then stirred at room temperature for 15 h. The reaction mixture was cooled again and water (8 ml) was slowly added dropwise at 0 °C. Potassium carbonate (4.21 g, 30.65 mmol) was then added and the mixture was stirred for 30 min. After phase separation the aqueous phase was extracted with diethyl ether (2 x 30 ml) and the combined organic phases were washed with

saturated sodium chloride solution (30 ml), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel) with hexane / ethyl acetate 2 / 1.

Yield: 3.98 g (83%)

**Step (ii): (S)-(1,2,3,4-Tetrahydroquinolin-2-yl)methanol hydrochloride**

Hydrogen chloride in methanol (1.25 mol/l, 60 ml) was added to (S)-tert-butyl 2-(hydroxymethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (3.98 g, 15.1 mmol) and the mixture was refluxed for 2 h. The solvent was removed *in vacuo*, the residue was taken up in ethanol (5 ml) and the mixture was cooled. Diethylether (200 ml) was added and the mixture was stirred in an ice bath for 30 min. The precipitate was filtered off with suction, washed with diethylether and dried *in vacuo*.

Yield: 2.72 g, 90%

**Step (iii): (S)-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methanol**

(a) Chlorosulfonic acid (2 eq.) in dichloromethane (0.2 ml/mmol) was added dropwise at 0°C to a solution, cooled to, of 3,5-dimethylanisole (1 eq.) in dichloromethane (1.3 ml/mmol). When the reaction was complete (TLC monitoring), ice-water was added and the organic phase was extracted with water and saturated sodium chloride solution. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The sulfonyl chloride so obtained was reacted further directly without being purified further.

Yield: 70%

(b) Pyridine (5.5 ml, 68.11 mmol) was added dropwise to a cooled solution of (S)-(1,2,3,4-tetrahydroquinolin-2-yl)methanol hydrochloride (2.72 g, 13.62 mmol) in dichloromethane (50 ml) and triethylamine (5.66 ml, 40.87 mmol) at 0 °C, followed by 4-dimethylaminopyridine (16 mg, catalytic). 4-Methoxy-2,6-dimethylbenzenesulfonyl chloride (3.836 g, 16.35 mmol, synthesis see above), dissolved in dichloromethane (35 ml), was slowly added dropwise and the mixture was then warmed to room temperature and stirred for 15 h. The reaction mixture was washed with saturated copper sulfate solution (20 ml) and saturated sodium chloride solution (20 ml), dried

over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel) with hexane / ethyl acetate 2 / 1.

Yield: 1.22 g (24%)

**Step (iv): (S)-tert-Butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methoxy)acetate**

tert-Butyl 2-bromoacetate (1.358 g, 6.972 mmol) and tetra-n-butylammonium hydrogen sulfate (110 mg, 0.332 mmol) were stirred in sodium hydroxide solution (26 ml, 50 % aq) and toluene (20 ml). A solution of (S)-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methanol (1.2 g, 3.32 mmol) in toluene (10 ml) was added slowly. The addition was exothermic, cooling was achieved with an ice bath. After stirring at room temperature for 1 h, the phases were separated and the aqueous phase was extracted with diethylether (2 x 50 ml). The combined organic phases were washed with saturated sodium chloride solution (30 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel) with hexane / ethyl acetate 5 / 1.

Yield: 1.03 g (65%)

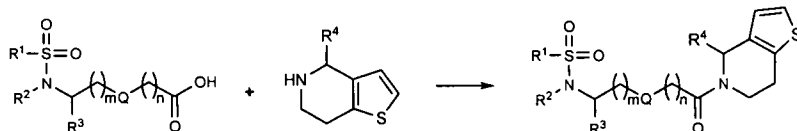
**Step (v): (S)-2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methoxy)acetic acid (AC31)**

(S)-tert-Butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)-1,2,3,4-tetrahydroquinoline-2-yl)methoxy)acetate (1 g, 2.103 mmol) was dissolved in dichloromethane (15 ml) and trifluoroacetic acid (3.24 ml, 42.05 mmol) was added slowly. After stirring at room temperature for 2 h, the solvent was removed *in vacuo* and the residue was co-evaporated twice more with 20 ml of toluene each time.

Yield: 0.84 g (95%)

2.) Synthesis of example compounds by reaction of thiophenepiperidines with carboxylic acids:

A.) Reaction of thiophenepiperidines with carboxylic acids:



**Method 1:**

The corresponding amine (1.1 eq.), HATU (1 eq.) and triethylamine (1.9 eq.) were added to a solution of the particular acid (1 eq.) in THF (5 ml) and the mixture was stirred at room temperature. The reaction was monitored by means of thin layer chromatography. When the conversion was complete, ethyl acetate (30 ml) was added to the reaction mixture and the mixture was extracted in each case twice with saturated  $\text{NH}_4\text{Cl}$  solution and saturated  $\text{NaHCO}_3$  solution. The combined organic phases were dried with  $\text{MgSO}_4$  and concentrated to dryness in vacuo. Purification is carried out by chromatography on silica gel.

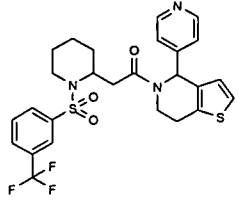
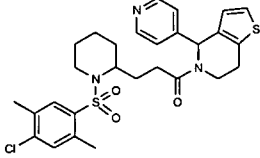
**Method 2:**

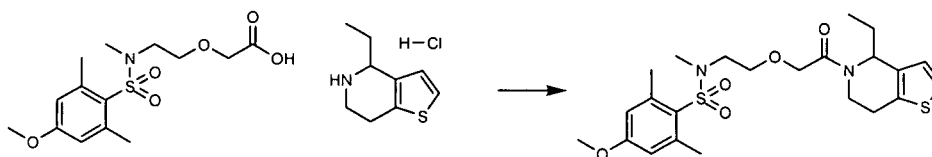
Polystyrene-bonded dicyclohexylcarbodiimide (0.68 g, 2 eq., loading 1.36 mmol/g) was initially introduced into the reaction vessel and the acid (1.5 eq.), dissolved in MC, was added. The mixture was stirred at room temperature for 5 minutes. The amine (1 eq.) was then added. The mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and washing was carried out with methylene chloride. The filtrate was concentrated to dryness in vacuo and the residue was purified by means of column chromatography on silica gel.

The example compounds listed in the following table were synthesized by Method 1 or 2.



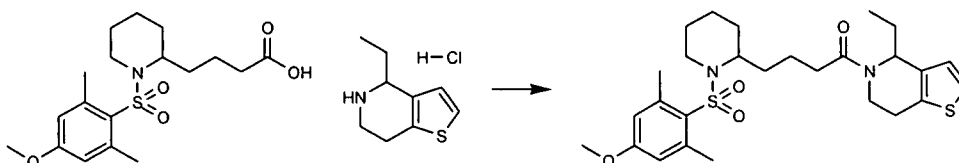
|    |  |     |     |   |                                                         |
|----|--|-----|-----|---|---------------------------------------------------------|
| 19 |  | AC2 | TP5 | 1 | MS, $R_t = 5.9$ min,<br>$m/z = 567.1$ [MH] <sup>+</sup> |
| 20 |  | AC1 | TP4 | 1 | MS, $R_t = 6.5$ min,<br>$m/z = 567.1$ [MH] <sup>+</sup> |
| 21 |  | AC1 | TP5 | 1 | MS, $R_t = 6.3$ min,<br>$m/z = 571.0$ [MH] <sup>+</sup> |
| 33 |  | AC3 | TP6 | 1 | MS, $R_t = 6.7$ min,<br>$m/z = 591.9$ [MH] <sup>+</sup> |
| 34 |  | AC3 | TP8 | 1 | MS, $R_t = 7.4$ min,<br>$m/z = 625.0$ [MH] <sup>+</sup> |
| 35 |  | AC3 | TP9 | 1 | MS, $R_t = 7.1$ min,<br>$m/z = 575.0$ [MH] <sup>+</sup> |
| 36 |  | AC5 | TP7 | 1 | MS, $R_t = 4.2$ min,<br>$m/z = 570.0$ [MH] <sup>+</sup> |

|    |                                                                                   |     |     |   |                                              |
|----|-----------------------------------------------------------------------------------|-----|-----|---|----------------------------------------------|
| 54 |  | AC2 | TP7 | 1 | MS, $R_t = 4.11$ min, $m/z = 549.2$ $[MH]^+$ |
| 55 |  | AC3 | TP7 | 1 | MS, $R_t = 4.8$ min, $m/z = 557.9$ $[MH]^+$  |

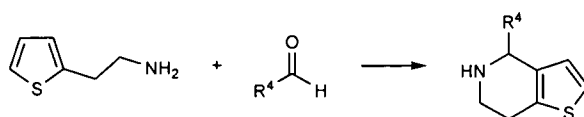
**Example 18****N-(2-(2-(4-Ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide**

2-(2-(4-Methoxy-N,2,6-trimethylphenyl)sulfonamido)ethoxy)acetic acid (AC6) (120 mg, 362  $\mu$ mol) and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (103 mg, 543  $\mu$ mol) were dissolved in MC (8 ml) under an inert gas and N-hydroxybenzotriazole (HOBt) (53 mg, 398  $\mu$ mol), 4-ethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (110 mg, 543  $\mu$ mol) and N-ethyldiisopropylamine (0.19 ml, 1.09  $\mu$ mol) were added. The resulting reaction mixture was stirred at room temperature for 3 days. It was diluted with MC (30 ml) and washed with saturated sodium bicarbonate solution. The aqueous phase was extracted with MC (2 x 30 ml) and the combined organic phases were dried ( $MgSO_4$ ) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) with ethyl acetate / hexane 200 / 10. The yield was 180 mg (100 %, white, resin).

MS,  $R_t = 5.0$  min,  $m/z = 481.1$   $[MH]^+$

**Example 23****1-(4-Ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butan-1-one**

N-Ethyl-diisopropylamine (0.21 ml, 1.218 mmol), 1-hydroxybenzotriazole hydrate (60 mg, 0.447 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (116 mg, 0.609 mmol) and 4-ethyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (123 mg, 0.609 mmol) were added to a solution of 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butanoic acid (AC7) (0.15 g, 0.406 mmol) in MC (10 ml) and the mixture was stirred at room temperature for 15 hours. Saturated sodium bicarbonate solution (20 ml) was added to the mixture and the aqueous phase was then extracted with MC (2 x 30 ml). The combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) with hexane / ethyl acetate 2 / 1. The yield was 200 mg (94 %, white, resin). MS,  $R_t = 5.6$  min,  $m/z = 519.1$   $[\text{MH}]^+$

**B.) Synthesis of the thiophenepiperidines (amines TP)****Method 1:**

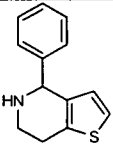
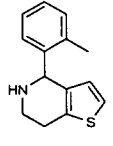
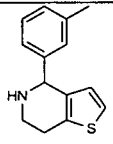
Thiophenethylamine (5 g, 39.3 mmol) was dissolved in toluene (80 ml), the aldehyde (39.3 mmol) was added, and a molecular sieve (4 Å spheres) was added. The mixture was stirred under reflux for 3 days using a water separator. The molecular sieve was then filtered off and the filtrate was concentrated in vacuo. After addition of trifluoroacetic acid (112 ml), the mixture was stirred at room temperature for a further 3

days. The reaction mixture was concentrated on a rotary evaporator, the residue was dissolved in ether (200 ml) and the solution was washed with 2 M sodium hydroxide solution (100 ml). The combined organic phases were dried with  $MgSO_4$ , filtered and concentrated. The purity of the compounds obtained was checked by means of NMR and recrystallization was carried out if appropriate.

**Method 2:**

Thiophenethylamine (39.3 mmol) was dissolved in ethanol (41 ml), and triethylamine (2.4 ml) and the aldehyde (39.3 mmol) were added. The mixture was stirred at room temperature for 15 hours. The reaction mixture was then concentrated in vacuo and trifluoroacetic acid (100 ml) was cautiously added to the residue. The mixture was stirred at room temperature for a further 3 days. The reaction mixture was then concentrated in vacuo. The residue was dissolved in ether (200 ml) and the solution was washed with 2 M sodium hydroxide solution (100 ml). The combined organic phases were dried over  $MgSO_4$ , filtered and concentrated. Purification was carried out by chromatography on silica gel. The purity of the products obtained was checked by means of NMR.

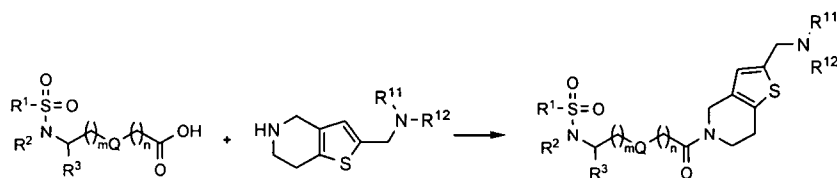
The thiophenepiperidines listed in the following table were synthesized by Method 1 or 2.

| Amine no. | Name                                              | Structure                                                                             | Method |
|-----------|---------------------------------------------------|---------------------------------------------------------------------------------------|--------|
| TP1       | 4-Phenyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine  |  | 2      |
| TP2       | 4-o-Tolyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine |  | 1      |
| TP3       | 4-m-Tolyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine |  | 2      |

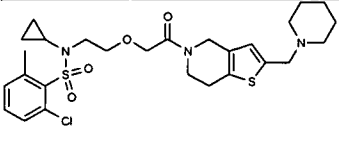
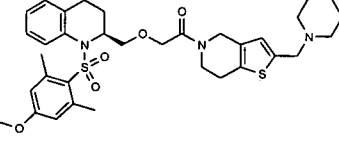
|     |                                                                       |  |   |
|-----|-----------------------------------------------------------------------|--|---|
| TP4 | 4-p-Tolyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine                     |  | 1 |
| TP5 | 4-(4-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine            |  | 1 |
| TP6 | 4-(6-Chloropyridin-3-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine      |  | 2 |
| TP7 | 4-(Pyridin-4-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine              |  | 2 |
| TP8 | 4-(3-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine |  | 1 |
| TP9 | 4-(3-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine            |  | 1 |

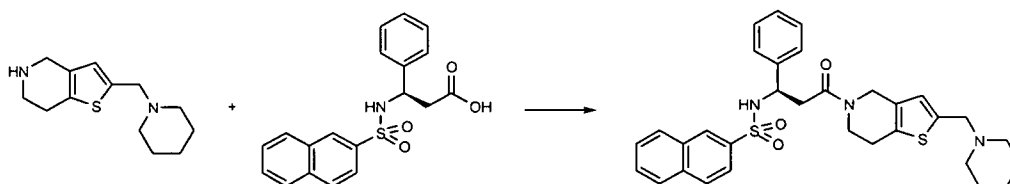
3.) Synthesis of example compounds by reaction of aminomethylated thiophenepiperidines with carboxylic acids:

A.) Reaction of aminomethylated thiophenepiperidines with carboxylic acids:



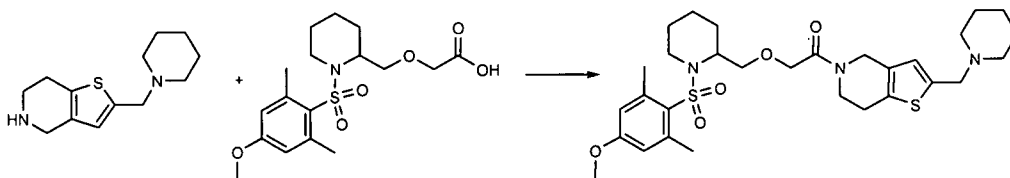


|    |                                                                                   |      |      |    |                                             |
|----|-----------------------------------------------------------------------------------|------|------|----|---------------------------------------------|
| 60 |  | AC27 | TP10 | 34 | MS, $R_t = 3.4$ min, $m/z = 566.1$ $[MH]^+$ |
| 61 |  | AC31 | TP10 | 38 | MS, $R_t = 3.8$ min, $m/z = 638.2$ $[MH]^+$ |

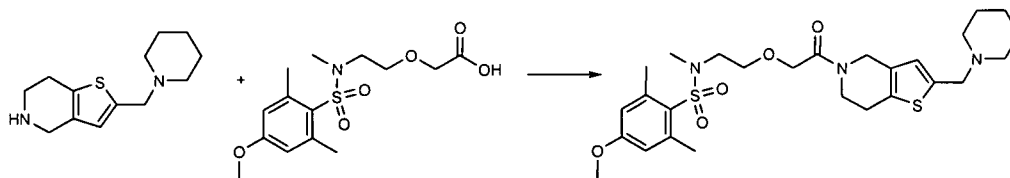
**Example 26****(R)-N-(3-Oxo-1-phenyl-3-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide**

Diisopropylethylamine (0.78 ml, 4.44 mmol) was added to a solution of (3R)-naphthalene-2-sulfonamido-3-phenylpropionic acid (AC1) (174 mg, 0.49 mmol) in MC (1.5 ml) and the mixture was cooled to 0 °C. HATU (186 mg, 0.49 mmol) and 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10) (105 mg, max. 0.42 mmol) were then added. The mixture was stirred at room temperature for 18 hours and then washed with  $\text{NaHCO}_3$  solution. The aqueous phase was extracted with methylene chloride (2 x 10 ml) and the combined organic phases were dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. Purification was carried out by chromatography on silica gel (MC/(7 M  $\text{NH}_3$  in MeOH), gradient 1.0 after 2.2% (7 M  $\text{NH}_3$  in MeOH)). The yield was 121 mg (50 % over 3 stages).

MS,  $R_t = 3.3$  min,  $m/z = 574.2$   $[MH]^+$

**Example 27****2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone**

2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC5) (396 mg, 1.07 mmol), diisopropylethylamine (372  $\mu$ l, 2.13 mmol), HOAt (15 mg, 107  $\mu$ mol) and EDCI (306 mg, 1.60 mmol) were added to a solution of 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10) (277 mg, max. 425  $\mu$ m) in MC (25 ml) and the mixture was stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo and the residue obtained was purified by chromatography on silica gel (MC/(7 M  $\text{NH}_3$  in MeOH), 99:1). The product fractions were combined and evaporated to dryness. The residue was dissolved in dry acetonitrile (5 ml), the solution was dried by means of freeze drying and the solid was then dissolved in MC (10 ml). Solid  $\text{NaHCO}_3$  (approx. 500 mg) was added to this solution and the mixture was stirred for 1 hour. The mixture was then filtered and the filtrate was concentrated in vacuo. The yield was 88 mg (35 % over 2 stages). MS,  $R_t$  = 3.6 min,  $m/z$  = 590.2  $[\text{MH}]^+$

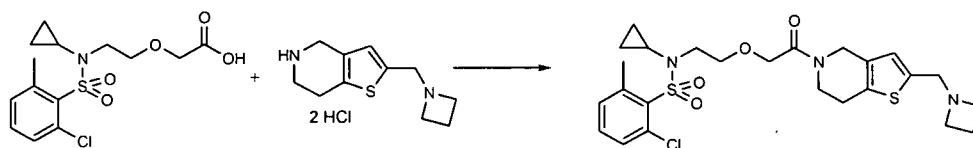
**Example 28****4-Methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide**

2-(2-(4-Methoxy-N,2,6-trimethylphenylsulfonamido)ethoxy)acetic acid (AC6) (353 mg, 1.06 mmol), diisopropylethylamine (372  $\mu$ l, 2.13 mmol), HOAt (15 mg, 107  $\mu$ mol) and EDCI (306 mg, 1.60 mmol) were added to a solution of 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10) (277 mg, max. 425  $\mu$ m) in MC (25 ml) and the mixture was stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo and the residue obtained was purified by chromatography on silica gel (MC/(7 M NH<sub>3</sub> in MeOH), 98:2 and 99:1). The product fractions were combined and evaporated to dryness. The residue was dissolved in dry acetonitrile (5 ml), the solution was dried by means of freeze drying and the solid was then dissolved in methylene chloride (10 ml). Solid NaHCO<sub>3</sub> (approx. 500 mg) was added to this solution and the mixture was stirred for 1 hour. The mixture was then filtered and the filtrate was concentrated in vacuo. The yield was 105 mg (45 % over 2 stages).

MS, R<sub>t</sub> = 3.0 min, m/z = 550.1 [MH]<sup>+</sup>

#### Example 56

**N-[2-[2-[2-(Azetidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-2-chloro-N-cyclopropyl-6-methyl-benzenesulfonic acid amide**



2-(2-(2-Chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetic acid (AC27) (100 mg, 0.288 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (92 mg, 0.288 mmol) and 1-hydroxybenzotriazole hydrate (40 mg, 0.288 mmol) were dissolved in tetrahydrofuran (3.5 ml) and the mixture was stirred at room temperature for 30 min. A solution of 2-(azetidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine dihydrochloride (TP13) (97 mg, 0.346 mmol) and N-ethyl-diisopropylamine (146  $\mu$ l, 0.864 mmol) in tetrahydrofuran (3.5 ml) was added and the mixture was stirred at room temperature overnight. The solvent was removed *in*

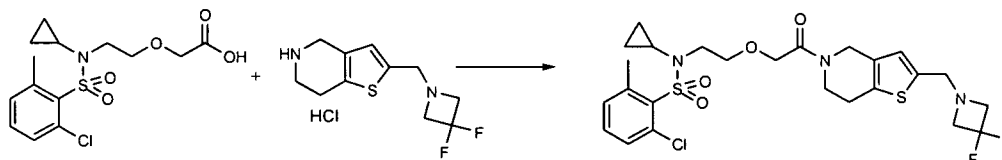
*vacuo*, the residue was dissolved in ethyl acetate and saturated sodium hydrogen carbonate solution and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x) and the combined organic layers were washed with saturated sodium chloride solution (1 x), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (silica) with ethyl acetate / methanol 5 / 1.

Yield: 100 mg (64 %)

MS,  $R_t = 3.1$  min,  $m/z = 538.2$  [MH]<sup>+</sup>

### Example 57

**2-Chloro-N-cyclopropyl-N-[2-[2-[2-[(3,3-difluoro-azetid-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-6-methyl-benzenesulfonic acid amide**



2-(2-(2-Chloro-N-cyclopropyl-6-methylphenylsulfonamido)ethoxy)acetic acid (AC27) (120 mg, 0.345 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (110 mg, 0.345 mmol) and 1-hydroxybenzotriazole hydrate (48 mg, 0.345 mmol) were dissolved in tetrahydrofuran (4 ml) and the mixture was stirred at room temperature for 30 min. A solution of 2-((3,3-difluoroazetid-1-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (TP14) (116 mg, 0.414 mmol) and N-ethyl-diisopropylamine (175  $\mu$ l, 1.035 mmol) in tetrahydrofuran (4 ml) was added and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and saturated sodium hydrogen carbonate solution and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x) and the combined organic layers were washed with saturated

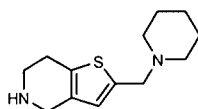
sodium chloride solution (1 x), dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (silica) with ethyl acetate / hexane 2 / 1.

Yield: 130 mg (66 %)

MS,  $R_t = 3.8$  min,  $m/z = 574.2$  [MH]<sup>+</sup>

B.) Synthesis of the aminomethylated thiophenepiperidines (amines TP):

**Synthesis of 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10)**



**Stage 1. tert-Butyl 2-(methoxy(methyl)carbamoyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

5-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (968 mg, 3.42 mmol) and N,O-dimethylhydroxylamine hydrochloride (333 mg, 3.42 mmol) were dissolved in MC (50 ml) and the solution was cooled to 0 °C. HOAt (46.5 mg, 0.34 mmol), diisopropylethylamine (0.66 ml, 3.76 mmol) and EDCI (720 mg, 3.76 mmol) were added to this mixture and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride (50 ml) and washed with 0.5 M KHSO<sub>4</sub> solution (100 ml), NaHCO<sub>3</sub> solution and NaCl solution. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The product obtained in this way (1.13 g) was employed in the next stage without further purification.

**Stage 2. 5-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carbaldehyde**

The crude product of the precursor (1.04 g, 3.18 mmol) was dissolved in dry THF (30 ml) and the solution was cooled to -78 °C under a nitrogen atmosphere. LiAlH<sub>4</sub>

(1 M in THF, 3.18 ml, 3.18 mmol) was added dropwise to this solution and the mixture was stirred at this temperature for 2 hours.  $\text{Na}_2\text{SO}_4 \cdot 10 \text{ x H}_2\text{O}$  was then added until no further evolution of gas was to be observed, and the mixture was stirred for a further 24 hours. The solids were then filtered off and the residue was washed thoroughly with methylene chloride. The filtrate was concentrated in vacuo and the residue was purified by means of chromatography on silica gel (heptane/ethyl acetate, gradient 80:20 to 65:35). The yield was 580 mg (68 %).

**Stage 3. tert-Butyl 2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

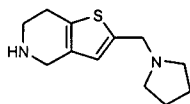
5-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carbaldehyde (440 mg, 1.65 mmol) and piperidine (0.18 ml, 1.81 mmol) were dissolved in THF (10 ml), and  $\text{NaBH}(\text{OAc})_3$  (523 mg, 2.47 mmol) and glacial acetic acid (94  $\mu\text{l}$ , 1.65 mmol) were added. This mixture was stirred under a nitrogen atmosphere at room temperature for 24 hours. The solvent was then distilled off in vacuo and the residue was taken up in ethyl acetate (25 ml). The solution obtained was washed with  $\text{NaHCO}_3$  solution and  $\text{NaCl}$  solution and the combined organic phases were dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The crude product (580 mg) was employed directly in the next stage without further purification.

**Stage 4. 2-(Piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10)**

The resulting crude product of the precursor (147 mg, max. 0.42 mmol) was dissolved in methylene chloride (6 ml), trifluoroacetic acid (1.68 ml, 21.84 mmol) was added and the mixture was stirred at room temperature for 4 hours. The mixture was then concentrated to dryness in vacuo and codistilled again with methylene chloride. The product obtained in this way was employed directly in the next stage.

[The synthesis of 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP10) may also be accomplished in analogy to 2-(pyrrolidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine TP11.]

### Synthesis of 2-(Pyrrolidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP11)



#### Step-1: Ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate

$\text{POCl}_3$  (2.18 g, 23.4 mmol) was added very slowly to dry DMF (2.7 ml) at  $0^\circ\text{C}$  and the resulting mixture was allowed to stir at  $25^\circ\text{C}$  for 15 min. The reaction mixture was again cooled to  $0^\circ\text{C}$ , and N-ethoxycarbonyl piperidone (11.7 mmol) was added. The resulting reaction mixture was allowed to stir at  $25^\circ\text{C}$  for 3 h. It was then stirred with sodium acetate (7 g) and water (8.5 ml) and extracted with benzene. The organic layer was successively washed with water, sodium hydrogencarbonate an brine and was finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product, which was used directly in the next step without further purification.

Yield: 63%

#### Step-2: Diethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate

To a solution of ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (7.4 mmol) in pyridine (3 ml) was added triethylamine (9.62 mmol) at  $0^\circ\text{C}$  and the resulting reaction mixture was allowed to stir at  $25^\circ\text{C}$  for 3 h. 50% aqueous KOH solution (5 ml) was then added and the mixture stirred at the same temperature for 3 h. It was diluted with ethyl acetate and the organic layer was washed with water and brine. After drying over sodium sulfate the organic layer was evaporated under reduced pressure to give the crude product which was purified by column chromatography (50% ethyl acetate in hexane).

Yield : 25%

**Step-3: 4,5,6,7-Tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid hydrochloride**

Diethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate (1.76 mmol) in 3.5 N KOH solution (3 ml) was refluxed for 3 h (monitored by TLC). The reaction mixture was cooled to 0°C and acidified with conc. HCl. The solid was collected by filtration and dried to give the desired product.

Yield : 30%

**Step-4 and Step-5: 5-tert-Butyl 2-methyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate**

To a suspension of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid hydrochloride (1.9 mmol) in methanol (10 ml) was added thionyl chloride (1.5 eq.) at 0°C and the resulting reaction mixture was refluxed for 16 h. The solvent was completely evaporated off and the residue dissolved in dichloromethane (10 ml) and cooled to 0°C. To this cold mixture were added triethylamine (3 eq.) and Boc-anhydride (1.2 eqv) and the resulting reaction mixture was allowed to stir at 25°C for 12 h. The mixture was diluted with dichloromethane and successively washed with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was purified by column chromatography (10% ethyl acetate in hexane).

Yield : 50%

**Step-6: tert-Butyl 2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

To a solution of 5-tert-butyl 2-methyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate (1.5 g, 5.3 mmol) in dry toluene (30 ml) was added DIBAL (1M, 11.1 mmol) at -78°C and the reaction mixture was allowed to stir at this temperature for 1.5 h (monitored by TLC). The reaction was quenched with methanol (12 ml) and slowly brought to 25°C. Brine (25 ml) was added and it was filtered through a bed of Celite. The residue was washed with ethyl acetate and the combined organic layers were evaporated to give the crude aldehyde, which was used directly in the next step without further purification.

Yield: 1.4 g

**Step-7: tert-Butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

To a dichloromethane solution (22 ml) of tert-butyl 2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (5.3 mmol) was added triethylamine (21.2 mmol) and methane sulfonyl chloride (7.95 mmol) at 0°C and the resulting reaction mixture was allowed to stir at same temperature for 2 h (monitored by TLC). The reaction was diluted with dichloromethane, successively washed with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was used directly in the next step. Yield: quantitative

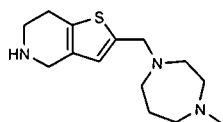
**Step-8: tert-Butyl 2-(pyrrolidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

To a toluene solution (30 ml) of tert-butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (5.3 mmol) was added potassium carbonate (26.5 mmol) and pyrrolidine (6.36 mmol) and the resulting reaction mixture was refluxed for 16 h. It was cooled to 25°C, diluted with ethyl acetate and the organic layer was successively washed with water and brine. After drying over sodium sulfate, the organic layer was evaporated under reduced pressure to give the crude product which was purified by column chromatography (5% methanol in dichloromethane). Yield: 35%

**Step-9: 2-(Pyrrolidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP11)**

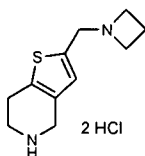
tert-Butyl 2-(pyrrolidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (0.235 mmol) was dissolved in dichloromethane and cooled to 0°C. Trifluoroacetic acid (2 ml/mmol) was added and the reaction mixture stirred for 2 h. The solvent was completely evaporated and kept under the high vacuum to give the desired product which was used in the next step without further purification. Yield: quantitative

**Synthesis of 2-((4-methyl-1,4-diazepan-1-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP12)**



The preparation of this amine was carried out in analogy to that described for 2-(pyrrolidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (TP11) employing 1-methyl-1,4-diazepane in step-8.

### Synthesis of 2-(azetidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine dihydrochloride (TP13)



#### Step-1: Piperidin-4-one hydrochloride

Methanolic HCl (50 ml) was added dropwise to a solution of N-Boc-4-piperidone (5 g) in dichloromethane (50 ml) over 5–10 min and the reaction mixture was allowed to stir for 2–2.5 h at room temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). Upon completion of the reaction the reaction contents were concentrated under reduced pressure and the residue obtained was directly used for the next step.

Yield: 4.4 g

#### Step-2: Benzyl 4-oxopiperidine-1-carboxylate

To a solution of piperidin-4-one hydrochloride (32 g, 0.23 mol) in tetrahydrofuran (320 ml, 10 x) was added  $K_2CO_3$  (64.2 g) dissolved in water (160 ml) at room temperature. The mixture was cooled to 0–5°C and then Cbz chloride (50%) (74.28 ml, 1.1 eq.) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir for 1–2 h. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). Upon disappearance of the starting material the mixture was filtered

and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 300 ml) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica, 12% ethyl acetate/hexane).

Yield: 40.7 g (74%)

**Step-3: Benzyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate**

POCl<sub>3</sub> (26.35 g, 16.06 ml, 1.6 eq.) was added dropwise to DMF (16.4 ml, 2 eq.) at 0–5°C. To the mixture was added dichloromethane (50 ml) in a dropwise fashion and it was stirred for 2 h at room temperature. A solution of benzyl 4-oxopiperidine-1-carboxylate (25 g, 0.10 mol) in dichloromethane (200 ml) was added dropwise to the mixture and it was allowed to stir for 2 h at room temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). Upon completion of the reaction the mixture was poured into crushed ice and basified to a pH~8 with sodium carbonate. Then the dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (2 × 200 ml). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and the crude product obtained was purified by column chromatography (silica, 8% ethyl acetate/hexane).

Yield: 14.5 g (48%)

**Step-4: 5-Benzyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate**

To a solution of Benzyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (14.5 g, 0.05 mol) in dichloromethane (145 ml, 10 x) was added ethyl mercapto acetate (9.3 g, 8.56 ml, 1.09 mol, 1.5 eq.) followed by triethylamine (10.4 g, 14.35 ml, 0.73 mol, 2 eq.) dropwise at 0°C. The reaction mixture was warmed to room temperature and allowed stir for 4 h. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). On completion of the reaction the mixture was diluted with water. Then the dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (2 × 150 ml). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure and the crude product obtained was purified by column chromatography (silica, 12% ethyl acetate/hexane).

Yield: 9.12 g (51%)

**Step-5: 5-tert-Butyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate**

To 10% Pd/C (2 g) in ethanol (100 ml) was added 5-benzyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate (12.5 g, 0.03 mol) dissolved in ethanol (400 ml). Then, Boc-anhydride (12.4 ml, 1.5 eq.) followed by triethylamine (7.5 ml, 1.5 eq.) were added slowly and the reaction mixture was hydrogenated for 13–14 h at 90 psi. Progress of the reaction was monitored by TLC (20% ethyl acetate/hexane). As the starting material had not been completely consumed, stirring was continued for another 14 h and the progress checked by TLC. Starting material was still present but hydrogenation was stopped and the reaction mixture filtered over a bed of celite. The filtration bed was washed with ethanol (200 ml) and the filtrate was concentrated under reduced pressure. The crude product obtained was purified by column chromatography (silica, 10% ethyl acetate/hexane).

Yield: 2.5 g (22%)

(Note : 7 g of starting material were recovered.)

**Step-6: tert-Butyl 6,7-dihydro-2-(hydroxymethyl)thieno[3,2-c]pyridine-5(4H)-carboxylate**

Tetrahydrofuran (10 ml) was added dropwise to lithium aluminium hydride (0.46 g, 2 eq.) at 0°C and the mixture was stirred for 10–15 min at the same temperature. Then a solution of 5-tert-butyl 2-ethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate (2 g, 0.006 mol) in tetrahydrofuran (10 ml) was added dropwise to the mixture at 0°C and the resulting reaction mixture was stirred for 1–2 h at the same temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). Upon completion of the reaction the reaction mixture was poured into ice water and quenched with saturated sodium sulfate solution at 0°C. The mixture was filtered over a bed of Celite and the filtrate was extracted with ethyl acetate (2 × 150 ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to yield the crude product as a pale yellow colored liquid. The crude product obtained was directly employed in the next step.

Yield: 1.6 g (92%)

**Step-7: tert-Butyl 2-formyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

To a solution of tert-butyl 6,7-dihydro-2-(hydroxymethyl)thieno[3,2-c]pyridine-5(4H)-carboxylate (1.6 g, 0.006 mol) in dichloromethane (18 ml), sodium hydrogen carbonate (1.06 g) dissolved in water was added and the resulting mixture was cooled to 0°C. Then a catalytic amount of TEMPO followed by NaOCl (18 ml, 10 x) were added at 0°C and the reaction mixture was allowed to stir for 1–2 h at room temperature. Progress of the reaction was monitored by TLC (30% ethyl acetate/hexane). Upon completion of the reaction, the reaction mixture were diluted with water (20 ml) and dichloromethane (20 ml). Then the dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane. The combined extract was dried over sodium sulfate, concentrated under reduced pressure and the crude so obtained was purified by column chromatography (silica, 7% ethyl acetate/hexane) to yield the titled compound as a pale yellow solid.

Yield: 1.1 g (70%)

**Step-8: tert-Butyl 2-(azetidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

tert-Butyl 2-formyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (0.3 g, 0.122 mmol) and azetidine (96 mg, 1.683 mmol) were dissolved in 1,2-dichloroethane (7 ml) and stirred at room temperature for 10 min. Sodium triacetoxyborohydride (0.331 g, 1.571 mmol) was added and the resulting mixture stirred at room temperature for 48 h. Saturated sodium hydrogen carbonate solution was added and the phases were separated. The aqueous phase was extracted with diethylether (3 x) and the organics were washed with saturated sodium chloride solution (1 x). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate / methanol, 10:1).

Yield: 0.28 g (81%)

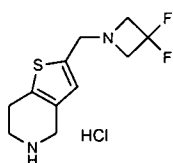
**Step-9: 2-(Azetidin-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine dihydrochloride (TP13)**

tert-Butyl 2-(azetidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (0.28 g, 0.908 mmol) was dissolved in methanol (1 ml) and HCl in methanol (1.25 M, 3.63 ml, 4.54 mmol) was added. The reaction mixture was heated at reflux for 1 h.

After cooling to room temperature the solvent was removed *in vacuo*. The crude product was re-dissolved in ethanol, diethylether was added and the mixture was stirred at 0°C for 20 min. The solid was collected by filtration, washed with diethylether and dried *in vacuo*.

Yield: 0.2 g (78%)

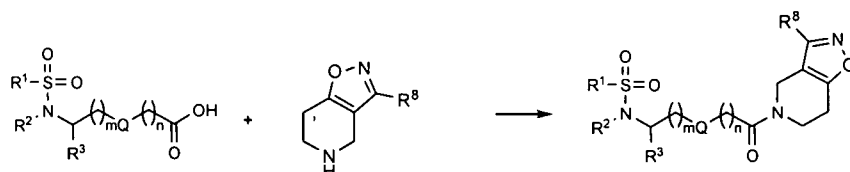
#### Synthesis of 2-((3,3-difluoroazetid-1-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (TP14)



The synthesis of 2-((3,3-difluoroazetid-1-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (TP14) was carried out in analogy to the synthesis of 2-(Azetid-1-ylmethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine dihydrochloride (TP13) employing 3,3-difluoroazetidine hydrochloride plus 3 eq. of triethylamine instead of azetidine in Step-7.

#### 4.) Synthesis of example compounds by reaction of isoxazole derivatives with carboxylic acids:

##### A.) Reaction of isoxazole derivatives with carboxylic acids:

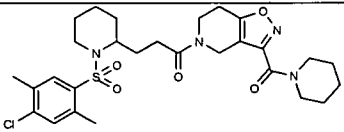
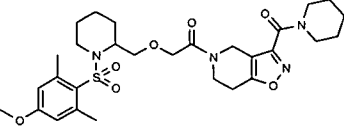
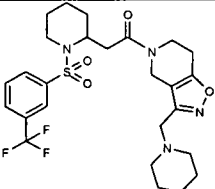


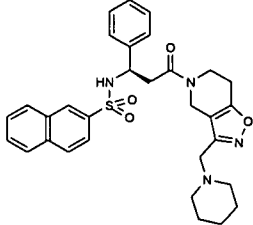
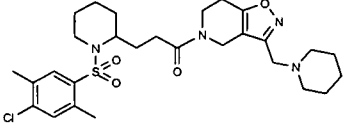
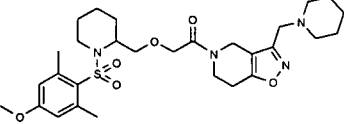
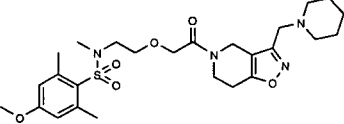
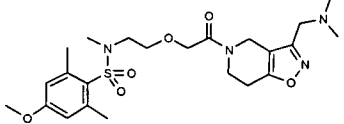
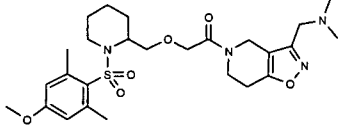
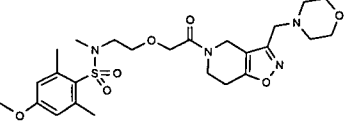
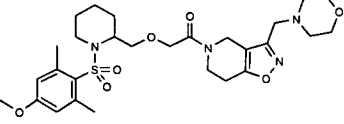
## Method A

### General synthesis instructions:

A solution of 1,1'-carbonyldiimidazole (0.209 g, 1.29 mmol) and the particular acid (1.23 mmol) in MC (15 ml) was stirred at room temperature for 1 hour. A solution of triethylamine (2.46 mmol) and amine (isoxazole derivative) (1.23 mmol) in MC was stirred in a second flask for 30 minutes and then added to the acid. The reaction mixture was stirred at room temperature for 16 hours and then diluted with methylene chloride and washed with NaHCO<sub>3</sub> solution and NaCl solution. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Purification was carried out by chromatography on silica gel.

The example compounds listed in the following table were prepared from the corresponding carboxylic acids and amines (isoxazole derivatives) in accordance with the general working instructions.

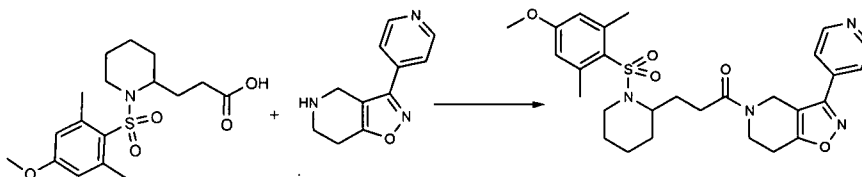
| Ex. no. | Structure                                                                           | Acid | Amine | HPLC-MS                                                     |
|---------|-------------------------------------------------------------------------------------|------|-------|-------------------------------------------------------------|
| 04      |  | AC3  | AM4   | MS, R <sub>t</sub> = 5.4 min, m/z = 577.3 [MH] <sup>+</sup> |
| 14      |  | AC5  | AM4   | MS, R <sub>t</sub> = 4.9 min, m/z = 589.3 [MH] <sup>+</sup> |
| 05      |  | AC2  | AM2   | MS, R <sub>t</sub> = 2.8 min, m/z = 555.3 [MH] <sup>+</sup> |

|    |                                                                                     |     |     |                                                      |
|----|-------------------------------------------------------------------------------------|-----|-----|------------------------------------------------------|
| 17 |    | AC1 | AM2 | MS, $R_t = 3.2$ min, $m/z = 559.2$ [MH] <sup>+</sup> |
| 06 |    | AC3 | AM2 | MS, $R_t = 3.3$ min, $m/z = 563.3$ [MH] <sup>+</sup> |
| 09 |    | AC5 | AM2 | MS, $R_t = 2.9$ min, $m/z = 575.3$ [MH] <sup>+</sup> |
| 13 |    | AC6 | AM2 | MS, $R_t = 2.8$ min, $m/z = 535.2$ [MH] <sup>+</sup> |
| 32 |   | AC6 | AM1 | MS, $R_t = 2.3$ min, $m/z = 495.1$ [MH] <sup>+</sup> |
| 31 |  | AC5 | AM1 | MS, $R_t = 3.0$ min, $m/z = 535.1$ [MH] <sup>+</sup> |
| 30 |  | AC6 | AM3 | MS, $R_t = 2.9$ min, $m/z = 537.1$ [MH] <sup>+</sup> |
| 29 |  | AC5 | AM3 | MS, $R_t = 3.4$ min, $m/z = 577.1$ [MH] <sup>+</sup> |

## Method B

### Example 01

#### 3-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one



3-(1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)propionic acid (AC4) (0.15 g, 0.42 mmol) was dissolved in MC (5 ml) and 1,1'-carbonyldiimidazole (72 mg, 0.44 mmol) was added. After the mixture had been stirred at room temperature for 1 hour, 3-(pyridin-4-yl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM5) (84 mg, 0.42 mmol) in MC (5 ml) was added and the mixture was stirred at room temperature for 3 days. Saturated sodium bicarbonate solution (10 ml) was added to the reaction mixture, the aqueous phase was extracted with MC (3 x 30 ml) and the combined organic phases were washed with saturated sodium chloride solution, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) with ethyl acetate / hexane 10 / 1. The yield was 0.18 g (79 %, white, finely crystalline).

MS,  $R_t = 4.0$  min,  $m/z = 539.3$   $[\text{MH}]^+$

The example compounds listed in the following table were prepared from 3-(pyridin-4-yl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM5) by reaction of the corresponding acid units analogously to the process described for Example 01.

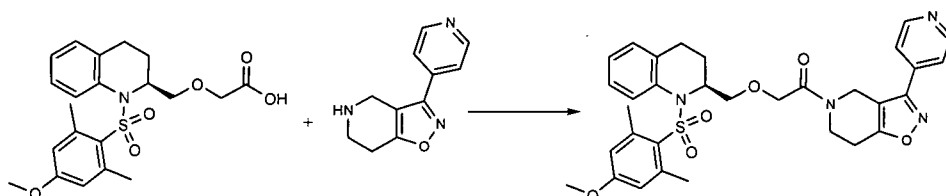
| Example no. | Structure | Acid                                                                                  | Yield (%) | HPLC-MS                                              |
|-------------|-----------|---------------------------------------------------------------------------------------|-----------|------------------------------------------------------|
| 02          |           | 2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)-piperidin-2-yl)methoxy)acetic acid (AC5) | 7.1       | MS, $R_t = 3.9$ min, $m/z = 555.3$ [MH] <sup>+</sup> |
| 03          |           | (R)-3-(Naphthalene-2-sulfonamide)-3-phenylpropionic acid (AC1)                        | 70        | MS, $R_t = 3.8$ min, $m/z = 539.2$ [MH] <sup>+</sup> |

The example compounds listed in the following table were prepared from 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid AC5 by reaction with the corresponding amines analogously to the process described for Example 01.

| Example no. | Structure | Amine                                                         | Yield (%) | HPLC-MS                                              |
|-------------|-----------|---------------------------------------------------------------|-----------|------------------------------------------------------|
| 24          |           | 3-(4-Chlorophenyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine | 71        | MS, $R_t = 6.0$ min, $m/z = 588.1$ [MH] <sup>+</sup> |
| 25          |           | 3-(4-Fluorophenyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine | 82        | MS, $R_t = 5.7$ min, $m/z = 572.1$ [MH] <sup>+</sup> |

## Example 125

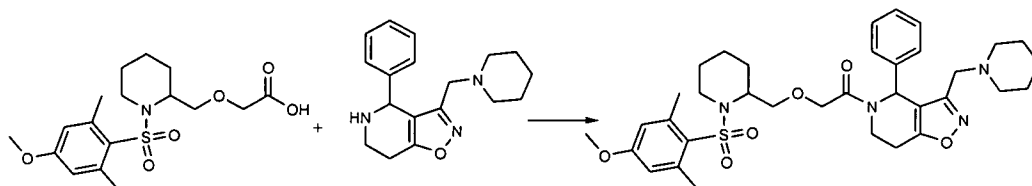
**2-[[[(2S)-1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-(3-pyridin-4-yl-4,5,6,7-tetrahydro-isoxazolo[4,5-c]pyridin-5-yl)-ethanone**



(S)-2-((1-(4-Methoxy-2,6-dimethylphenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-2-yl)methoxyacetic acid (AC31) (0.13 g, 0.31 mmol) was dissolved in dichloromethane (4 ml) and 1,1'-carbonyldiimidazole (53 mg, 0.325 mmol) was added. After the mixture had been stirred at room temperature for 1 h, 3-(pyridin-4-yl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM5) (62 mg, 0.31 mmol) in dichloromethane (4 ml) was added and the mixture was stirred at room temperature overnight. Saturated sodium hydrogen carbonate solution was added to the reaction mixture, the aqueous phase was extracted with dichloromethane (2 x) and the combined organic phases were washed with saturated sodium chloride solution, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica) with ethyl acetate / hexane 20 / 1.

Yield: 0.13 g (77 %)

MS,  $R_t = 4.8$  min,  $m/z = 603.1$   $[\text{MH}]^+$

**Example 126****2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-phenyl-3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone**

To a solution of 2-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)acetic acid (AC5) (0.673 mmol, 1.0 eq.) in dichloromethane (10 ml/mmol) was added di-isopropyl ethylamine (5.0 eq.) at 0°C followed by the addition of HOBT (1.0 eq.) and EDCI (1.5 eq.). The resultant solution was allowed to stir at room temperature for 15 min. It was again cool to 0°C and 4-phenyl-3-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM7) (1.0 eq.), dissolved in dichloromethane (1 ml/mmol), was added. The reaction mixture was allowed to stir at room temperature for 24 h. The mixture was diluted with dichloromethane, washed with saturated ammonium chloride solution, brine, saturated sodium bicarbonate and finally again with brine. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure to give the crude product which was purified by column chromatography (neutral alumina).

Yield: 35%

MS,  $R_t = 3.7$  min,  $m/z = 651.5$  [MH]<sup>+</sup>

**B.) Synthesis of the isoxazole derivatives (amines AM):****Synthesis of the amines AM1 to AM3****Stage 1. tert-Butyl 4-(pyrrolidin-1-yl)-5,6-dihydropyridine-1(2H)-carboxylate**

Catalytic amounts of p-toluenesulfonic acid (0.47 g, 0.27 mmol) were added to a solution of N-Boc-4-piperidone (5 g, 25.12 mmol) and pyrrolidine (1.96 g, 27.63 mmol) in toluene (100 ml) and the mixture was stirred under reflux for 2 hours, using a water

separator. The solution formed was concentrated to dryness in vacuo and the residue obtained was employed directly in the next stage.

**Stage 2. 5-tert-Butyl 3-ethyl 7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridine-3,5(6H)-dicarboxylate**

The crude product of the preceding stage was dissolved in methylene chloride (50 ml) and a solution of 2-chlorohydroxyiminoacetic acid ethyl ester (5.3 g, 35.17 mmol) followed by triethylamine (4.8 ml, 35.17 mmol) were added with vigorous stirring. The reaction was stirred at room temperature for 16 hours and ended by addition of 10 % strength citric acid. The mixture was extracted with methylene chloride and the organic phases were washed with NaHCO<sub>3</sub> solution and NaCl solution, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification of the crude product was carried out by chromatography on silica gel (100-200 mesh silica gel, 8 % acetone in hexane). The yield was 60 %.

**Stage 3. Ethyl 4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylate**

Trifluoroacetic acid (6.67 ml, 89.9 mmol) was added to a solution of 5-tert-Butyl 3-ethyl 7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridine-3,5(6H)-dicarboxylate (5.5 g, 14.98 mmol) in MC (100 ml) at 0 °C and the mixture was stirred under reflux for 16 hours. Thereafter, the mixture was cooled to 0 °C and NaHCO<sub>3</sub> solution was added. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product obtained was employed directly in the next stage without further purification.

*[The regiochemistry was assigned by NMR experiments.]*

**Stage 4. 5-tert-Butyl 3-ethyl 6,7-dihydroisoxazolo[4,5-c]pyridine-3,5(4H)-dicarboxylate**

Triethylamine (2.8 ml, 20.45 mmol) and Boc anhydride (3.5 ml, 16.36 mmol) were added to a solution of ethyl 5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylate (2.7 g, 13.63 mmol) in MC (50 ml) at 0 °C and the mixture was stirred at room temperature for 3 hours. Water was then added and the mixture was extracted with MC. The combined organic phases were washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and

concentrated in vacuo. The crude product was purified by means of chromatography on silica gel (100-200 silica gel, 10 % ethyl acetate in hexane). The crude yield was 80 %.

**Stage 5. 5-(tert-Butoxycarbonyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylic acid**

An aqueous lithium hydroxide solution (0.54 g, 12.88 mol in 12.8 ml) was added dropwise to a solution of 5-tert-butyl 3-ethyl 6,7-dihydroisoxazolo[4,5-c]pyridine-3,5(4H)-dicarboxylate (3.2 g, 10.73 mmol) in ethanol (48 ml) at 0 °C and the mixture was stirred at room temperature for 3 hours. The mixture was then concentrated in vacuo, the residue was acidified with 10 % strength citric acid and the mixture was extracted three times with ethyl acetate. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was employed directly in the next stage without further purification.

**General synthesis instructions 1 (explained by way of example for amine AM2)**

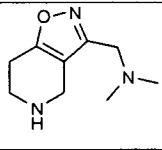
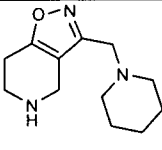
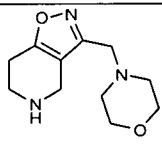
**Stage 6. tert-Butyl 3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate**

Piperidine (1.1 ml, 11.18 mmol), N-methylmorpholine (3.68 ml, 33.54 mmol) and BOP reagent (6.42 g, 14.53 mmol) were added to a solution of 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylic acid (3 g, 11.18 mmol) in dry dimethylformamide (100 ml) and the reaction mixture was stirred at room temperature for 16 hours. The solution was then concentrated in vacuo, the residue was taken up in ethyl acetate and the mixture was washed with NaHCO<sub>3</sub> solution and NaCl solution. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Purification was carried out by chromatography on silica gel (100-200 mesh silica gel, 30 % ethyl acetate in hexane). The yield was (71 %).

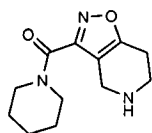
**General synthesis instructions 2 (explained by way of example for amine AM2)****Stage 7. 3-(Piperidin-1-ylmethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM2)**

BH<sub>3</sub>.SMe<sub>2</sub> (2 M in THF, 11.92 ml, 23.85 mmol) was added to a solution of tert-butyl 3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (2 g, 5.96 mmol) in dry THF (50 ml) and the solution was stirred under reflux for 6 hours. The reaction mixture was then cooled to 0 °C, methanol (20 ml) was added and the mixture was stirred at room temperature for a further 16 hours. 6 N HCl was then added and the mixture was boiled under reflux for 1 hour. After cooling to room temperature, the mixture was concentrated to dryness in vacuo, the residue was taken up in ethyl acetate and the mixture was adjusted to pH = 9 - 10 with NaHCO<sub>3</sub>. The organic phase was separated off, washed with NaCl solution, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Purification was carried out by chromatography on silica gel (methanol/ethyl acetate, gradient 1/1 to 5/1). The yield was 77 %.

The following amines were prepared by the synthesis process described, dimethylamine being employed in stage 6 in the case of **AM1** and morpholine in the case of **AM3**.

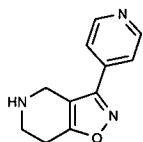
| Amine no.  | Name                                                                       | Structure                                                                             |
|------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| <b>AM1</b> | N,N-Dimethyl-1-(4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-yl)methanamine |  |
| <b>AM2</b> | 3-(Piperidin-1-ylmethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine        |  |
| <b>AM3</b> | 3-(Morpholinomethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine            |  |

**Stage 8. Piperidin-1-yl(4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-yl)methanone (amine AM4)**



tert-Butyl 3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (0.3 g, 0.89 mmol) (product of stage 6) was dissolved in 7 ml of methanol, concentrated HCl (0.56 ml, 17.8 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was then distilled off in vacuo, the residue was taken up in NaHCO<sub>3</sub> solution and the mixture was extracted with ethyl acetate. The combined organic phases were dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was employed in the next stage without further purification.

**Synthesis of 3-(pyridin-4-yl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM5)**



**Stage (i): 1-(4-(Pyrrolidin-1-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone**

Pyridine-4-carbaldoxime (1 g, 8.19 mmol) was dissolved in DMF (10 ml), a solution of N-chlorosuccinimide (1.31 g, 9.83 mmol) in DMF (5 ml) was slowly added dropwise and the reaction mixture was stirred at room temperature. When the reaction was complete (thin layer chromatography control, here 6 h), diethyl ether (50 ml) and water (20 ml) were added, phase separation, extraction of the aqueous phase with diethyl ether (5 x 30 ml). The combined organic phases were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude yield was reacted without further purification and analysis. The yield was 0.74 g (>99 %).

**Stage (ii): 1-(3-(Pyridin-4-yl)-7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridin-5(6H)-yl)ethanone**

1-(4-(Pyrrolidin-1-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone (1.2 g, 6.176 mmol) (synthesis: see below) was dissolved in methylene chloride (10 ml) and the solution was cooled to 0 °C under an inert gas. (Z)-N-Hydroxyisonicotinimidoyl chloride (1.45 g, 9.264 mmol), dissolved in methylene chloride (5 ml), and triethylamine (2.1 ml, 14.82 mmol), dissolved in methylene chloride (5 ml), were added, stir for 15 h, during this allow to warm to room temperature. The mixture was diluted with methylene chloride (30 ml) and washed water (20 ml) and citric acid (10 %, 20 ml). The aqueous phase was neutralized with sodium bicarbonate and extracted with methylene chloride and the combined organic phases were washed with saturated sodium chloride solution, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel) with ethyl acetate / methanol / ammonia (25 % eq.) 100 / 10 / 1. The yield was 0.64 g (33 %).

**Stage (iii): 3-(Pyridin-4-yl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM5)**

1-(3-(Pyridin-4-yl)-7a-(pyrrolidin-1-yl)-3a,4,7,7a-tetrahydroisoxazolo[4,5-c]pyridin-5(6H)-yl)ethanone (0.63 g, 2 mmol) was initially introduced into water (14 ml) and sulfuric acid (95 %, 14 ml) was added. The reaction mixture was refluxed for 5 hours, cooled with an ice bath, neutralized with sodium hydroxide solution (5 mol/l) and concentrated in vacuo. Ethyl acetate (10 ml) was added to the residue and the suspension was stirred at room temperature for 30 minutes. The precipitate was filtered off with suction and the mother liquor was extracted with ethyl acetate (4 x 20 ml). The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The yield was 0.34 g (84 %).

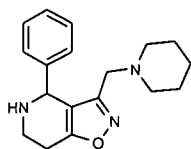
*[The regiochemistry was assigned in analogy to AM1 - AM4.]*

**Preparation of 1-(4-(pyrrolidin-1-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone (employed in stage (ii))**

N-Acetyl-4-piperidinone (1.3 g, 9.2 mmol) was dissolved in toluene (10 ml), and pyrrolidine (0.72 g, 10.13 mmol) and p-toluenesulfonic acid hydrate (catalytic) were added. The reaction mixture was refluxed under an inert gas for 2 hours using a water

separator, cooled slowly under an inert gas and concentrated in vacuo and the residue was dried. The crude product was employed immediately without purification. The yield was 1.87 g (>99 %).

### Synthesis of 4-phenyl-3-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine (AM7)



#### Step (i) and step (ii): 1-Acetyl-2-phenyl-2,3-dihydropyridin-4(1H)-one

To a solution of 4-methoxypyridine (45.871 mmol, 1.0 eq.) in dry tetrahydrofuran (200 ml) was added acetyl chloride (45.871 mmol, 1.0 eq.), followed by TMSOTf (45.871 mmol, 1.0 eq.) at room temperature. The reaction mixture was cooled to  $-78^{\circ}\text{C}$  and stirred for 1 h. PhMgCl (3.0 eq., 2M solution in THF) was added dropwise to the reaction mixture at  $-78^{\circ}\text{C}$  and mixture was allowed to stir at same temperature for additional 1h. The reaction mixture was quenched with 2M HCl and warmed to room temperature. The mixture was extracted with ethyl acetate, dried over sodium sulfate and solvent was evaporated under reduced pressure to get crude product which was purified by column chromatography.

Yield: 65%

#### Step (iii): 1-Acetyl-2-phenylpiperidin-4-one

To a solution of compound 1-acetyl-2-phenyl-2,3-dihydropyridin-4(1H)-one (4.65 mmol, 1.0 eq.) in tetrahydrofuran (40 ml) was added a 1M solution of L-selectride in THF (11.62 mmol, 2.5 eq.) at  $-78^{\circ}\text{C}$ . The mixture was stirred at same temperature for 30 min and then allowed to warm to room temperature. After completion (progress monitored by TLC), tetrahydroforan was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. It was washed successively with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the crude product which was purified by gel column chromatography (silica). Yield: 73%

**Step (iv): 1-(2-Phenyl-4-(pyrrolidin-1-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone**

To a mixture of 1-acetyl-2-phenylpiperidin-4-one (3.364 mmol, 1.0 eq.) and pyrrolidine (3.7 mmol, 1.1 eq.) in toluene (16 ml) was added PTSA (0.336 mmol, 0.1 eq.) and the reaction mixture was heated to reflux for 5 h using a Dean-Stark apparatus. After completion of the reaction, the solvent was evaporated under reduced pressure to obtain the crude product which was used in the next step without further purification.

**Step (v): Ethyl 5-acetyl-4-phenyl-7a-(pyrrolidin-1-yl)-3a,4,5,6,7,7a-hexahydroisoxazolo[4,5-c]pyridine-3-carboxylate**

To a solution of 1-(2-phenyl-4-(pyrrolidin-1-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone in dichloromethane (15 mL) was added a solution of ethyl 2-chloro-2-(hydroxyimino)acetate (4.709 mmol, 1.4 eq.) in dichloromethane (5 ml) at 0°C. Then triethylamine (1.4 eq.) was added dropwise at same reaction conditions and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with 10% citric acid solution and extracted with dichloromethane (3x). The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, concentrated to dryness to give the desired product, which was used in the next step without further purification.

Yield: 80% (over two steps)

**Step (vi): Ethyl 4-phenyl-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylate**

Conc. HCl (12 ml) was added to ethyl 5-acetyl-4-phenyl-7a-(pyrrolidin-1-yl)-3a,4,5,6,7,7a-hexahydroisoxazolo[4,5-c]pyridine-3-carboxylate (2 g) at 0°C, and the reaction mixture was heated to 130°C for 5 h. The hydrochloric acid was evaporated under reduced pressure and the residue was dissolved in dichloromethane and basified with sodium carbonate solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine solution and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the crude compound which was used in the next step without further purification.

Yield: 50%

**Step (vii): 5-tert-Butyl 3-ethyl 4-phenyl-6,7-dihydroisoxazolo[4,5-c]pyridine-3,5(4H)-dicarboxylate**

To a solution of ethyl 4-phenyl-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylate (2.57 mmol, 1.0 eq.) and triethylamine (3.0 eq.) in dichloromethane (10 ml) was added  $\text{Boc}_2\text{O}$  (1.2 eq.) and the reaction mixture was stirred at room temperature for 2 h. After completion (progress monitored by TLC), the reaction mixture was diluted with dichloromethane and the organic layer was washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the crude compound which was purified by column chromatography (silica).

Yield: 68%

**Step (viii): 5-(tert-Butoxycarbonyl)-4-phenyl-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylic acid**

5-tert-Butyl 3-ethyl 4-phenyl-6,7-dihydroisoxazolo[4,5-c]pyridine-3,5(4H)-dicarboxylate (1.75 mmol) was hydrolyzed to corresponding acid by using  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.5 eq.) as a base in ethanol-water (10 ml, 4:1).

Yield: quantitative

**Step (ix): tert-Butyl 4-phenyl-3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate**

To a solution of 5-(tert-butoxycarbonyl)-4-phenyl-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine-3-carboxylic acid (1.747 mmol, 1.0 eq.) in DMF (2 ml) was added BOP reagent (2.27 mmol, 1.3 eq.) and N-methyl morpholine (5.24 mmol, 3.0 eq.). The reaction mixture was allowed to stir at room temperature for 15 min. A solution of piperidine (1.747 mmol, 1.0 eq.) in DMF (0.5 ml) was added to the reaction mixture and it was stirred for 12 h. The mixture was poured into water and resulting aqueous solution was extracted with ethyl acetate. The organic layer was successively washed with water and brine, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give the crude product which was purified by column chromatography (silica).

Yield: 23%

**Step (x): 4-Phenyl-3-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridine**

To solution of tert-butyl 4-phenyl-3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (3.16 mmol, 1.0 eq.) in THF (6.5 ml) was added  $\text{BH}_3$ -DMS (1.2 ml, 4.0 eq.) and the reaction mixture was heated at  $110^\circ\text{C}$  for 6 h. The mixture was cooled to room temperature and MeOH (5 ml) was added dropwise at  $0^\circ\text{C}$ . The reaction mixture was allowed to stir at room temperature for overnight. 6N HCl (1.5 ml) was added and the mixture was again heated at  $110^\circ\text{C}$  for 2 h. The reaction mixture was concentrated to dryness and the residue was dissolved in dichloromethane, and basified with saturated sodium carbonate solution. The organic layer was separated, dried over sodium sulfate and the solvent was evaporated under reduced pressure to give the crude product which was purified by column chromatography.

Yield: 40%

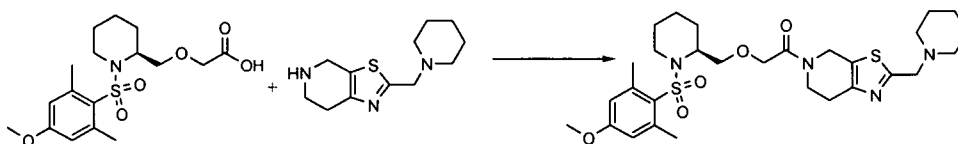
[The regiochemistry was assigned by NMR experiments (COSY; HSQC, HMBC).]

**5.) Synthesis of an example compound by reaction of a thiazolopiperidine with a carboxylic acid:**

**A.) Reaction of a thiazolopiperidine derivative with a carboxylic acid:**

Example 58

**2-[[[(2S)-1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-yl]-ethanone**



To a solution of (S)-2-((1-(4-methoxy-2,6-dimethylphenyl)sulfonyl)piperidin-2-yl)methoxy)acetic acid (AC28) (0.449 mmol, 1.0 eq.) in dichloromethane (10 ml/mmol) was added Diisopropyl ethylamine (3.0 eq.) at  $0^\circ\text{C}$  followed by the addition of HOBT (1.0 eq.) and EDCI (1.5 eq.). The resultant solution was allowed to stir at room

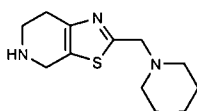
temperature for 15 min. It was again cool to 0°C and the 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (AM6) (1.2 eq.) was added. The reaction mixture was allowed to stir for 16 h at room temperature. The mixture was diluted with dichloromethane, washed with saturated ammonium chloride solution, brine, saturated sodium bicarbonate and finally with brine. The organic layer was dried over sodium sulfate and evaporated to dryness under reduced pressure to get the crude product. The crude material was purified by column chromatography.

Yield: 20 %

MS,  $R_t = 3.2$  min,  $m/z = 591.4$  [MH]<sup>+</sup>

#### B.) Synthesis of the thiazolopiperidine (amine AM6):

##### **Synthesis of 2-(piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (AM6)**



##### **Step-1: Ethyl 3-bromo-4-oxopiperidine-1-carboxylate**

To a refluxing solution of ethyl 4-oxopiperidine-1-carboxylate (2 g, 11.6 mmol) in 1:1 chloroform-ethyl acetate (23 ml) was added copper(II)bromide (5.2 g, 23.38 mmol) with a constant stream of nitrogen bubbling through the reaction mixture. After complete addition, the reaction mixture was heated for 45 min until the green color of the mixture and the dark solid had disappeared. The mixture was cooled to 25°C and filtered. The filtrate was evaporated completely and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, sodium bicarbonate solution and brine. After drying over sodium sulfate the organic layer was evaporated under reduced pressure to yield the crude product which was used in the next step without further purification.

Yield: 70%

**Step-2: Diethyl 6,7-dihydrothiazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate**

To a 2-propanol solution (60 ml) of ethyl 3-bromo-4-oxopiperidine-1-carboxylate (5 g, 20 mmol) were added ethyl thiooxamate (18 mmol) (preparation: see below) and calcium carbonate (200 mmol) and the resulting reaction mixture was allowed to reflux for 48 h (monitored by TLC). The reaction mixture was cooled to 25°C, filtered through a bed of celite and the residue was washed repeatedly with ethyl acetate. The combined organic layers were evaporated completely, the residue again dissolved in ethyl acetate and the organics washed successively with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was purified by column chromatography (30% ethyl acetate in hexane).

Yield: 30%

**Preparation of ethyl thiooxamate:**

H<sub>2</sub>S gas was passed through a toluene solution (15 ml) of ethyl cyanofornate (10 g) for 10 min and triethylamine (2 ml) was added to it. The resulting reaction mixture was allowed to stir for 16 h at ambient temperature and then the solid was filtered off, washed with ether and finally dried to get the crude ethyl thiooxamate which was used directly in the next step without further purification.

Yield: 6.2 g

**Step-3: 4,5,6,7-Tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid hydrochloride**

Diethyl 6,7-dihydrothiazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate (1.76 mmol) in 3.5 N KOH solution (3 ml) was refluxed for 3 h (monitored by TLC). The reaction mixture was cooled to 0°C and acidified with conc. HCl. The solid was collected by filtration and dried to yield the desired product.

Yield: 60%

**Step-4 and step-5: 5-tert-Butyl 2-methyl 6,7-dihydrothiazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate**

To a suspension of 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid hydrochloride (1.9 mmol) in methanol (10 ml) was added thionyl chloride (1.5 eq.) at 0°C and the resulting reaction mixture was refluxed for 16 h. The solvent was

completely evaporated off and the residue dissolved in dichloromethane (10 ml) and cooled to 0°C. To this cold mixture were added triethylamine (3 eq.) and Boc-anhydride (1.2 eq.) and the resulting reaction mixture was allowed to stir at 25°C for 12 h. The mixture was diluted with dichloromethane, washed successively with water and brine and the organics finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was purified by column chromatography (10% ethyl acetate in hexane).

Yield: 45%

**Step-6: tert-Butyl 2-(hydroxymethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate**

To a suspension of lithium aluminium hydride (3.986 mmol) in dry tetrahydrofuran (12 ml) was added 5-tert-butyl 2-methyl 6,7-dihydrothiazolo[5,4-c]pyridine-2,5(4H)-dicarboxylate (3.22 mmol) in tetrahydrofuran (10 ml) at 0°C and the resulting reaction mixture was allowed to stir at the same temperature for 1 h. It was quenched with saturated aqueous sodium sulfate solution, diluted with ethyl acetate and filtered. The filtrate was evaporated under reduced pressure to give the crude product which was used in the next step without further purification.

Yield: 66%

**Step-7: tert-Butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate**

To a dichloromethane solution (15 ml) of tert-butyl 2-(hydroxymethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (1 eq.) was added triethylamine (2.5 eq.) and methane sulfonylchloride (1.2 eq.) at 0°C and the resulting reaction mixture was allowed to stir at ambient temperature for 2 h. The reaction was quenched with ice and diluted with dichloromethane. The organic layer was successively washed with water and brine and finally dried over sodium sulfate. Evaporation of the organic layer under reduced pressure gave the crude product which was used directly in the next step without further purification.

Yield: 80%

**Step-8: tert-Butyl 2-(piperidin-1-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate**

To a toluene solution (14 ml) of tert-butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (2.01 mmol) was added potassium carbonate (10 mmol) and piperidine (1.1 eq.) and the resulting reaction mixture was refluxed for 16 h. It was cooled to room temperature, diluted with ethyl acetate and the organic layer was washed successively with water and brine. After drying over sodium sulfate, the organic layer was evaporated under reduced pressure to give the crude product which was purified by column chromatography (silica).

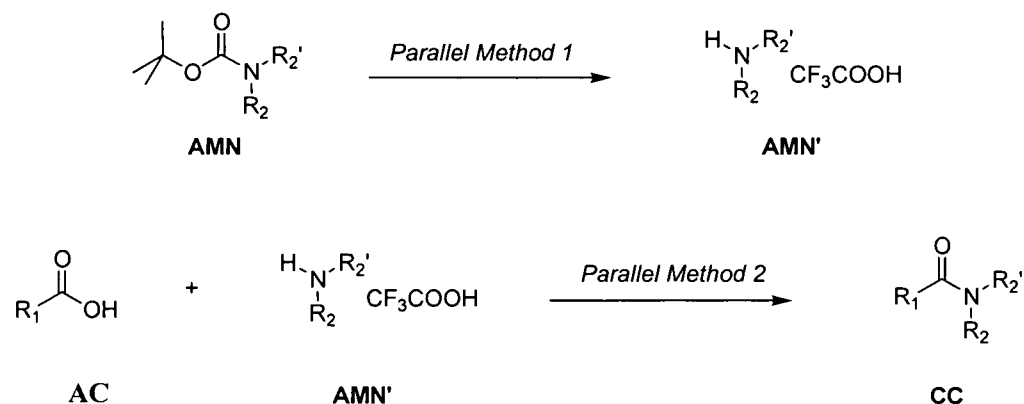
Yield: 30%

**Step-9: 2-(Piperidin-1-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (AM6)**

To a cooled (0 °C) solution of tert-butyl 2-(piperidin-1-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (0.534 mmol) in dichloromethane (3 ml) was added trifluoroacetic acid (1 ml) and reaction mixture was allowed to stir at room temperature for 2 h. Solvent was evaporated under reduced pressure and residue was azeotroped twice with dichloromethane and used in the next step.

## II. Parallel synthesis

### General:



The amine units **AMN'** were prepared from the Boc-protected amines **AMN** by Parallel Method 1 in accordance with the above equation. The amine trifluoroacetic acid salts **AMN'** obtained in this way were reacted in parallel synthesis by Parallel Method 2 with the acids **AC** to give the amidic products **CC**.

#### Parallel Method 1: Amine liberation

20 % trifluoroacetic acid in MC (10 ml/mol) was added to the corresponding Boc-protected amine (1 eq., **AMN**) at 0 °C. The reaction mixture obtained was stirred at 25 °C for 4 hours. The course of the reaction was monitored by means of thin layer chromatography. The solvent was then removed under reduced pressure and the residue was dried thoroughly in order to remove traces of trifluoroacetic acid. The crude product obtained in this way was used for synthesis of the libraries without further purification.

#### Parallel Method 2: Amide formation

EDCI (1.5 eq.), HOBT (1 eq.) and DIPEA (2.5 eq.) were added in succession to a solution of the corresponding acid unit (unit **AC**, 1 eq.) in MC (3 ml / mmol). The reaction mixture obtained was stirred at 25 °C for 15 minutes.

A solution of the corresponding Boc-protected amine unit (**AMN**; 1.5 eq.) in MC (1 ml / mmol) was cooled in an ice bath in a further flask, and DIPEA (4 eq.) was added.

The solutions from the two flasks were combined. The reaction mixture obtained in this way was stirred at 25 °C for 16 hours and then diluted with methylene chloride. The organic phase was washed successively with aqueous ammonium chloride solution, sodium carbonate and saturated sodium chloride solution. The organic phase was dried over sodium sulfate. After the solvent had been removed under reduced pressure, the crude product obtained was purified by column chromatography.

The crude products of the parallel synthesis were purified by column chromatography. It was possible to demonstrate the identity of the products by analytical HPLC-MS measurements (cf. HPLC-MS data).

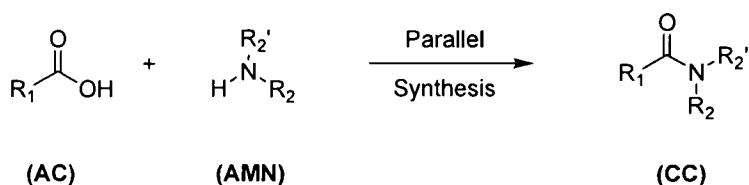
The example compounds described in the following table were prepared in this manner from the corresponding acid units **AC** and the corresponding amines **AMN**.

| Example no. |  | Acid           | Amine  | MS, m/z<br>(MH <sup>+</sup> ) | Rt [min] |
|-------------|--|----------------|--------|-------------------------------|----------|
| 37          |  | AC2            | AMN-01 | 551.1                         | 2.98     |
| 38          |  | AC5            | AMN-02 | 585.2                         | 2.84     |
| 39          |  | AC6            | AMN-02 | 545.2                         | 2.71     |
| 40          |  | AC2            | AMN-02 | 565.2                         | 2.85     |
| 41          |  | AC4            | AMN-02 | 569.2                         | 2.87     |
| 42          |  | AC1 (racemate) | AMN-02 | 569.3                         | 2.85     |

|    |  |                |        |       |      |
|----|--|----------------|--------|-------|------|
| 43 |  | AC7            | AMN-02 | 583.4 | 2.89 |
| 44 |  | AC2            | AMN-03 | 585.3 | 2.85 |
| 45 |  | AC4            | AMN-03 | 589.4 | 2.87 |
| 46 |  | AC1 (racemate) | AMN-03 | 589.3 | 2.86 |
| 47 |  | AC7            | AMN-03 | 603.3 | 2.90 |
| 48 |  | AC5            | AMN-01 | 571.2 | 3.00 |
| 49 |  | AC6            | AMN-01 | 531.2 | 2.94 |
| 50 |  | AC5            | AMN-03 | 605.3 | 2.92 |
| 51 |  | AC6            | AMN-03 | 565.3 | 2.81 |
| 52 |  | AC4            | AMN-01 | 555.2 | 9.96 |
| 53 |  | AC7            | AMN-01 | 569.3 | 5.12 |

### Parallel Method 3

#### Parallel synthesis method for the preparation of CC amides



Acid building blocks AC were converted with amines AMN to amides CC in parallel fashion. The correlation between product and reagent, building block and method can be taken from the synthesis matrix.

The crude products from the parallel synthesis were analyzed by HPLC-MS<sup>[1]</sup> and afterwards purified via reverse phase HPLC-MS<sup>[2]</sup>. The identification of the products was demonstrated by analytical HPLC-MS<sup>[1]</sup> measurements.

#### Parallelsynthesis: Protocol for the synthesis of CC amides

To a solution of acid AC (100 µmol) in 1 ml dichlormethane a solution of 1,1'-carbonyldiimidazole (150 µmol) in 1 ml dichlormethane was added and the reaction mixture was stirred at room temperature for 1.5 h. Afterwards a solution of amine AMN (150 µmol) and Hünigs base (500 µmol) in 1 ml dichlormethane was added. The mixture was stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure in a vacuum centrifuge (brand: GeneVac). The final purification resulted from HPLC-MS<sup>[2]</sup>. The final analytics resulted from LC-MS<sup>[1]</sup>.

#### [1] Equipment and Methods for HPLC-MS Analytics:

Parallelsynthesis Method: HPLC: Waters Alliance 2795 with PDA Waters 2996; MS: ZQ 2000 MassLynx Single Quadrupol MS Detector; Column: Atlantis dC18 30 x 2.1 mm, 3 µm; Col. temp.: 40 °C, Eluent A: purified water + 0.1% formic acid; Eluent B: methanol (gradient grade) + 0.1% formic acid; Gradient: 0% B to 100% B in 2.3 min, 100% B for 0.4 min, 100% B to 0% B in 0.01 min, 0% B for 0.8 min; Flow: 1.0

mL/min; Ionisation: ES+, 25V; make up: 100µL/min 70% methanol + 0.2% formic acid;  
UV: 200 – 400 nm.

[2] Equipment and Methods for HPLC-MS Purification:

Prep Pump: Waters 2525; Make Up Pump: Waters 515; Auxiliary Detector: Waters DAD 2487; MS Detector: Waters Micromass ZQ; Injector/Fraction Collector: Waters Sample Manager 2767; Gradient: Initial: 60% Water 40% Methanol -> 12-14.5 min: 0% Water 100% Methanol -> 14.5-15 min: 60% Water 40% Methanol; Flow: 35 ml/min  
Column: *Macherey-Nagel, C18 Gravity*, 100x21 mm, 5µ. A variety of products was purified by a slightly modified method.

The example compounds described in the following table were prepared in this manner from the corresponding acid units and the corresponding amines.

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| Example No. | Name                                                                                                                                                                       | Acid (S)                                                                                | Amine (A)                                                                                               | [M+] <sup>+</sup> found | R.t. [min] |
|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------|------------|
| 66          | 4-Methoxy-N,2,6-trimethyl-N-[2-(2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy)ethyl]-benzenesulfonic acid amide                               | 2-[2-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-methyl-amino]-ethoxy]-acetic acid (AC6) | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    |                         |            |
| 68          | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]piperidin-2-yl]-piperidin-2-yl]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-butan-1-one | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-11)          | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 593.2                   | 1.80       |
| 69          | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one                                         | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-11)          | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 541.2                   | 1.88       |
| 71          | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one                                    | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC7)       | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 551.2                   | 1.88       |
| 73          | 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-1-yl)sulfonyl]-piperidin-2-yl]-butan-1-one                          | 4-[1-(Naphthalen-1-yl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-12)                    | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 595.3                   | 1.83       |
| 74          | 4-[1-(Naphthalen-1-yl)sulfonyl]-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one                                                  | 4-[1-(Naphthalen-1-yl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-12)                    | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 543.4                   | 2.24       |

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|    |                                                                                                                                                                                              |                                                                                                                    |                                                                                                         |       |      |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------|------|
| 75 | 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]butan-1-one                                              | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-13)                                                | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 595.3 | 1.88 |
| 76 | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one                                                                     | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-13)                                                | 4-Pyridin-4-Yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 543.2 | 1.94 |
| 78 | N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-benzenesulfonic acid amide | 2-[2-(4H-[1,3]Benzodioxin-7-yl-methyl)-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-26) | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 699.3 | 1.85 |
| 81 | N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide                     | 2-[2-Benzyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-21)                            | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 641.3 | 1.91 |
| 82 | N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide                                          | 2-[2-Benzyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-21)                            | 4-Pyridin-4-Yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 589.2 | 1.96 |
| 83 | 4-Methoxy-2,6-Dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide                     | 2-[2-(N-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl-anilino]-ethoxy)-acetic acid (AC-20)                              | 2-[(4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 627.3 | 1.79 |
| 84 | 4-Methoxy-2,6-Dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide                                          | 2-[2-(N-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl-anilino]-ethoxy)-acetic acid (AC-20)                              | 4-Pyridin-4-Yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 575.2 | 1.85 |

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|    |                                                                                                                                                                                             |                                                                                                                  |                                                                              |       |      |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------|------|
| 85 | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]-1-[2-[(4-methylpiperazin-1-yl)-methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]-ethanone      | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]acetic acid (AC-22)     | 2-[(4-Methyl)Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 653.3 | 1.88 |
| 86 | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone                            | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]acetic acid (AC-22)     | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 601.2 | 1.95 |
| 87 | 1-[2-[(4-Methyl)piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-[2-(trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one                                 | 4-[1-[2-(Trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]butyric acid (AC-15)                                    | 2-[(4-Methyl)Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 613.2 | 1.77 |
| 88 | 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-4-[1-[2-(trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one                                                         | 4-[1-[2-(Trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]butyric acid (AC-15)                                    | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 561.2 | 1.87 |
| 91 | 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-[2-[(4-methylpiperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone | 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]acetic acid (AC-23) | 2-[(4-Methyl)Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 655.3 | 1.89 |
| 92 | 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone                        | 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]acetic acid (AC-23) | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 603.2 | 1.95 |

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|    |                                                                                                                                                                                           |                                                                                                                |                                                                              |       |      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------|------|
| 93 | 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone | 2-[[4-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid (AC-25) | 2-[(4-Methyl-Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 665.2 | 1.83 |
| 94 | 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone                         | 2-[[4-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid (AC-25) | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 613.2 | 1.93 |
| 95 | 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl-benzenesulfonic acid amide                     | 2-[2-[[4-Methoxy-2,3,6-trimethyl-phenyl]sulfonyl]-methyl-amino-ethoxy]-acetic acid (AC-10)                     | 2-[(4-Methyl-Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 579.2 | 1.75 |
| 96 | 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide                                         | 2-[2-[[4-Methoxy-2,3,6-trimethyl-phenyl]sulfonyl]-methyl-amino-ethoxy]-acetic acid (AC-10)                     | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 527.2 | 1.83 |
| 97 | 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone                      | 2-[[1-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid (AC-16)                      | 2-[(4-Methyl-Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 615.2 | 1.72 |
| 98 | 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone                                              | 2-[[1-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid (AC-16)                      | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)         | 563.1 | 1.74 |
| 99 | 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propan-1-one               | 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-propionic acid (AC-19)                | 2-[(4-Methyl-Piperazin-1-yl)-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 619.3 | 1.82 |

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|     |                                                                                                                                                                        |                                                                                                |                                                                                                         |       |      |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------|------|
| 100 | 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-methoxy]-1-imidazo[4,5-c]pyridin-5-yl]-propan-1-one                                                     | 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-methoxy]-propionic acid (AC-19) | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 567.2 | 1.90 |
| 101 | 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-ethoxy]-1-[2-(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone | 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-ethoxy]-acetic acid (AC-18)   | 2-[[4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 619.3 | 1.78 |
| 102 | 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-ethoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone                        | 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-ethoxy]-acetic acid (AC-18)   | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 567.2 | 1.90 |
| 103 | N-Methyl-N-[4-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-oxo-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide          | 4-[Methyl-[[3-(trifluoromethyl)phenyl]sulfonyl]-amino]-butyric acid (AC-08)                    | 2-[[4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 559.2 | 1.70 |
| 104 | N-Methyl-N-[4-Oxo-4-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide                                  | 4-[Methyl-[[3-(trifluoromethyl)phenyl]sulfonyl]-amino]-butyric acid (AC-08)                    | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 507.1 | 1.78 |
| 105 | 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[4-(naphthalen-2-yl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-ethanone    | 2-[4-(Naphthalen-2-yl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-acetic acid (AC-17)       | 2-[[4-Methyl-Piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trihydrochloride (AMN-03) | 617.2 | 1.93 |
| 106 | 2-[4-(Naphthalen-2-yl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone                            | 2-[4-(Naphthalen-2-yl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-acetic acid (AC-17)       | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                    | 565.2 | 1.98 |

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|     |                                                                                                                                                                  |                                                                                            |                                                                                               |       |      |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------|------|
| 107 | 4-Methoxy-N,2,6-trimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide                        | 2-[2-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-methyl-amino]-ethoxy]-acetic acid (AC6)    | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 514.1 | 2.30 |
| 108 | 4-Methoxy-N,2,6-trimethyl-N-[2-[2-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide   | 2-[2-[[[4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-methyl-amino]-ethoxy]-acetic acid (AC6)    | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 505.1 | 2.14 |
| 109 | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-ethanone                      | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid (AC5) | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 554.2 | 2.39 |
| 110 | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl)-ethanone | 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid (AC5) | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 545.1 | 2.27 |
| 111 | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-butan-1-one                                  | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-11)             | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 542.1 | 2.43 |
| 112 | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one             | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-11)             | 1-Phenyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-08) | 595.1 | 2.57 |
| 113 | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one             | 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-butyric acid (AC-11)             | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 533.1 | 2.33 |

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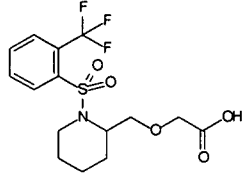
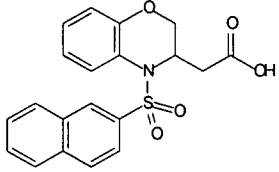
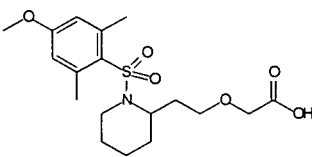
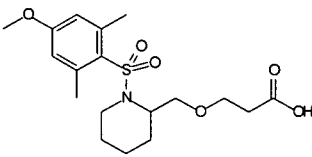
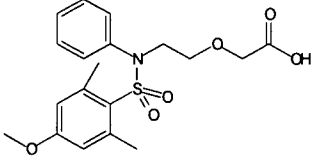
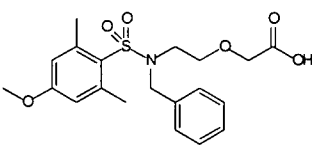
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|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------|------|
| 114 | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-butan-1-one                      | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-butyric acid (AC7) | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 552.2 | 2.43 |
| 115 | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-butyric acid (AC7) | 1-Phenyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-08) | 605.2 | 2.58 |
| 116 | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-1-(1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl)-butan-1-one | 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]piperidin-2-yl]-butyric acid (AC7) | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 543.2 | 2.35 |
| 117 | 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-butan-1-one                                     | 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-12)              | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 544.2 | 2.41 |
| 118 | 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-4-[1-(naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butan-1-one                | 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-12)              | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 535.2 | 2.32 |
| 119 | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-butan-1-one                                     | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-13)              | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 544.2 | 2.45 |
| 120 | 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-4-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butan-1-one                | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-13)              | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 535.1 | 2.33 |

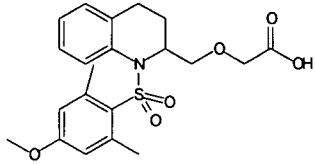
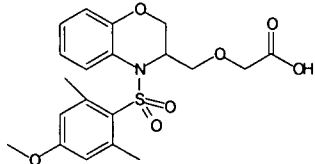
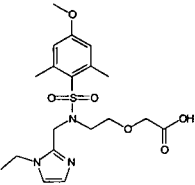
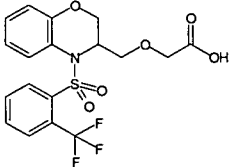
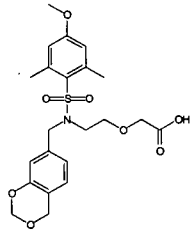
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|     |                                                                                                                                                                                                   |                                                                                                                      |                                                                                               |       |      |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-------|------|
| 121 | N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide                      | 2-[2-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-24) | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 608.2 | 1.87 |
| 122 | N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide | 2-[2-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-24) | 1-Phenyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-08) | 661.2 | 2.03 |
| 123 | N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-(1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl)-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide | 2-[2-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-24) | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) | 599.2 | 1.76 |
| 124 | N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide                        | 2-[2-[4H-[1,3]Benzodioxin-7-yl-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl-amino]-ethoxy]-acetic acid (AC-26)   | 2-Phenyl-4,5,6,7-tetrahydro-oxazol[5,4-c]pyridine hydrochloride (AMN-04)                      | 648.2 | 2.43 |

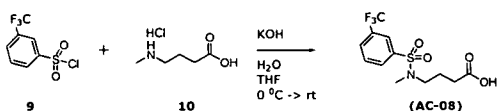
## Synthesis of the acid units for the parallel synthesis

| Acid  | Structure | Name                                                                                |
|-------|-----------|-------------------------------------------------------------------------------------|
| AC-08 |           | 4-[Methyl-[[3-(trifluoromethyl)phenyl]sulfonyl]-amino]-butyric acid                 |
| AC-10 |           | 2-[2-[[[4-Methoxy-2,3,6-trimethylphenyl]sulfonyl]-methyl-amino]-ethoxy]-acetic acid |
| AC-11 |           | 4-[1-[[2-Chloro-6-methyl-phenyl]sulfonyl]-piperidin-2-yl]-butyric acid              |
| AC-12 |           | 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butyric acid                         |
| AC-13 |           | 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butyric acid                         |
| AC-15 |           | 4-[1-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-butyric acid            |

|       |                                                                                     |                                                                                         |
|-------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| AC-16 |    | 2-[[1-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid       |
| AC-17 |    | 2-[4-(Naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-acetic acid         |
| AC-18 |    | 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-acetic acid   |
| AC-19 |  | 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-propionic acid |
| AC-20 |  | 2-[2-(N-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-anilino)-ethoxy]-acetic acid          |
| AC-21 |  | 2-[2-[Benzyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic acid       |

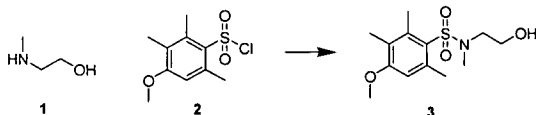
|              |                                                                                     |                                                                                                                      |
|--------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <p>AC-22</p> |    | <p>2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-acetic acid</p>        |
| <p>AC-23</p> |    | <p>2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid</p>     |
| <p>AC-24</p> |    | <p>2-[2-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic acid</p> |
| <p>AC-25</p> |  | <p>2-[[4-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid</p>        |
| <p>AC-26</p> |  | <p>2-[2-[4H-[1,3]Benzodioxin-7-yl-methyl]-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic acid</p>   |

**Synthesis of acid building block AC-08: 4-[Methyl-[[3-(trifluoromethyl)phenyl]sulfonyl]-amino]-butyric acid (AC-08)**

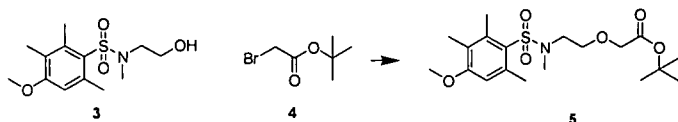


To a solution of KOH (16.5 g, 294 mmol) in H<sub>2</sub>O (75 ml) was added 4-(methylamino)butyric acid hydrochloride (**10**, 15.1 g, 98.1 mmol) and the reaction mixture was cooled with an icebath. A solution of 3-(trifluoromethyl)benzenesulphonyl chloride (**9**, 12.0 g, 49.1 mmol) in THF (75 ml) was dropwise added to the reaction mixture and stirring was continued at room temperature overnight. Aqueous 6 M HCl (75 ml) was added to the reaction mixture while cooling with an icebath, after which CH<sub>2</sub>Cl<sub>2</sub> was added. The organic layer was separated, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and co-evaporated with a minimal amount of Et<sub>2</sub>O. Crystallization of the residue out of EtOAc/heptane resulted in **AC-08** (11.32 g, 71%).

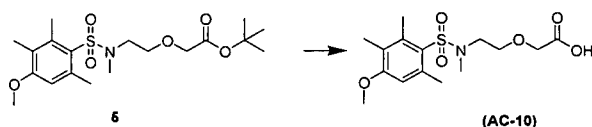
**Synthesis of acid building block AC-10: 2-[2-[[[4-Methoxy-2,3,6-trimethylphenyl]sulfonyl]-methyl-amino]-ethoxy]-acetic acid (AC-10)**



**Step-1:** To a solution of 2-Methylaminoethanol **1** (1 eq., 79.9 mmol) in 500 ml Dichloromethane was added triethylamine (1.2 eq., 95.9 mmol) and a solution of sulfonylchloride **2** (1.2 eq., 95.9 mmol) in 60 ml dichloromethane. The reaction mixture was stirred for 4 h at room temperature (TLC control). H<sub>2</sub>O (100 ml) and sat. NaHCO<sub>3</sub>-solution (100 ml) were added. After separation of the two phases, the aqueous phase was extracted 3x with Dichloromethane (250 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by column chromatography (Silica, Diethyl ether/Hexane 8:2 → 9:1), to afford the alcohol **3** (66.3 mmol, 83 % yield).

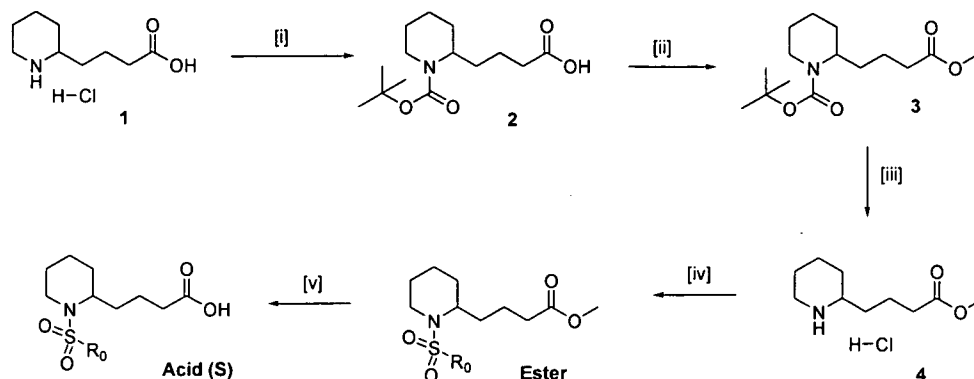


**Step-2:** A mixture of alcohol **3** (1 eq., 74.8 mmol), tert.-butylbromacetate (2.1 eq., 157 mmol), tetrabutylammoniumhydrogensulfate (0.1 eq., 7.48 mmol), 50 % NaOH-solution and toluene was stirred vigorously for 3,5 h at room temperature. After separation of the two phases, the aqueous phase was extracted 2x with diethyl ether (450 ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. Product **5** (67.3 mmol, 90 %) was obtained and it was used in the next step without further purification.



**Step-3:** Product **5** (1 eq., 67.3 mmol) was dissolved in dichlormethane and TFA (20 eq., 1345 mmol) was added. The reaction mixture was stirred for 4 h at room temperature (TLC controlled). The reaction mixture was dried over MgSO<sub>4</sub>, filtered and completely evaporated. The residue was co-evaporated 2x with toluene (300 ml). The residue was then washed 3x with diisopropylether, whereas diisopropylether was decanted from the residue. The residue was suspended in Dichloromethane and was evaporated to dryness, to afford product **AC-10** (101.9 mmol, '151 %').

**Synthesis of acid building blocks AC-11, AC-15, AC-13:** 4-(1-(2-Chloro-6-methylphenyl)sulfonyl)piperidin-2-yl)butanoic acid (**AC-11**), 4-(1-(2-(trifluoromethyl)phenyl)sulfonyl)piperidin-2-yl)butanoic acid (**AC-15**) and 4-(1-(naphthalen-2-yl)sulfonyl)piperidin-2-yl)butanoic acid (**AC-13**)



**Step (i): 4-(1-*tert*-Butoxycarbonyl) piperidin-2-yl)butanoic acid (2)**

4-Piperidin-2-ylbutanoic acid Hydrochloride (10.0 g, 48.3 mmol), and  $K_2CO_3$  (26.6 g, 193.1 mmol) was dissolved in dest. water (70 ml) and Dioxane (124 ml). The reaction mixture was cooled to  $0^\circ C$  and at this temperature Di-*tert*-butyldicarbonate (11.4 g, 53.1 mmol) was added slowly. The reaction mixture was stirred for 24 h at room temperature. After completion of the reaction water and Ethylacetate were added, the two phases were separated. The aqueous Phase was extracted once with Ethylacetate. Afterwards the aqueous Phase was triturated with 2 M HCL (aqueous) to reach pH= 2. At this pH the aqueous phase was extracted 4 x with Dichloromethane. The combined organic layers were dried over Magnesium sulfate, filtered off and evaporated to complete dryness to give **(2)** (13.13 g, 100 %).

**Step (ii): *tert*-Butyl-2-(4-methoxy-4-oxobutyl)piperidine-1-carboxylate (3)**

To a solution of 4-(1-*tert*-Butoxycarbonyl) piperidin-2-yl)butanoic acid **(2)** (26 g, 95.8 mmol) in Dichloromethane, 1,1'-carbonyldiimidazole (23.3 g, 143.7 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. Subsequently Methanol (19.4 ml, 479 mmol) was added and the reaction mixture was stirred over night. The completion of the reaction was controlled via Thin-layer chromatography. After completion the reaction mixture was washed 3 x with saturated solution  $NH_4Cl$  (aqueous) and 2 x with brine. The organic layer was dried over Magnesium sulfate, filtered off and evaporated in vacuum to afford *tert*-Butyl-2-(4-methoxy-4-oxobutyl)piperidine-1-carboxylate **(3)** (25.67 g, 94 %).

**Step (iii): Methyl 4-(piperidin-2-yl)butanoate hydrochloride (4)**

To a solution of tert-Butyl-2-(4-methoxy-4-oxobutyl)piperidine-1-carboxylate (**3**) (25.67 g, 89.9 mmol) in Methanol was added dropwise acetyl chloride. The reaction mixture was stirred for 5 h at room temperature. The completion of the reaction was controlled via Thin-layer chromatography. After completion the reaction mixture was evaporated in vacuum to give Methyl 4-(piperidin-2-yl)butanoate hydrochloride (**4**) (20.14 g, 100 %)

**General procedure GP I – Sulfonylation (Ester 11, 13 & 15)**

**Step (iv):** To a solution of methyl 4-(piperidin-2-yl)butanoate hydrochloride (**4**) (1 Equiv.) in Dichloromethane the sulfonyl chloride (3 Equiv.) was added. Subsequently N-Ethyl-diisopropylamine (3 Equiv.) was added dropwise. The reaction mixture was stirred overnight at room temperature. The completion of the reaction was controlled via Thin-layer chromatography. After completion the reaction mixture was made acidic with 1 M HCl (aqueous) and the aqueous phase was saturated with brine and then extracted 3 x with Dichloromethane. The combined organics layers were dried over Magnesium sulfate, filtered off and evaporated in vacuum. Purification by column chromatography ( Aluminiumoxide; Hexan/Ethylacetate) gave us the desired product.

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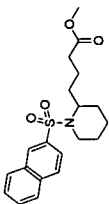
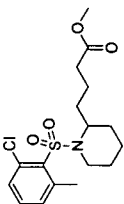
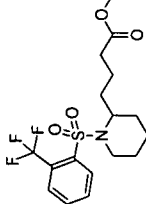
| Ester No. | Structure                                                                            | Name                                                                            | Aminoacid ester (4)                                  | Sulfonylchloride                              | Synthesis according to | Yield               | Comment                                                                    |
|-----------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------|------------------------|---------------------|----------------------------------------------------------------------------|
| Ester 13  |   | Methyl 4-(1-(naphthalene-2-ylsulfonyl)piperidin-2-yl)butanoate (iv-01)          | Methyl 4-(piperidin-2-yl)butanoate hydrochloride (4) | Naphthalene-2-sulfonylchloride                | GP I                   | 80 %<br>(18.1 mmol) | Columnchromatography:<br>Aluminiumoxide;<br>Hexane/Ethylacetate 5:1 → 4:1  |
| Ester 11  |   | Methyl 4-(1-(2-chloro-6-methylphenylsulfonyl)piperidin-2-yl)butanoate (iv-03)   | Methyl 4-(piperidin-2-yl)butanoate hydrochloride (4) | 2-Chloro-6-methylbenzene-1-sulfonylchloride   | GP I                   | 93 %<br>(10.4 mmol) | Columnchromatography:<br>Aluminiumoxide;<br>Hexane/Ethylacetate 98:2 → 8:2 |
| Ester 15  |  | Methyl 4-(1-(2-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)butanoate (iv-04) | Methyl 4-(piperidin-2-yl)butanoate hydrochloride (4) | 2-(trifluoromethyl)benzene-1-sulfonylchloride | GP I                   | 61 %<br>(11.5 mmol) | Columnchromatography:<br>Aluminiumoxide;<br>Hexane/Ethylacetate 95:5 → 8:2 |

Table 1: Synthesis of the sulfonylated amino acid ester

**General procedure GP III – Saponification (AC-11, AC-13 & AC-15):****Step (v):**

To a solution of **(Ester 11, 13 & 15)** (1 Equiv.) in Methanol/Water Lithiumhydroxide was added and the reaction mixture was stirred over night at room temperature. The completion of the reaction was controlled via Thin-layer chromatography. After completion the Methanol was evaporated in vacuum, and the residue was triturated with Ethylacetate. The mixture was made acidic with diluted HCl. The aqueous layer was extracted 2 x with Ethylacetate, the combined organic layers were dried over sodium sulfate and were evaporated in vacuum to give the desired Product **(AC-13, AC-11 & AC-15)**.

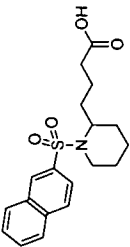
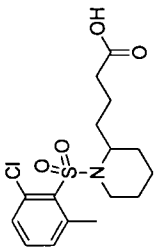
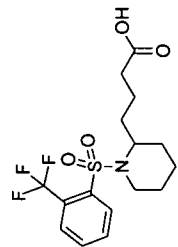
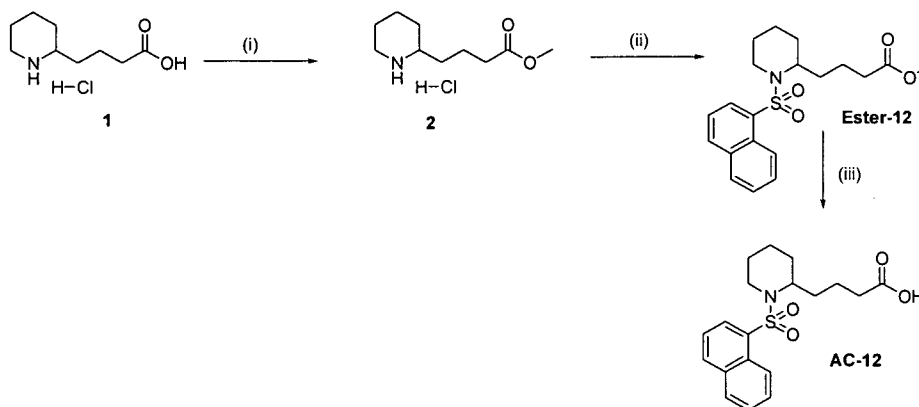
| Acid No. | Structure                                                                            | Name                                                                         | Sulfonamide ester (Ester)                                                             | Synthesis according to | Yield               |
|----------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------|---------------------|
| AC-13    |   | 4-(1-(2-(naphthalen-2-ylsulfonyl)piperidin-2-yl)butanoic acid (v-01)         | Methyl 4-(1-(2-(naphthalene-2-ylsulfonyl)piperidin-2-yl)butanoate (Ester 30)          | GP II                  | 102%<br>(23.2 mmol) |
| AC-11    |   | 4-(1-(2-(2-chloro-6-methylphenylsulfonyl)piperidin-2-yl)butanoic acid (v-03) | Methyl 4-(1-(2-(2-chloro-6-methylphenylsulfonyl)piperidin-2-yl)butanoate (Ester 32)   | GP II                  | 112%<br>(8.22 mmol) |
| AC-15    |  | 4-(1-(2-(2-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)butanoic acid      | Methyl 4-(1-(2-(2-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)butanoate (Ester 34) | GP II                  | 125%<br>(11.1 mmol) |

Table 2: Synthesis of Sulfonamide acids

**Synthesis of acid building block AC-12: 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butyric acid (AC-12)**



**Step (i): Methyl 4-(piperidin-2-yl)butanoate hydrochloride (2)**

A solution of 4-(2-piperidinyl)butanoic acid hydrochloride (5.95 g, 34.8 mmol) in Methanol (104 ml) is cooled to 0°C. At this temperature thionylchloride (7.54 ml, 104.3 mmol) is added slowly. The reaction mixture is heated to reflux for 12 h. The solvent is evaporated in vacuum. The residue is suspended in ethylacetate and is heated to reflux. The suspension is filtered off while it is still hot. In the filtrate a white solid dropped out, which was filtered off and dried in vacuum to give Methyl 4-(piperidin-2-yl)butanoate hydrochloride (**2**) (3.49 g, 45 %)

**Step (ii): Methyl 4-(1-(naphthalene-1-ylsulfonyl)piperidin-2-yl)butanoate (Ester-21)**

To a solution of Methyl 4-(piperidin-2-yl)butanoate hydrochloride (**2**) (3.74 g, 20.2 mmol) in Dichloromethane (143 ml) Naphthalene-1-sulfonylchloride (13.7 g, 60.55 mmol) was added. Subsequently N-Ethyl-diisopropylamine (10.2 ml, 60.55 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The completion of the reaction was controlled via Thin-layer chromatography. After completion the reaction mixture was made acidic with 1 M HCl (aqueous) and the aqueous phase was saturated with brine and then extracted 4 x with Dichloromethane. The combined organics layers were dried over Magnesium sulfate, filtered off and evaporated in vacuum. Purification by

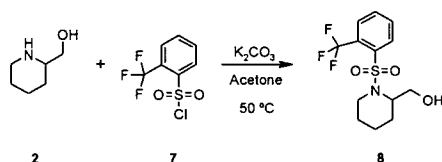
column chromatography (Aluminiumoxid; Hexan/Ethylacetate 97:3 → 9:1) gave us the desired Product Methyl 4-(1-(naphthalene-1-ylsulfonyl)piperidin-2-yl)butanoate (**Ester 12**) (4.95 g, 65 %)

**Step (iii): 4-(1-(Naphthalen-1-ylsulfonyl)piperidin-2-yl)butanoic acid (AC-12)**

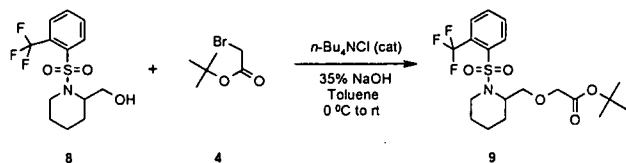
To a solution of Methyl 4-(1-(naphthalene-1-ylsulfonyl)piperidin-2-yl)butanoate (**Ester-12**) (4.95 g, 13.18 mmol.) in Methanol/Water (54 ml/36 ml)

Lithiumhydroxide (1.58 g, 65.9 mmol) was added and the reaction mixture was stirred over night at room temperature. The completion of the reaction was controlled via Thin-layer chromatography. After completion the Methanol was evaporated in vacuum, and the residue was triturated with Ethylacetate. The mixture was made acidic with diluted HCl. The aqueous layer was extracted 2x with Ethylacetate, the combined organic layers were dried over Sodium sulfate and were evaporated in vacuum to give the desired Product 4-(1-(Naphthalen-1-ylsulfonyl)piperidin-2-yl)butanoic acid (**AC-12**) (4.38 g, 91 %).

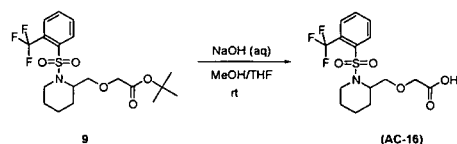
**Synthesis of acid building block AC-16: 2-[[1-[[2-(Trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-acetic acid (AC-16)**



**8.** Alcohol **2** (4.3 g, 37.2 mmol) was suspended in acetone (150 ml).  $K_2CO_3$  (10.27 g, 74.3 mmol) and 2-(trifluoromethyl)benzenesulfonyl chloride (**7**, 10 g, 40.9 mmol) were subsequently added. The mixture was stirred overnight at 50 °C. The reaction mixture was filtered after cooling to room temperature and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (silica, heptane/EtOAc 2:1) to afford 8.95 g (75%) of alcohol **8**.

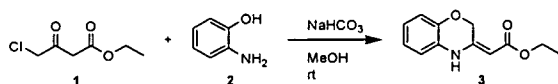


**9.** To a solution of alcohol **8** (8.95 g, 27.7 mmol) in toluene (100 ml) was added  $n\text{-Bu}_4\text{NCl}$  (2.54 g, 9.1 mmol). The reaction mixture was cooled to 0 °C after which aqueous 35% NaOH (100 ml) was added, followed by the addition of *tert*-butyl bromoacetate (**4**, 6.05 ml, 41.5 mmol). After stirring for 3 h at room temperature no more starting material was seen on TLC (silica, heptane/EtOAc, 2:1). The organic layer was separated and washed with H<sub>2</sub>O (4 x 200 ml) and brine (200 ml) until neutral, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by column chromatography (silica, heptane/EtOAc 4:1) afforded 11.57 g (96%) of ester **9**.

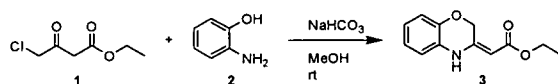


A mixture of ester **9** (11.57 g, 26.4 mmol), aqueous 6 M NaOH (88 ml, 528 mmol), MeOH (85 ml) and THF (85 ml) was stirred at room temperature for 30 min. The reaction was complete according to TLC (silica, heptane/EtOAc 2:1). The solution was then concentrated under reduced pressure to remove MeOH. The resulting suspension was acidified with aqueous 6 M HCl (120 ml) at 0 °C. CH<sub>2</sub>Cl<sub>2</sub> (300 ml) was added and after separation of the layers, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure affording 9.89 g (98%) of carboxylic acid **AC-16**.

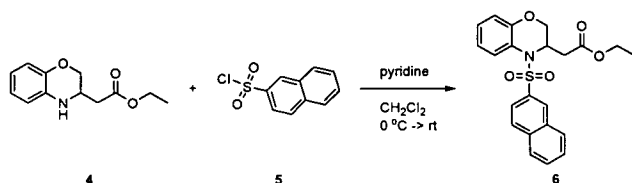
**Synthesis of acid building block AC-17: 2-[4-(Naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-acetic acid (AC-17)**



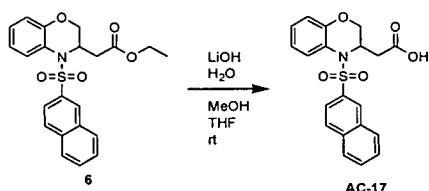
3. NaHCO<sub>3</sub> (35.1 g, 418 mmol) was added to a suspension of 2-aminophenol (2, 30.4 g, 279 mmol) and ethyl 4-chloro-3-oxobutanoate (1, 45.9 g, 279 mmol) in MeOH (280 ml) and the reaction mixture was stirred at room temperature for 2 days. After the addition of H<sub>2</sub>O (280 ml), the reaction mixture was extracted with Et<sub>2</sub>O (2x), washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (silica, heptane/EtOAc, 6:1) to yield **3** (33.71 g, 55%).



4. A suspension of Raney nickel 50% slurry in water (~3 ml) was added to a solution of **3** (16.0 g, 73.0 mmol) in THF (150 ml) and the reaction mixture was stirred under an hydrogen atmosphere of 9 bar at 40 °C for 2 days. The reaction mixture was filtered over Celite, eluted with THF and the combined filtrate was concentrated. A suspension of Raney nickel 50% slurry in water (~3 ml) was added to the residue in THF (150 ml) and the reaction mixture was stirred under an hydrogen atmosphere of 9 bar at 40 °C overnight. The reaction mixture was filtered over Celite, eluted with THF and the combined filtrate was concentrated and purified by column chromatography (silica, heptane/EtOAc, 6:1 -> 4:1) to give **4** (13.73 g, 85%).

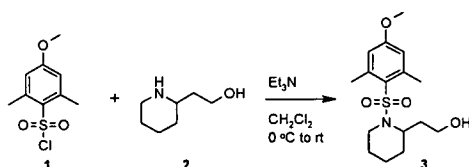


6. A solution of 2-naphthalenesulfonyl chloride (**5**, 9.22 g, 40.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) was added to a solution of **4** (9.00 g, 40.7 mmol) and pyridine (4.93 ml, 61.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 ml) while cooling with an icebath. The reaction mixture was stirred at room temperature overnight, and extra 2-naphthalenesulfonyl chloride (**5**, 0.92 g, 4.07 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and extra pyridine (4.93 ml, 61.0 mmol) were added. The reaction mixture was stirred at room temperature overnight, after which aqueous 1 M HCl was added. The organic layer was separated, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, purified by column chromatography (silica, heptane/EtOAc, 4:1) and co-evaporated with CH<sub>2</sub>Cl<sub>2</sub> (2x) resulting in **6** (13.08 g, 75%).



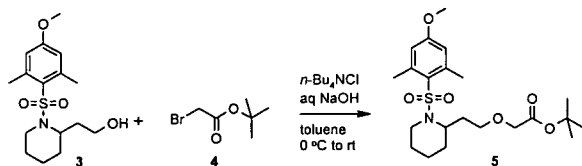
Respectively H<sub>2</sub>O (60.0 ml) and LiOH•H<sub>2</sub>O (5.20 g, 124 mmol) were added to a solution of **6** (12.74 g, 31.0 mmol) in MeOH (60 ml) and THF (60.0 ml). The reaction mixture was stirred at room temperature overnight, acidified with aqueous 1 M HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and co-evaporated with CH<sub>2</sub>Cl<sub>2</sub> to yield **AC-17** (11.63 g, 98%).

**Synthesis of acid building block AC-18: 2-[2-[1-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-acetic acid (AC-18)**

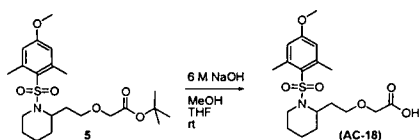


3. To a solution of 2-piperidineethanol (**2**, 5.63 g, 43.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added Et<sub>3</sub>N (14.1 ml, 109 mmol). At 0 °C was added 4-methoxy-2,6-dimethylbenzenesulfonyl chloride (**1**, 10.23 g, 43.6 mmol). The reaction mixture

was stirred for 1 h at 0 °C and overnight at room temperature. Aqueous 1 M HCl (150 ml) was added and after separation of the layers the organic layer was washed with brine (150 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness to afford compound **3** (14.85 g, '104%').

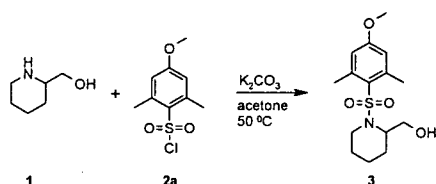


**5.** To a solution of alcohol **3** (14.8 g, max. 43.6 mmol) in toluene (200 ml) was added  $n\text{-Bu}_4\text{NCl}$  (4.04 g, 14.5 mmol). After cooling to 0 °C, an aqueous 35% NaOH solution (200 ml) was added, followed by a dropwise addition of *tert*-butyl bromoacetate (**4**, 9.53 ml, 65.4 mmol). The reaction mixture was stirred at room temperature for 3 h. The organic layer was separated and washed with  $\text{H}_2\text{O}$  (3  $\times$  200 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. Purification by column chromatography (silica, heptane/EtOAc, 4:1) yielded compound **5** (12.90 g, 67%, 2 steps).

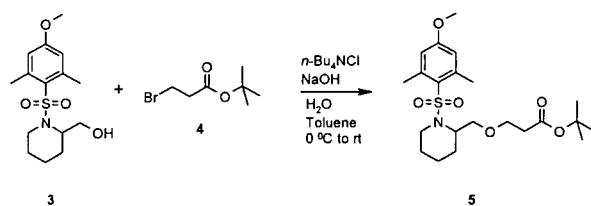


To a solution of ester **5** (12.90 g, 29.2 mmol) in THF (95 ml) and MeOH (95 ml) was added aqueous 6 M NaOH (95 ml). After 1 h organic solvents were evaporated and aqueous 6 M HCl (95 ml) was added at 0 °C. The mixture was extracted with EtOAc (500 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and co-evaporated with  $\text{Et}_2\text{O}$  (2x) to afford compound **AC-18** (11.07 g, 98%).

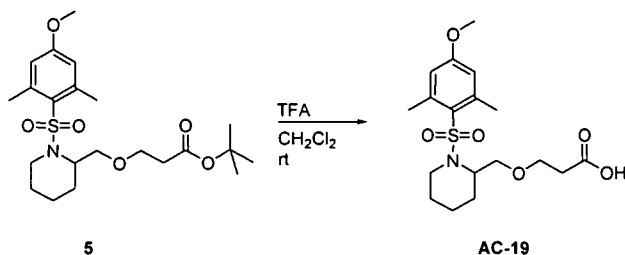
**Synthesis of acid building block AC-19: 3-((1-(4-Methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)propanoic acid (AC-19)**



**3.** 2-Piperidinemethanol (**1**, 8.1 g, 70.11 mmol) was suspended in acetone (350 ml).  $K_2CO_3$  (19.4 g, 140.22 mmol) was added followed by sulfonyl chloride **2a** (18.1 g, 77.12 mmol). The mixture was stirred overnight at  $50\text{ }^\circ\text{C}$ . After cooling to room temperature, the reaction mixture was filtered and the filtrate was evaporated to dryness. Purification by column chromatography (silica, heptane/EtOAc 2:1) gave **3** (12.9 g, 59%) as a white solid.

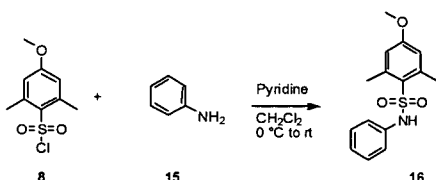


**5.** To a solution of alcohol **3** (12.8 g, 40.84 mmol) in toluene (200 ml) was added  $\text{Bu}_4\text{NCl}$  (3.7 g, 13.48 mmol). The reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  after which aqueous 35%  $\text{NaOH}$  (250 ml) was added followed by a dropwise addition of *tert*-butyl 3-bromopropionate (**4**, 8.2 ml, 49.01 mmol) in toluene (50 ml). The mixture was stirred overnight at room temperature. The organic layer was separated and washed with  $\text{H}_2\text{O}$  until neutral, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and co-evaporated with  $\text{CH}_2\text{Cl}_2$  (3x). Purification by column chromatography (silica, heptane/EtOAc 4:1) gave **5** (11.2 g, 62%) as a yellow oil.

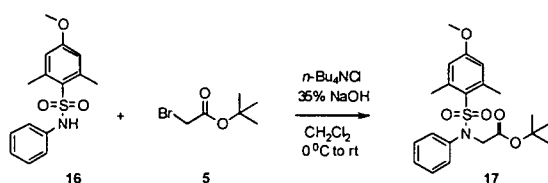


*tert*-Butyl ester **5** (10.9 g, 24.68 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (150 ml). TFA (75 ml) was added and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3x) and CH<sub>2</sub>Cl<sub>2</sub> (3x). The crude product was purified by column chromatography (silica, heptane/EtOAc 2:1 + 2% HOAc). Co-evaporation with toluene (2x) and CH<sub>2</sub>Cl<sub>2</sub> (3x) gave **AC-19** (9.2 g, 97%) as a yellow oil.

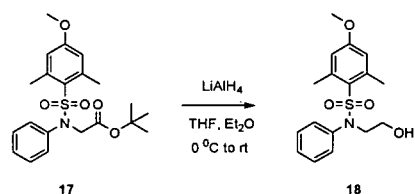
**Synthesis of acid building block AC-20: 2-[2-(N-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]-anilino)-ethoxy]-acetic acid (AC-20)**



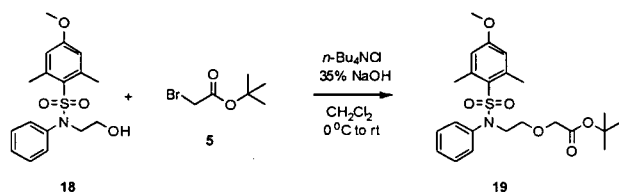
**16.** A solution of sulfonyl chloride **8** (10.1 g, 43.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added dropwise to a stirred and cooled (0°C) solution of aniline (**15**, 3.92 ml, 43.0 mmol) and pyridine (10.4 ml, 129 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (250 ml) and the reaction mixture was stirred at room temperature for 3 h. The mixture was washed with aqueous 0.5 M KHSO<sub>4</sub> (100 ml) and saturated aqueous NaHCO<sub>3</sub> (100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to afford crude sulfonamide **16** (14.87 g, '119%').



**17.** A solution of sulfonamide **16** (14.72 g, max. 43.0 mmol) and *n*-Bu<sub>4</sub>NCl (1.50 g, 5.40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 ml) was cooled to 0 °C and aqueous 35% NaOH (150 ml) was added. After 10 min *tert*-butyl bromoacetate (**5**, 11.2 ml, 76.0 mmol) was added and the mixture was stirred at room temperature for 3 h. The layers were separated and the organic layer was washed with H<sub>2</sub>O (3x 200 ml). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to afford crude ester **17** (22.6 g, '130%').

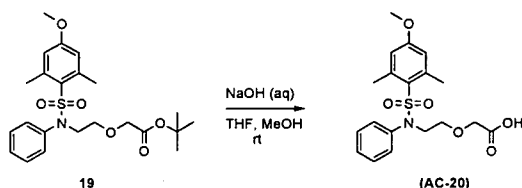


**18.** A solution of 4 M LiAlH<sub>4</sub> in Et<sub>2</sub>O (20.9 ml, 84.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ester **17** (22.6 g, max. 43.0 mmol) in THF (225 ml). The reaction mixture was stirred for 15 min at 0 °C after complete addition and Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O was added until gas evolution stopped and was stirred at room temperature overnight. The mixture was filtered over a small pad of Na<sub>2</sub>SO<sub>4</sub> and the filtrate was evaporated to dryness. The crude product was purified by column chromatography (silica, heptane/EtOAc, 2:1) to afford alcohol **18** (11.25 g, 78% over 3 steps).



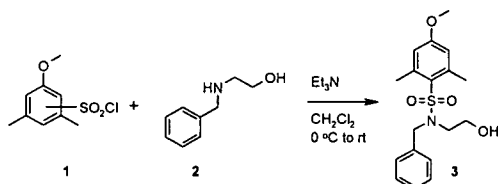
**19.** To a solution of alcohol **18** (11.24 g, 33.5 mmol) and *n*-Bu<sub>4</sub>NCl (992 mg, 3.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (120 ml) was added aqueous 35% NaOH (120 ml) at 0 °C followed by *tert*-butyl bromoacetate (**5**, 7.43 ml, 50.3 mmol) and the reaction mixture was then stirred at room temperature. After 3 h the layers were separated and the organic phase was washed with H<sub>2</sub>O (3x 250 ml). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness. Purification by column

chromatography (silica, heptane/EtOAc, 3:1) afforded ester **19** (12.00 g, 80%) as a yellow oil.

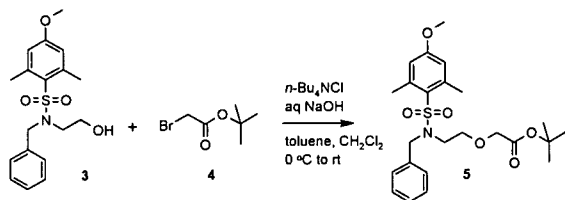


To a solution of ester **19** (12.00 g, 26.70 mmol) in MeOH (200 ml) and THF (200 ml) was added aqueous 4 M NaOH (200 ml, 800 mmol) and the reaction mixture was stirred at room temperature. After 3 h the organic solvents were evaporated and the aqueous layer was acidified with aqueous 6 M HCl (250 ml). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 ml) and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to afford building block **AC-20** (11.27 g, '107%').

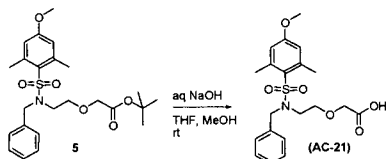
**Synthesis of acid building block AC-21: 2-[2-[Benzyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic acid (AC-21)**



**3.** To a solution of N-benzylaminoethanol (**2**, 10.0 ml, 70.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml) was added Et<sub>3</sub>N (22.5 ml, 160 mmol). The mixture was cooled to 0 °C after which a solution of compound **1** (15.0 g, 63.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added dropwise. The mixture was stirred for 3 h at room temperature. Aqueous 1 M HCl (150 ml) was added. After phase separation the organic layer was washed with water (100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. Purification by column chromatography (silica, heptane/EtOAc, 2:1) afforded sulfonamide **3** (14.93 g, 67%).

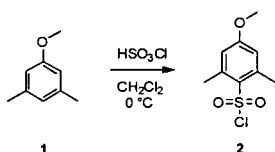


**5.** To a solution of compound **3** (14.9 g, 42.6 mmol) in toluene (100 ml) and  $\text{CH}_2\text{Cl}_2$  (100 ml) was added  $n\text{-Bu}_4\text{NCl}$  (3.95 g, 14.2 mmol). After cooling to 0 °C, an aqueous 35% NaOH solution (175 ml) was added, followed by a dropwise addition of *tert*-butyl bromoacetate (**4**, 9.32 ml, 64 mmol). The reaction mixture was stirred at room temperature for 3 h. The organic layer was separated and washed with  $\text{H}_2\text{O}$  (3 × 300 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. Purification by column chromatography (silica, heptane/EtOAc, 3:1) afforded compound **5** (19.40 g, 98%).

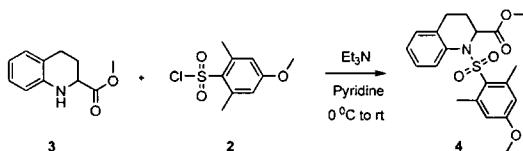


To a solution of compound **5** (19.4 g, 41.8 mmol) in THF (165 ml) and MeOH (150 ml) was added aqueous 6 M NaOH (150 ml, 900 mmol). The reaction mixture was stirred at room temperature. After 1 h the organic solvents were evaporated and aqueous 6 M HCl (155 ml) was added at 0 °C. The aqueous layer was extracted with EtOAc (2x 150 ml). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. The product was co-evaporated with  $\text{Et}_2\text{O}$  and  $i\text{-Pr}_2\text{O}$  (2x) to yield compound **AC-21** (17.05 g, 100%).

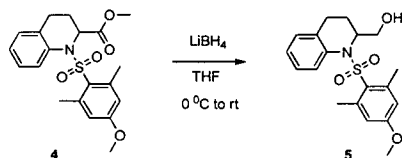
**Synthesis of acid building block AC-22: 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-acetic acid (AC-22)**



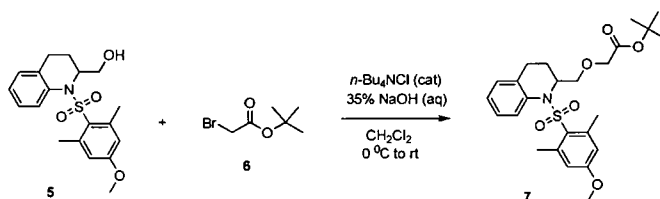
2. A solution of chlorosulfonic acid (247 ml, 3687 mmol) in  $\text{CH}_2\text{Cl}_2$  (250 ml) was added dropwise to a solution of 3,5-dimethylanisole (1, 100.44 g, 737 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 L) at  $0^\circ\text{C}$ . After 15 min, the reaction mixture was poured into ice-water (1.5 L) and extracted with  $\text{CH}_2\text{Cl}_2$  (250 ml). The organic layer was quickly washed with ice-cold  $\text{H}_2\text{O}$  (1 L), ice-cold aqueous saturated  $\text{NaHCO}_3$  (1 L), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Purification by column chromatography (silica, heptane/ $\text{CH}_2\text{Cl}_2$ , 5:1) afforded sulfonyl chloride 2 (79.64 g, 46%) as a yellow oil which crystallised at  $-20^\circ\text{C}$  in the freezer overnight. The product was stored under argon in a freezer due to instability issues.



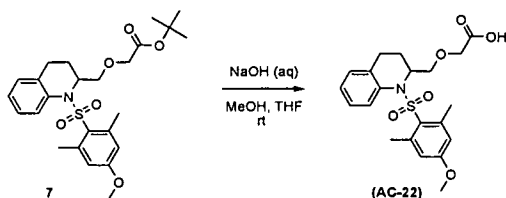
4. To a mixture of ester 3 (8.24 g, 43.1 mmol) in dry pyridine (10.5 ml, 129 mmol) was added sulfonyl chloride 2 (20.23 g, 86 mmol) and the mixture was stirred overnight at  $40^\circ\text{C}$ .  $\text{CH}_2\text{Cl}_2$  (100 ml) was added and the reaction mixture was washed with aqueous 1 M  $\text{HCl}$  (100 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness under reduced pressure. Purification by column chromatography (silica, toluene/ $\text{EtOAc}$ , 24:1) afforded sulfonamide 4 (14.39 g, 86%).



5. Sulfonamide **4** (14.29 g, 36.7 mmol) was dissolved in dry THF (100 ml). After cooling to 0°C a solution of 2 M LiBH<sub>4</sub> in THF (33.0 ml, 66.0 mmol) was added dropwise slowly and the reaction mixture was stirred at room temperature overnight. The reaction was not complete according to TLC (silica, heptane/EtOAc, 1:1), additional 2 M LiBH<sub>4</sub> in THF (18.35 ml, 36.7 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was complete according to TLC. The reaction mixture was quenched by adding Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O and H<sub>2</sub>O, additional Na<sub>2</sub>SO<sub>4</sub> was added to remove any residual H<sub>2</sub>O, filtered, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 ml), washed with H<sub>2</sub>O (100 ml) and evaporated to dryness under reduced pressure to afford alcohol **5** (14.01 g, '106%').

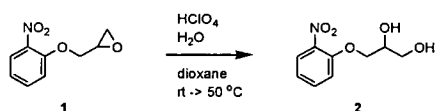


7. To a solution of alcohol **5** (13.23 g, max 34.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (80 ml) was added *n*-Bu<sub>4</sub>NCl (3.36 g, 12.1 mmol). The reaction mixture was cooled to 0°C after which aqueous 35% NaOH (84 ml) was added, followed by the addition of *tert*-butyl 2-bromoacetate (**6**, 6.40 ml, 43.9 mmol). After stirring for 4 h at room temperature no more starting material was observed on TLC (silica, heptane/EtOAc, 1:1). The organic layer was separated, washed with H<sub>2</sub>O (3x 150 ml) and brine (150 ml) until neutral, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification was carried out by subjecting the crude compound twice to column chromatography (silica, heptane/EtOAc, 4:1) and afforded ester **7** (14.90 g, 90% over 2 steps).

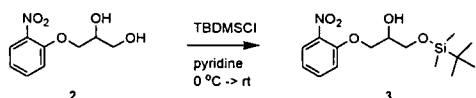


A mixture of ester **7** (14.82 g, 31.2 mmol), MeOH (110 ml), THF (110 ml) and aqueous 4 M NaOH (117 ml, 467 mmol) was stirred at room temperature for 2 h. The reaction was complete according to TLC (silica, heptane/EtOAc 2:1). The solution was then concentrated under reduced pressure to remove the organic solvents. The resulting suspension was acidified with aqueous 6 M HCl (120 ml) while cooling at 0°C. CH<sub>2</sub>Cl<sub>2</sub> (250 ml) was added and after separation of the layers, the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure affording carboxylic acid **AC-22** (12.64 g, 97%).

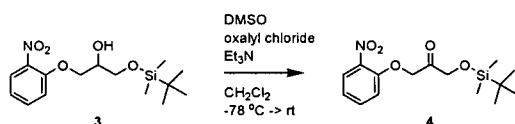
**Synthesis of acid building block AC-23: 2-[[4-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid (AC-23)**



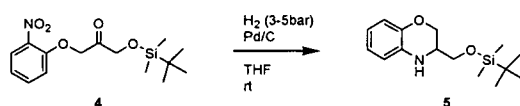
**2.** Perchloric acid (3.30 ml, 38.2 mmol) was added to a solution of **1** (37.3 g, 191 mmol) in dioxane (746 ml) and H<sub>2</sub>O (568 ml) and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was concentrated to half its volume and aqueous saturated NaHCO<sub>3</sub> was added. The H<sub>2</sub>O layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x) and the combined organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification by column chromatography (silica, heptane/EtOAc, 2:3) yielded **2** (30.6 g, 75%).



3. To a solution of **2** (30.6 g, 143 mmol) in pyridine (75 ml) was added *tert*-butyldimethylsilyl chloride (23.8 g, 158 mmol) while cooling with an icebath. The reaction mixture was stirred at room temperature for 2 h and afterwards concentrated and co-evaporated with toluene. The residue was dissolved in EtOAc, washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give **3** (46.7 g, 99%).



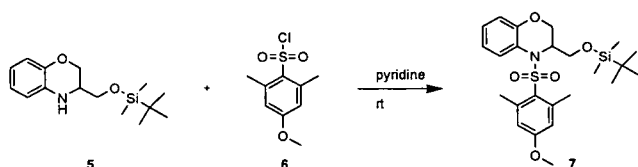
4. A solution of DMSO (21.24 ml, 299 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (600 ml) was dropwise added to a solution of oxalyl chloride (15.0 ml, 171 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 ml) in 30 min while maintaining the internal temperature below –65 °C. A solution of **3** (46.7 g, 142 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 ml) was added dropwise in 15 min. while maintaining the temperature below –65 °C. The reaction mixture was stirred an additional 45 minutes at –78 °C, after which Et<sub>3</sub>N (99.0 ml, 712 mmol) was added. After the reaction mixture was stirred at –78 °C for 45 min, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional hour. The reaction mixture was washed with H<sub>2</sub>O and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was dissolved in Et<sub>2</sub>O, filtered and the filtrate was concentrated and crystallized (Et<sub>2</sub>O/heptane) to result in **4** (30.9 g, 67%). The mother liquor was concentrated and crystallized (Et<sub>2</sub>O/heptane) and gave extra **4** (2.27 g, 5%).



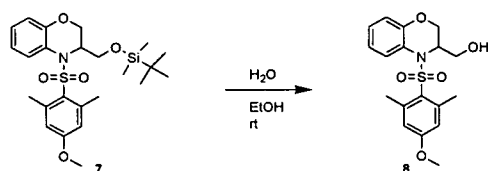
5. A mixture of **4** (18 g, 55.3 mmol) and 10% Pd/C (1.8 g, 1.7 mmol) in dry THF (150 ml) was stirred under an hydrogen atmosphere of ~3 bar for 2 days and then under an hydrogen atmosphere of 5 bar for 1 d. The reaction mixture was

filtered over Celite and eluted with THF. The filtrate was concentrated and 10% Pd/C (1.8 g, 1.7 mmol) was added to the residue in dry THF (150 ml) and the resulting reaction mixture was stirred under a hydrogen atmosphere of ~5 bar for 1 d. The reaction mixture was filtered over Celite and eluted with THF. The filtrate was concentrated and purified by column chromatography (silica, heptane/Et<sub>2</sub>O, 9:1) to yield **5** (7.11 g, 46%).

Another batch of **4** (15.06 g, 46.3 mmol) and Pd/C 10% Pd/C (1.5 g, 1.4 mmol) in dry THF (150 ml) was stirred under a hydrogen atmosphere (~5 bar) for 2 days. The reaction mixture was filtered over Celite and eluted with THF. The filtrate was concentrated and purified by column chromatography (silica, heptane/Et<sub>2</sub>O, 9:1) to yield extra **5** (3.20 g, 25%).

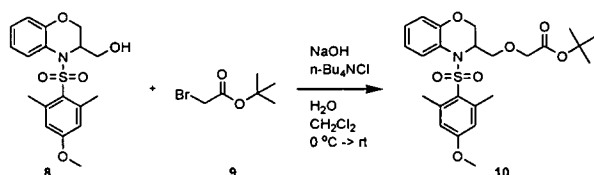


**7**. Sulfonyl chloride **6** (8.96 g, 38.2 mmol) was added to a solution of **5** (9.70 g, 34.7 mmol) in pyridine (8.42 ml) and the reaction mixture was stirred at room temperature for 2 d. The reaction mixture was concentrated, dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give crude **7**, which was directly used in the next step.

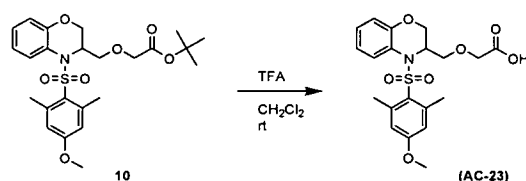


**8**. Crude **7** was dissolved in EtOH (~100 ml) and H<sub>2</sub>O (~100 ml) with heating and was left standing overnight. The reaction mixture was concentrated, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with aqueous saturated NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was solidified with EtOAc/heptane (2:1) and some

CH<sub>2</sub>Cl<sub>2</sub>. The resulting precipitate was washed with EtOAc/heptane (2:1) and dried on filter to yield **8** (9.68 g, 77% over 2 steps).

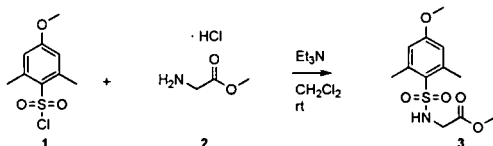


**10.** To an ice-cooled solution of **8** (9.68 g, 26.6 mmol) and *n*-Bu<sub>4</sub>NCl (2.44 g, 8.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (130 ml) was sequentially added aqueous 35% NaOH solution (130 ml) and *tert*-butyl bromoacetate (**9**, 11.6 ml, 80.0 mmol). The reaction mixture was stirred at room temperature for 4.5 h, after which H<sub>2</sub>O was added. The organic layer was separated, washed with H<sub>2</sub>O (2x), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (silica, heptane/EtOAc, 4:1 -> 3:1) to provide **10** (11.9 g, 94%).

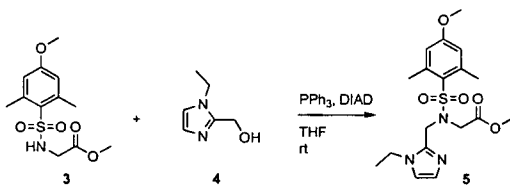


A solution of **10** (11.80 g, 24.7 mmol) and TFA (25 ml, 324 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (125 ml) was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, co-evaporated with toluene (2x) and CH<sub>2</sub>Cl<sub>2</sub> (2x). The residue was dried under vacuum for 1 day to furnish **AC-23** (10.26 g, 99%).

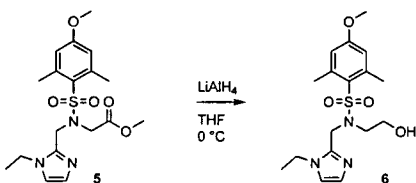
**Synthesis of acid building block AC-24: 2-[2-[(1-Ethyl-1H-imidazol-2-yl)-methyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic acid (AC-24)**



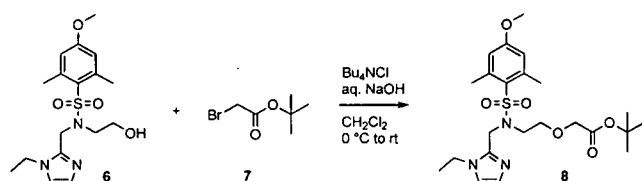
3. A solution of sulfonyl chloride **1** (15.0 g, 63.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 ml) was added dropwise to a stirred solution of methyl 2-aminoacetate hydrochloride (**2**, 8.83 g, 70.3 mmol) and  $\text{Et}_3\text{N}$  (31.2 ml, 224 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 ml). The reaction mixture was stirred at room temperature for 2 h and washed with aqueous 1 M HCl (100 ml). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness to afford compound **3** (19.3 g, '105%').



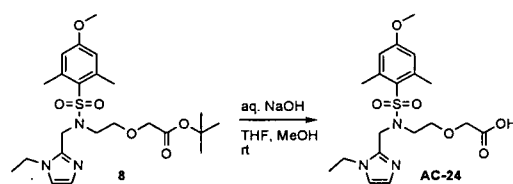
5. To a solution of compound **3** (9.50 g, max. 31.5 mmol) in dry THF (200 ml) were added (1-ethyl-1H-imidazol-2-yl)methanol (**4**, 5.01 g, 39.7 mmol),  $\text{PPh}_3$  (10.41 g, 39.7 mmol) and DIAD (7.71 ml, 39.7 mmol) and the reaction was stirred at room temperature overnight. The mixture was evaporated to dryness and purified by column chromatography ( $\text{CH}_2\text{Cl}_2$ /(7 M  $\text{NH}_3$  in MeOH), 99:1 to 98:2) to afford compound **5** (10.17 g, 82%, 2 steps).



6. A solution of ester **5** (10.17 g, 25.7 mmol) in dry THF (50 ml) was added dropwise to a stirred and cooled (0°C) solution of LiAlH<sub>4</sub> (2.4 M in THF, 36 ml, 86 mmol) in THF (50 ml). After 15 min the reaction mixture was quenched with a mixture of THF/H<sub>2</sub>O (1:1, 36 ml). The suspension was filtered over a small pad of Na<sub>2</sub>SO<sub>4</sub>. The residue was refluxed in THF (500 ml) for 1 h and the warm mixture was filtered over a small path of Na<sub>2</sub>SO<sub>4</sub>. The combined filtrates were evaporated to dryness to afford alcohol **6** (8.17 g, 86%).



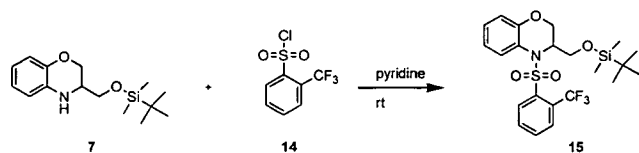
8. To a solution of alcohol **6** (8.17 g, 22.2 mmol) and Bu<sub>4</sub>NCl (2.04 g, 7.34 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added aqueous 35% NaOH (50.8 ml) at 0 °C followed by *tert*-butyl bromoacetate (**7**, 6.48 ml, 44.5 mmol). The reaction mixture was stirred at room temperature and after 1 h more *tert*-butyl bromoacetate (3.24 ml, 22.2 mmol) was added. After 1 h the layers were separated. The organic layer was washed with H<sub>2</sub>O (500 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and directly purified by column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/(7 M NH<sub>3</sub> in MeOH), 98:2) to afford ester **8** (6.50 g, 61%).



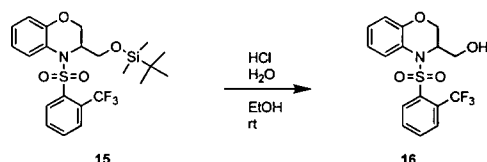
To a solution of ester **8** (6.50 g, 13.50 mmol) in THF (50 ml) and MeOH (50 ml) was added aqueous 6 M NaOH (45.0 ml, 270 mmol) and the reaction mixture was stirred at room temperature. After 1 h the organic solvents were evaporated and the residue was acidified with aqueous 6 M HCl (50 ml). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 150 ml). The combined organic layers were dried

( $\text{Na}_2\text{SO}_4$ ) and evaporated to dryness. Crystallization from *i*-PrOH afforded building block **AC-24** (4.30 g, 75%).

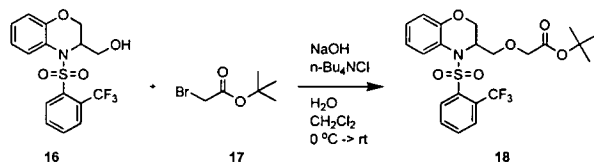
**Synthesis of acid building block AC-25: 2-[[4-[[2-(Trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-acetic acid (AC-25)**



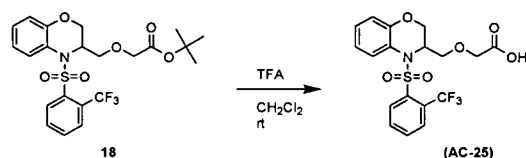
**15.** 2-(trifluoromethyl)benzenesulfonyl chloride (**14**, 8.50 g, 34.8 mmol) was added to a solution of **7** (8.83 g, 31.6 mmol) in pyridine (7.67 ml, 95.0 mmol) and the reaction mixture was stirred at room temperature overnight.  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$  were added to the reaction mixture and the organic layer was separated, washed with brine and concentrated to give crude **15**, which was directly used as such in the next step.



**16.** Aqueous 1 M HCl (50 ml, 50 mmol) was added to crude **15** in EtOH (200 ml) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated, dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with aqueous saturated  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified by column chromatography (silica, heptane/EtOAc: 2:1) to yield **16** (10.29 g, 78%, 2 steps).

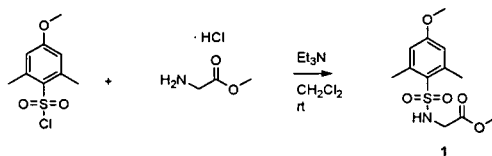


**18.** To an ice-cooled solution of **16** (10.29 g, 24.81 mmol) and *n*-Bu<sub>4</sub>NCl (2.28 g, 8.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (125 ml) was sequentially added aqueous 35% NaOH solution (125 ml) and *tert*-butyl bromoacetate (**17**, 10.83 ml, 74.4 mmol). The reaction mixture was stirred at room temperature for 4 h, after which H<sub>2</sub>O was added. The organic layer was separated, washed with H<sub>2</sub>O and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (silica, heptane/EtOAc, 4:1) to provide **18** (11.65 g, 93%).

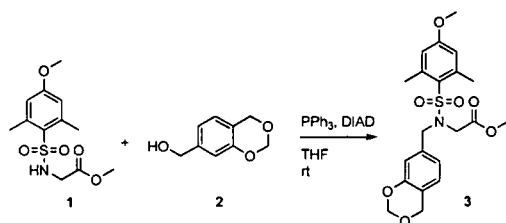


A solution of **18** (11.55 g, 22.98 mmol) and TFA (20 ml, 260 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated, co-evaporated with toluene (2x) and CH<sub>2</sub>Cl<sub>2</sub> (2x). The residue was transferred to a jar with CH<sub>2</sub>Cl<sub>2</sub>, concentrated and dried under vacuum overnight to furnish **AC-25** (10.18 g, '103%').

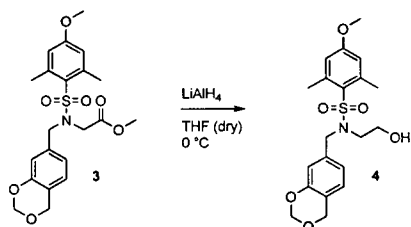
**Synthesis of acid building block AC-26: 2-[2-[4H-[1,3]Benzodioxin-7-yl-methyl-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-amino]-ethoxy]-acetic**



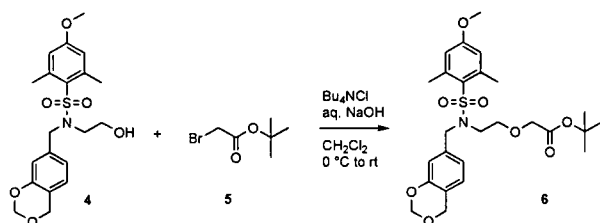
**3.** A solution of sulfonyl chloride **1** (15.0 g, 63.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added dropwise to a stirred solution of methyl 2-aminoacetate hydrochloride (**2**, 8.83 g, 70.3 mmol) and Et<sub>3</sub>N (31.2 ml, 224 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml). The reaction mixture was stirred at room temperature for 2 h and washed with aqueous 1 M HCl (100 ml). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness to afford compound **3** (19.3 g, '105%').



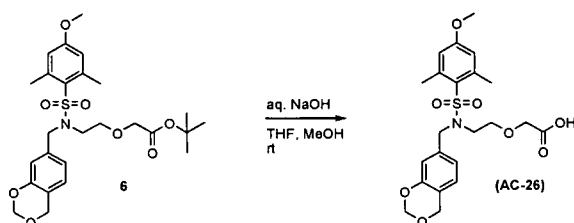
**3.** To a solution of compound **1** (9.08 g, max. 30.1 mmol), (4H-benzo[d][1,3]dioxin-7-yl)methanol (**2**, 5.25 g, 31.6 mmol) and  $\text{PPh}_3$  (9.95 g, 37.9 mmol) in dry THF (200 ml) was added DIAD (7.37 ml, 37.9 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated to dryness. Purification by column chromatography twice (silica, heptane/EtOAc, 3:1 and silica, toluene/EtOAc, 23:2) afforded sulfonamide **3** (5.29 g, 40%, 2 steps).



**4.** To a cooled ( $0^\circ\text{C}$ ) and stirred solution of  $\text{LiAlH}_4$  (2.4 M in THF, 15.2 ml, 36.4 mmol) in dry THF (50 ml), a solution of sulfonamide **3** (5.29 g, 12.2 mmol) in dry THF (100 ml) was added dropwise. After 5 min the reaction mixture was quenched with a mixture of THF/ $\text{H}_2\text{O}$  (1:1, 16 ml). The mixture was filtered over a small pad of  $\text{Na}_2\text{SO}_4$  and rinsed with THF. The filtrate was evaporated to dryness to afford alcohol **4** (5.03 g, '102%').

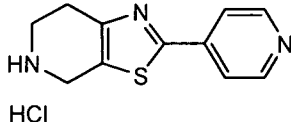
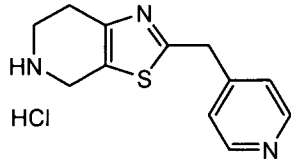
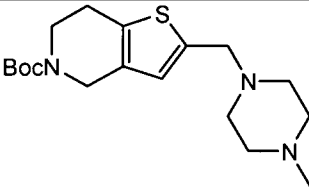
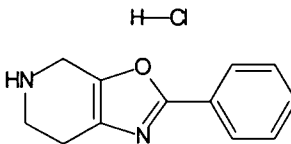
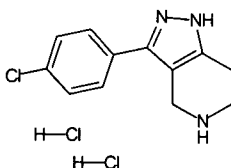
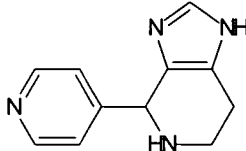


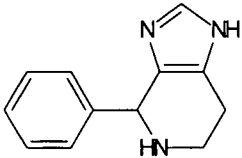
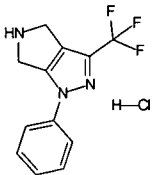
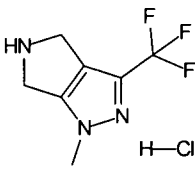
6. To a cooled (0°C) solution of alcohol 4 (5.03 g, max 12.2 mmol) and Bu<sub>4</sub>NCl (1.10 g, 3.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) was added aqueous 35% NaOH (27.5 ml) followed by *tert*-butyl bromoacetate (5, 2.63 ml, 18.04 mmol). The reaction mixture was then stirred at room temperature. After 2 h more *tert*-butyl bromoacetate (5, 438 µL, 3.01 mmol) was added. After 2 h the layers were separated and the organic layer was washed with H<sub>2</sub>O (3x 100 ml). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness. Purification by column chromatography (silica, toluene/EtOAc, 23:2) afforded ester 6 (6.29 g, 99%, 2 steps).



To a solution of ester 6 (6.25 g, 12.0 mmol) in THF (45 ml) and MeOH (45 ml) was added aqueous 6 M NaOH (39.9 ml, 240 mmol) and the reaction mixture was stirred at room temperature. After 1 h the organic solvents were evaporated. The residue was acidified with aqueous 6 M HCl (45 ml) and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x 100 ml). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness. Purification by column chromatography (silica, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 98:2 + 1% AcOH) afforded building block AC-26 (4.40 g, 79%)

## Synthesis of the amine units for the parallel synthesis

| Amine Building Block No. | Structure                                                                           | Name                                                                                                     |
|--------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| AMN-01                   |    | 2-(Pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride                                 |
| AMN-02                   |    | 2-(Pyridin-4-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride                           |
| AMN-03                   |   | <i>tert</i> -Butyl 2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate |
| AMN-04                   |  | 2-Phenyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine hydrochloride (AMN-04)                                 |
| AMN-05                   |  | 3-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine dihydrochloride (AMN-05)                |
| AMN-06                   |  | 4-Pyridin-4-yl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-06)                                     |

|        |                                                                                   |                                                                                               |
|--------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| AMN-07 |  | 4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (AMN-07)                                |
| AMN-08 |  | 1-Phenyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-08) |
| AMN-09 |  | 1-Methyl-3-(Trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazole hydrochloride (AMN-09) |

**2-(Pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride (AMN-01)**

**Stage 1: Ethyl 3-bromo-4-oxopiperidine-1-carboxylate**

Copper(II) bromide (5.2 g; 23.38 mmol) was added to a refluxing solution of N-ethoxycarbonylpiperidone (2 g; 11.6 mmol) in a chloroform/ethanol mixture (1:1, 23 ml) under an inert gas atmosphere. When the addition was complete, the reaction mixture was heated for 45 minutes until the green colour and the dark solid disappeared. Thereafter, the reaction mixture was cooled to 25 °C and filtered and the filtrate was concentrated under reduced pressure.

For working up, the residue was taken up in ethyl acetate and the mixture was washed with water, sodium carbonate solution and saturated sodium chloride solution. After the organic phase had been dried over sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was employed in the next stage without further purification. The crude yield was 70 %.

**Stage 2: Ethyl 2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate**

Thioisonicotinamide (18 mmol) and calcium carbonate (200 mmol) were added to a solution of ethyl 3-bromo-4-oxopiperidine-1-carboxylate (5 g; 20 mmol) in 2-propanol (60 ml). The reaction mixture obtained was heated under reflux for 48 hours. The course of the reaction was monitored by means of thin layer chromatography.

The reaction mixture was then cooled to 25 °C and filtered over Celite and the filter cake was washed several times with ethyl acetate.

The organic phase was concentrated under reduced pressure, the residue was taken up in ethyl acetate and the mixture was washed successively with water and saturated sodium chloride solution. After the organic phase had been dried over sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (30 % ethyl acetate in hexane). The desired product was obtained in a yield of 20 %.

**Stage 3: 2-(Pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride (AMN-01)**

A solution of ethyl 2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (1.8 mmol) in a 3.5 N potassium hydroxide solution (3 ml) was heated under reflux for 3 hours. The course of the reaction was monitored by means of thin layer chromatography. The reaction mixture was then cooled to 0 °C and acidified with concentrated hydrochloric acid. The solid which had precipitated out was filtered off and dried. The product was obtained in the form of the HCl salt. The yield was 30 %.

**2-(Pyridin-4-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride (AMN-02)**

**Stage 1: 2-(Pyridin-4-yl)ethanethioamide**

Hydrogen sulfide was passed through a solution of 2-(pyridin-4-yl)acetonitrile (2.5 g) in 30 % strength ammoniacal methanol (12 ml) at 0 °C for 30 minutes. The reaction mixture obtained was stirred at 25 °C for 16 hours. The solid which had precipitated out was filtered off, washed with ether and dried. The desired product was obtained in a yield of 76 %.

**Stage 2: Ethyl 2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate**

2-(Pyridin-4-yl)ethanethioamide (6 mmol) and 20 mmol of calcium carbonate were added to a solution of ethyl 3-bromo-4-oxopiperidine-1-carboxylate (1 g; 4 mmol; cf. AMN-01) in 20 ml of 2-propanol. The reaction mixture obtained was heated under reflux for 20 hours. The course of the reaction was monitored by means of thin layer chromatography. The reaction mixture was then cooled to 25 °C and filtered over Celite. The filter cake was washed several times with ethyl acetate. The organic phase was concentrated under reduced pressure, the residue was taken up in ethyl acetate and the mixture was washed successively with water and saturated sodium chloride solution. After the organic phase had been dried over sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (30 % ethyl acetate in hexane). The desired product was obtained in a yield of 70 %.

**Stage 3: 2-(Pyridin-4-ylmethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride**

A solution of ethyl 2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (3.7 mmol) in a 3.5 N potassium hydroxide solution (7 ml) was heated under reflux for 3 hours. The course of the reaction was monitored by means of thin layer chromatography. The reaction mixture was then cooled to

0 °C and acidified with concentrated hydrochloric acid. The solid which had precipitated out was filtered off and dried. The product was obtained in the form of the HCl salt. The desired product was obtained in a yield of 35 %.

***tert*-Butyl 2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (AMN-03)**

**Stage 1: Ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate**  
POCl<sub>3</sub> (2.18 g, 23.4 mmol) was added very slowly to 2.7 ml of dry DMF at 0 °C. The mixture obtained was stirred at 25 °C for 15 minutes. After the reaction temperature had been reduced again to 0 °C, N-ethoxycarbonylpiperidone (11.7 mmol) was added. The reaction mixture obtained was stirred at 25 °C for 3 hours. Thereafter, sodium acetate (7 g) and water (8.5 ml) were added and the mixture was stirred. The reaction mixture was extracted with benzene. The organic phase was washed successively with water, sodium carbonate and saturated sodium chloride solution. After the organic phase had been dried over sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was employed in the next stage without further purification. The crude yield was 63 %.

**Stage 2: Diethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4H)-dicarboxylate**  
Triethylamine (9.62 mmol) was added to a °C cold solution of ethyl 4-chloro-3-formyl-5,6-dihydropyridine-1(2H)-carboxylate (7.4 mmol) in pyridine (3 ml) and the reaction mixture obtained was stirred at 25 °C for 3 hours. 50 % strength aqueous potassium hydroxide solution (5 ml) was then added. The reaction mixture obtained was stirred at 25 °C for 3 hours and then diluted with ethyl acetate. The reaction mixture was washed with water and saturated sodium chloride solution and dried over sodium sulfate.  
After the solvent had been removed under reduced pressure, the crude product obtained was purified by column chromatography (50 % ethyl acetate in hexane). The desired product was obtained in a yield of 25 %.

**Stage 3: 4,5,6,7-Tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid hydrochloride**

A solution of diethyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4*H*)-dicarboxylate (1.76 mmol) in 3.5 N potassium hydroxide solution (3 ml) was heated under reflux for 3 hours.

The course of the reaction was monitored by means of thin layer chromatography. The reaction mixture was then cooled to 0 °C and acidified with concentrated hydrochloric acid. The solid which had precipitated out was filtered off and dried. The desired product was obtained in a yield of 30 %.

**Stage 4 and 5: 5-*tert*-Butyl 2-methyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4*H*)-dicarboxylate**

Thionyl chloride (1.5 eq.) was added to a 0 °C cold suspension of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid hydrochloride (1.9 mmol) in methanol (10 ml). The reaction mixture obtained was heated under reflux for 16 hours and the solvent was then removed under reduced pressure.

The residue was taken up in methylene chloride (10 ml) and cooled to 0 °C. Triethylamine (3 eq.) and Boc anhydride (1.2 eq.) were added to this ice-cold mixture. The reaction mixture obtained was stirred at 25 °C for 12 hours and then diluted with methylene chloride. The reaction mixture was washed with water and saturated sodium chloride solution and dried over sodium sulfate. After the solvent had been removed under reduced pressure, the crude product was purified by column chromatography (10 % ethyl acetate in hexane). The desired product was obtained in a yield of 50 %.

**Stage 6: *tert*-Butyl 2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-carboxylate**

DIBAL-H (11.1 mmol) was added to a -78 °C cold solution of 5-*tert*-butyl 2-methyl 6,7-dihydrothieno[3,2-c]pyridine-2,5(4*H*)-dicarboxylate (1.5 g, 5.3 mmol) in dry toluene (30 ml). The reaction mixture obtained was stirred at -78 °C for 1.5 hours. The course of the reaction was monitored by means of thin layer chromatography. Methanol (12 ml) was then added to the reaction mixture, the mixture was warmed slowly to 25 °C and thereafter saturated sodium chloride

solution was added. The reaction mixture was filtered over Celite and the filter cake was washed with ethyl acetate. The organic phases were concentrated under reduced pressure. The crude product obtained in this way was employed in the next stage without further purification. The crude yield was 1.4 g.

**Stage 7: *tert*-Butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate**

Triethylamine (21.2 mmol) and methanesulfonyl chloride (7.95 mmol) were added to a 0 °C cold solution of *tert*-butyl 2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (5.3 mmol) in methylene chloride (22 ml). The reaction mixture obtained was stirred at 0 °C for 2 hours. The course of the reaction was monitored by means of thin layer chromatography. The reaction mixture was then diluted with methylene chloride and washed successively with water and saturated sodium chloride solution. After the organic phase had been dried over sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was employed in the next stage without further purification.

**Stage 8: *tert*-Butyl 2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (AMN-03)**

Potassium carbonate (26.5 mmol) and N-methylpiperazine (6.36 mmol) was added to a solution of *tert*-butyl 2-((methylsulfonyloxy)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (5.3 mmol) in toluene (30 ml). The reaction mixture obtained was heated under reflux for 16 hours. The reaction temperature was then reduced to 25 °C and the reaction mixture was diluted with ethyl acetate. The reaction mixture was washed with water and saturated sodium chloride solution and dried over sodium sulfate. After the solvent had been removed under reduced pressure, the crude product obtained was purified by column chromatography (5 % methanol in methylene chloride). The desired product was obtained in a yield of 50 %.

**Amine-04: 2-Phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridine** [885272-73-1] commercially available at e.g. Chem-Impex. **Amine-05: 3-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1h-pyrazolo[4,3-c]pyridine Hydrochloride** [MFCD09763695] commercially available at e.g. Otava-BB. **Amine-06: 4-Pyridin-4-yl-4,5,6,7-tetrahydro-3h-imidazo[4,5-c]pyridine** [MFCD09749722] commercially available at e.g. Otava-BB. **Amine-07: 4-Phenyl-4,5,6,7-tetrahydro-1h-imidazo[4,5-c]pyridine** [4875-39-2] commercially available at e.g. BBB-SCI. **Amine-08: 1,4,5,6-Tetrahydro-1-phenyl-3-(trifluoromethyl)pyrrolo-[3,4-c]-pyrazole** [MFCD08447382] commercially available at e.g. BBB-SCI. **Amine-09: 1,4,5,6-Tetrahydro-1-methyl-3-(trifluoromethyl)pyrrolo-[3,4-c]-pyrazole** [MFCD08447379] commercially available at e.g. BBB-SCI.

### Pharmacological studies

The agonistic and antagonistic action of the compounds according to the invention on the bradykinin 1 receptor (B1R) of the human and rat species were determined as described above.

Antagonists lead to a suppression of the Ca<sup>2+</sup> inflow. % inhibition compared with the maximum achievable inhibition was calculated. The compounds according to the invention show a good activity on the human and on the rat receptor.

| Ex-ample | B1R antagonism, rat [10 µM]<br>% inhibition | B1R antagonism, human (10 µM)<br>% inhibition |
|----------|---------------------------------------------|-----------------------------------------------|
| 01       | 98                                          | 46                                            |
| 02       | 101                                         | 100                                           |
| 03       | 102                                         | 83                                            |
| 04       | 56                                          | ---                                           |
| 05       | 27                                          | 48                                            |
| 06       | 57                                          | 93                                            |
| 07       | 104                                         | 69                                            |
| 08       | 106                                         | 48                                            |
| 09       | 105                                         | 100                                           |
| 10       | 105                                         | 78                                            |
| 11       | 60                                          | 7                                             |
| 12       | 104                                         | 64                                            |
| 13       | 99                                          | 56                                            |
| 14       | 99                                          | 85                                            |
| 15       | 98                                          | 69                                            |
| 16       | 81                                          | 43                                            |
| 17       | 55                                          | 49                                            |
| 18       | 109                                         | 99                                            |
| 19       | 83                                          | 35                                            |

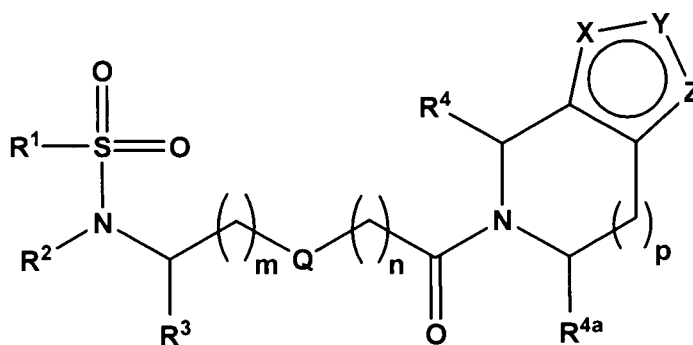
|    |     |     |
|----|-----|-----|
| 20 | 96  | 11  |
| 21 | 70  | 34  |
| 22 | 100 | 96  |
| 23 | 105 | 91  |
| 24 | 100 | 73  |
| 25 | 103 | 86  |
| 26 | 101 | 97  |
| 27 | 106 | 100 |
| 28 | 109 | 100 |
| 29 | 101 | 99  |
| 30 | 104 | 99  |
| 31 | 105 | 100 |
| 32 | 104 | 99  |
| 33 | 35  | 40  |
| 34 | 57  | 29  |
| 35 | 3   | 41  |
| 36 | 100 | 100 |
| 37 | 97  | 28  |
| 38 | 97  | 99  |
| 39 | 99  | 100 |
| 40 | 90  | 51  |
| 41 | 99  | 64  |
| 42 | 79  | 14  |
| 43 | 99  | 99  |
| 44 | 59  | 83  |
| 45 | 99  | 98  |
| 46 | 102 | 100 |
| 47 | 101 | 100 |
| 48 | 94  | 100 |
| 49 | 95  | 99  |
| 50 | 102 | 100 |
| 51 | 103 | 100 |

|    |     |     |
|----|-----|-----|
| 52 | 95  | 76  |
| 53 | 98  | 96  |
| 54 | 101 | 16  |
| 55 | 103 | 88  |
| 56 | 105 | 100 |
| 57 | 99  | 100 |
| 58 | 103 | 100 |
| 59 | 104 | 100 |
| 60 | 106 | 100 |
| 61 | 106 | 100 |
| 62 | 107 | 100 |
| 63 | 106 | 99  |
| 64 |     | 100 |
| 66 | 97  |     |
| 68 | 103 |     |
| 69 | 64  |     |
| 71 | 101 |     |
| 73 | 99  |     |
| 74 | 95  |     |
| 75 | 103 |     |
| 76 | 48  |     |
| 78 | 98  |     |
| 81 | 102 |     |
| 82 | 100 |     |
| 83 | 101 |     |
| 84 | 97  |     |
| 85 | 102 |     |
| 86 | 96  |     |

|     |     |    |
|-----|-----|----|
| 87  | 103 |    |
| 88  | 65  |    |
| 91  | 103 |    |
| 92  | 94  |    |
| 93  | 93  |    |
| 94  | 36  |    |
| 95  | 99  |    |
| 96  | 54  |    |
| 97  | 96  |    |
| 98  | 98  |    |
| 99  | 98  |    |
| 100 | 101 |    |
| 125 | 102 | 75 |
| 126 | 104 | 90 |

**Patent claims:**

## 1. Substituted sulfonamide derivatives of the general formula I



I,

wherein

m and n independently of one another each represent 0, 1 or 2;

p represents 0, 1 or 2;

Q represents a single bond, -CH<sub>2</sub>- or -O-;X represents N, NR<sup>5</sup>, O, S or CR<sup>8</sup>;Y represents N, NR<sup>6</sup>, O, S or CR<sup>9</sup>;Z represents N, NR<sup>7</sup>, O, S or CR<sup>10</sup>;R<sup>1</sup> represents CH(aryl)<sub>2</sub>, aryl, heteroaryl or a CH(aryl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;R<sup>2</sup> and R<sup>3</sup> are defined as described under (i) or (ii):

- (i)  $R^2$  represents H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, bicyclic 8- to 12-membered carbocyclyl,  $CH(aryl)_2$ , aryl or heteroaryl; or denotes a  $C_{3-8}$ -cycloalkyl, bicyclic 8- to 12-membered carbocyclyl,  $CH(aryl)_2$ , aryl or heteroaryl bonded via a  $C_{1-6}$ -alkylene group,  $C_{2-6}$ -alkenylene group or  $C_{2-6}$ -alkynylene group;

$R^3$  represents H,  $-C(=O)-NR^{11}R^{12}$ ,  $-C(=O)-OR^{13}$ ,  $C_{1-6}$ -alkyl, aryl or heteroaryl; or denotes an aryl or heteroaryl bonded via a  $C_{1-6}$ -alkylene group,  $C_{2-6}$ -alkenylene group or  $C_{2-6}$ -alkynylene group, wherein  $R^2$  and  $R^3$  do not both represent H, or

- (ii)  $R^2$  and  $R^3$  together with the  $-N-(CH)-$  group joining them form an unsubstituted or mono- or polysubstituted heterocyclic ring, which can be fused with an aryl or heteroaryl radical,

wherein the heterocyclic ring is saturated or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero atom to which the radical  $R^2$  is bonded, at least one further hetero atom or a hetero atom group chosen from the group consisting of N,  $NR^{14}$ , O, S, S=O or  $S(=O)_2$ ; wherein the radical  $R^{14}$  denotes H,  $C_{1-6}$ -alkyl,  $-C(=O)-R^{15}$ ,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $C_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group, and  $R^{15}$  denotes  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $C_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group,

$R^4$  and  $R^{4a}$  independently of one another each represent H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $C_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group;

$R^5$ ,  $R^6$  and  $R^7$  independently of one another each represent H,  $C_{1-6}$ -alkyl, aryl or heteroaryl;

$R^8$ ,  $R^9$  and  $R^{10}$  independently of one another each represent H,  $-CF_3$ ,  $-C(=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $C(=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $NR^{11}R^{12}$ ,  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a  $C_{1-6}$ -alkylene group,

wherein at least one of the radicals  $R^4$ ,  $R^{4a}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  is not H,

$R^{11}$  and  $R^{12}$  are defined as described under (iii) or (iv):

(iii)  $R^{11}$  and  $R^{12}$  independently of one another each denote H,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl,  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group;

or

(iv)  $R^{11}$  and  $R^{12}$  together with the nitrogen atom joining them form an unsubstituted or mono- or polysubstituted heterocyclic ring, which can be fused with a saturated, at least monounsaturated or aromatic, unsubstituted or mono- or polysubstituted ring system,

wherein the heterocyclic ring is saturated or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero atom to which the radicals  $R^{11}$  and  $R^{12}$  are bonded, at least one further hetero atom or a hetero atom group chosen from the group consisting of N,  $NR^{16}$ , O, S, S=O and  $S(=O)_2$ ,

the ring system is 4-, 5-, 6- or 7-membered, can contain at least one hetero atom or a hetero atom group chosen from the group consisting of N,  $NR^{17}$ , O, S, S=O and  $S(=O)_2$ ,

$R^{16}$  represents a radical chosen from the group consisting of H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or  $C_{3-8}$ -cycloalkyl bonded via a  $C_{1-3}$ -alkylene group and

R<sup>17</sup> represents a radical chosen from the group consisting of H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or C<sub>3-8</sub>-cycloalkyl bonded via a C<sub>1-3</sub>-alkylene group;

R<sup>13</sup> denotes H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;

wherein the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>1-3</sub>-alkylene, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene, C<sub>2-6</sub>-alkynylene, C<sub>3-8</sub>-cycloalkyl, heterocycloalkyl, bicyclic 8- to 12-membered carbocyclyl, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals and the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>1-3</sub>-alkylene, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene and C<sub>2-6</sub>-alkynylene can in each case be branched or unbranched;

optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of the enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides.

2. Substituted sulfonamide derivatives according to claim 1,

wherein

m and n independently of one another each represent 0, 1 or 2;

p represents 0, 1 or 2;

Q represents a single bond, -CH<sub>2</sub>- or -O-;

X represents N, NR<sup>5</sup>, O, S or CR<sup>8</sup>;

Y represents N, NR<sup>6</sup>, O, S or CR<sup>9</sup>;

Z represents N, NR<sup>7</sup>, O, S or CR<sup>10</sup>;

$R^1$  represents  $\text{CH}(\text{aryl})_2$ , aryl, heteroaryl or a  $\text{CH}(\text{aryl})_2$ , aryl or heteroaryl bonded via a  $\text{C}_{1-3}$ -alkylene group;

$R^2$  and  $R^3$  are defined as described under (i) or (ii):

- (i)  $R^2$  represents H,  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{3-8}$ -cycloalkyl, bicyclic 8- to 12-membered carbocyclyl,  $\text{CH}(\text{aryl})_2$ , aryl or heteroaryl; or denotes a  $\text{C}_{3-8}$ -cycloalkyl, bicyclic 8- to 12-membered carbocyclyl,  $\text{CH}(\text{aryl})_2$ , aryl or heteroaryl bonded via a  $\text{C}_{1-6}$ -alkylene group,  $\text{C}_{2-6}$ -alkenylene group or  $\text{C}_{2-6}$ -alkynylene group;

$R^3$  represents H,  $-\text{C}(=\text{O})-\text{NR}^{11}\text{R}^{12}$ ,  $-\text{C}(=\text{O})-\text{OR}^{13}$ ,  $\text{C}_{1-6}$ -alkyl, aryl or heteroaryl; or denotes an aryl or heteroaryl bonded via a  $\text{C}_{1-6}$ -alkylene group,  $\text{C}_{2-6}$ -alkenylene group or  $\text{C}_{2-6}$ -alkynylene group, wherein  $R^2$  and  $R^3$  do not both represent H, or

- (ii)  $R^2$  and  $R^3$  together with the  $-\text{N}(\text{CH}-)$  group joining them form an unsubstituted or mono- or polysubstituted heterocyclic ring, which can be fused with an aryl or heteroaryl radical,

wherein the heterocyclic ring is saturated or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero atom to which the radical  $R^2$  is bonded, at least one further hetero atom or a hetero atom group chosen from the group consisting of N,  $\text{NR}^{14}$ , O, S,  $\text{S}=\text{O}$  or  $\text{S}(=\text{O})_2$ ; wherein the radical  $R^{14}$  denotes H,  $\text{C}_{1-6}$ -alkyl,  $-\text{C}(=\text{O})-\text{R}^{15}$ ,  $\text{C}_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $\text{C}_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $\text{C}_{1-3}$ -alkylene group, and  $R^{15}$  denotes  $\text{C}_{1-6}$ -alkyl,  $\text{C}_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $\text{C}_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $\text{C}_{1-3}$ -alkylene group,

$R^4$  and  $R^{4a}$  independently of one another each represent H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, aryl, heteroaryl or a  $C_{3-8}$ -cycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group;

$R^5$ ,  $R^6$  and  $R^7$  independently of one another each represent H,  $C_{1-6}$ -alkyl, aryl or heteroaryl;

$R^8$ ,  $R^9$  and  $R^{10}$  independently of one another each represent H,  $-CF_3$ ,  $-C(=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $C(=O)-NR^{11}R^{12}$ ,  $-C_{1-6}$ -alkylene- $NR^{11}R^{12}$ ,  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a  $C_{1-6}$ -alkylene group,

wherein at least one of the radicals  $R^4$ ,  $R^{4a}$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  is not H,

$R^{11}$  and  $R^{12}$  are defined as described under (iii) or (iv):

(iii)  $R^{11}$  and  $R^{12}$  independently of one another each denote H,  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl,  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a  $C_{3-8}$ -cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a  $C_{1-3}$ -alkylene group;

or

(iv)  $R^{11}$  and  $R^{12}$  together with the nitrogen atom joining them form an unsubstituted or mono- or polysubstituted heterocyclic ring, which can be fused with a saturated, at least monounsaturated or aromatic, unsubstituted or mono- or polysubstituted ring system,

wherein the heterocyclic ring is saturated, or at least monounsaturated, but not aromatic, is 4-, 5-, 6- or 7-membered, can contain, in addition to the N hetero atom to which the radicals  $R^{11}$  and  $R^{12}$  are bonded, at least one further hetero atom or a hetero atom group chosen from the group consisting of N,  $NR^{16}$ , O, S, S=O and  $S(=O)_2$ ,

the ring system is 4-, 5-, 6- or 7-membered, can contain at least one hetero atom or a hetero atom group chosen from the group consisting of N, NR<sup>17</sup>, O, S, S=O and S(=O)<sub>2</sub>,

R<sup>16</sup> represents a radical chosen from the group consisting of H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or C<sub>3-8</sub>-cycloalkyl bonded via a C<sub>1-3</sub>-alkylene group and

R<sup>17</sup> represents a radical chosen from the group consisting of H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or an aryl, heteroaryl or C<sub>3-8</sub>-cycloalkyl bonded via a C<sub>1-3</sub>-alkylene group;

R<sup>13</sup> denotes H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl or a C<sub>3-8</sub>-cycloalkyl, 3- to 8-membered heterocycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group;

wherein the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>1-3</sub>-alkylene, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene, C<sub>2-6</sub>-alkynylene, C<sub>3-8</sub>-cycloalkyl, heterocycloalkyl, bicyclic 8- to 12-membered carbocyclyl, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals and the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>1-3</sub>-alkylene, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene and C<sub>2-6</sub>-alkynylene can in each case be branched or unbranched;

optionally in the form of an individual enantiomer or of an individual diastereomer, of the racemate, of the enantiomers, of the diastereomers, mixtures of the enantiomers and/or diastereomers, and in each case in the form of their bases, their physiologically acceptable salts and/or their N-oxides,

wherein

a substituted alkyl, alkenyl, alkylene, alkenylene, alkynylene or cycloalkyl is substituted once or several times by identical or different substituents chosen independently of one another from the group consisting of F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-

OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl and benzyl,

a substituted heterocycloalkyl is substituted once or several times by identical or different substituents chosen independently of one another from the group consisting of F, Cl, Br, I, -CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, pyrrolinyl, piperazinyl, morpholinyl, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl and benzyl or, if an N hetero atom is present, this can be substituted by a C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, aryl, heteroaryl or a C<sub>3-8</sub>-cycloalkyl, aryl or heteroaryl bonded via a C<sub>1-3</sub>-alkylene group, wherein these alkyl, cycloalkyl, alkylene and aryl and heteroaryl groups can be unsubstituted or substituted once or several times by identical or different substituents,

and substituted aryl or heteroaryl is substituted once or several times by identical or different substituents chosen independently of one another from the group consisting of F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NH-aryl<sup>1</sup>, N(aryl<sup>1</sup>)<sub>2</sub>, N(C<sub>1-6</sub>-alkyl)aryl<sup>1</sup>, pyrrolinyl, piperazinyl, morpholinyl, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkyl, O-C<sub>1-6</sub>-alkyl-OH, C(=O)C<sub>1-6</sub>-alkyl, NHSO<sub>2</sub>C<sub>1-6</sub>-alkyl, NHCOC<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CH<sub>2</sub>SO<sub>2</sub>-phenyl, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl, OCF<sub>3</sub>, CF<sub>3</sub>, -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, -O-C(CH<sub>3</sub>)<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, unsubstituted C<sub>1-6</sub>-alkyl, pyrrolidinyl, imidazolyl, piperidinyl, benzyloxy, phenoxy, phenyl, naphthyl, pyridinyl, -C<sub>1-3</sub>-alkylene-aryl<sup>1</sup>, benzyl, thienyl and furyl, wherein aryl<sup>1</sup> represents phenyl, furyl, thienyl or pyridinyl;

a substituted heterocyclic ring is substituted once or several times by identical or different substituents chosen independently of one another from the group consisting of F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl and benzyl,

a substituted, saturated or at least partly unsaturated ring system which is fused with the heterocyclic ring formed by R<sup>11</sup> and R<sup>12</sup> is substituted once or several times by identical or different substituents chosen independently of one another from the group consisting of F, Cl, Br, I, CN, NH<sub>2</sub>, NH-C<sub>1-6</sub>-alkyl, NH-C<sub>1-6</sub>-alkylene-OH, C<sub>1-6</sub>-alkyl, N(C<sub>1-6</sub>-alkyl)<sub>2</sub>, N(C<sub>1-6</sub>-alkylene-OH)<sub>2</sub>, NO<sub>2</sub>, SH, S-C<sub>1-6</sub>-alkyl, S-benzyl, O-C<sub>1-6</sub>-alkyl, OH, O-C<sub>1-6</sub>-alkylene-OH, =O, O-benzyl, C(=O)C<sub>1-6</sub>-alkyl, CO<sub>2</sub>H, CO<sub>2</sub>-C<sub>1-6</sub>-alkyl and benzyl, and

a substituted aromatic ring system which is fused with the heterocyclic ring formed by R<sup>11</sup> and R<sup>12</sup> is substituted as defined above for aryl or heteroaryl,

a substituted bicyclic 8- to 12-membered carbocyclyl is substituted once or several times by identical or different substituents, wherein the substituents which are bonded to a saturated or partly unsaturated ring system of the carbocyclyl are chosen from the groups of substituents defined above for cycloalkyl and the substituents which are bonded to an aromatic ring system of the carbocyclyl are chosen from the group of substituents defined above for aryl or heteroaryl.

3. Substituted sulfonamide derivatives according to claim 1 or 2, wherein R<sup>1</sup> represents CH(aryl)<sub>2</sub>, phenyl, naphthyl, Indolyl, benzofuranyl, benzothiophenyl (benzothienyl); benzoxazolyl, benzoxadiazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinolinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothienyl), benzyl or 2-phenylethyl, preferably CH(aryl)<sub>2</sub>, phenyl, naphthyl, benzothiophenyl, benzoxadiazolyl, thiophenyl, pyridinyl, imidazothiazolyl or dibenzofuranyl, particularly preferably phenyl or naphthyl, in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

4. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein  $R^2$  represents H,  $C_{1-6}$ -alkyl,  $C_{3-6}$ -cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl,  $CH(phenyl)_2$ , aryl or heteroaryl; or denotes a  $C_{3-6}$ -cycloalkyl, benzo-fused cycloalkyl,  $CH(phenyl)_2$ , aryl or heteroaryl bonded via a  $C_{1-6}$ -alkylene group,  $C_{2-6}$ -alkenylene group or  $C_{2-6}$ -alkynylene group, wherein the radicals  $C_{1-6}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkylene,  $C_{2-6}$ -alkenylene,  $C_{2-6}$ -alkynylene, aryl and heteroaryl are in each case unsubstituted or substituted once or several times, wherein aryl in particular is unsubstituted or substituted once or several times by identical or different radicals which are chosen independently of one another from the group consisting of  $-CH_2-O-CH_2-O-$ ,  $-O-CH_2-O-CH_2-$ ,  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl-O-, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ , OH and SH.

5. Substituted sulfonamide derivative according to one or more of the preceding claims, wherein  $R^3$  represents H,  $-C(=O)-NR^{11}R^{12}$ ,  $-C(=O)-OR^{13}$ ,  $C_{1-6}$ -alkyl, aryl or heteroaryl; wherein the radicals  $C_{1-6}$ -alkyl, aryl and heteroaryl are in each case unsubstituted or substituted once or several times, wherein the aryl in particular is unsubstituted or substituted once or several times by identical or different radicals chosen independently of one another from the group consisting of  $C_{1-6}$ -alkyl,  $C_{1-6}$ -alkyl-O-, F, Cl, Br, I,  $CF_3$ ,  $OCF_3$ , OH and SH.

6. Substituted sulfonamide derivative according to one or more of the preceding claims, wherein  $R^2$  and  $R^3$  together with the  $-N-(CH)-$  group joining them form a 4-, 5-, 6- or 7-membered, unsubstituted, mono- or polysubstituted heterocyclic ring, which may contain an oxygen atom as a ring-member and which can be fused with one or two 6-membered aromatic ring(s) (benzo group).

7. Substituted sulfonamide derivative according to one or more of the preceding claims, wherein  $R^4$  and  $R^{4a}$  independently of one another each represent H,  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a  $C_{1-3}$ -alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-$

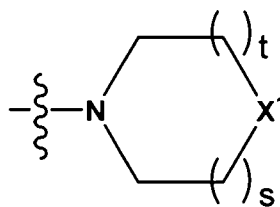
C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

8. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently of one another each represent H, C<sub>1-4</sub>-alkyl or phenyl.

9. Substituted sulfonamide derivative according to one or more of the preceding claims, wherein R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-NR<sup>11</sup>R<sup>12</sup>, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-6</sub>-alkylene group; wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times in an identical or different manner, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

10. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein R<sup>11</sup> and R<sup>12</sup> independently of one another each represent H, substituted or unsubstituted C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl; or

the group -NR<sup>11</sup>R<sup>12</sup> represents the heterocyclic radical of the type according to the general formula IIaa



IIaa

wherein

X<sup>1</sup> represents O, S, NR<sup>18</sup> CH<sub>2</sub>, C(H)(halogen) or C(halogen)<sub>2</sub>, wherein halogen preferably denotes F, Cl or Br, R<sup>18</sup> represents H; C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl; aryl, preferably phenyl or naphthyl; or heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl; or R<sup>18</sup> represents a C<sub>3-8</sub>-cycloalkyl bonded via a C<sub>1-3</sub>-alkylene group, an aryl, preferably phenyl or naphthyl, bonded via a C<sub>1-3</sub>-alkylene group; or a heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl, bonded via a C<sub>1-3</sub>-alkylene group; and

s and t independently of one another each represent 0, 1 or 2, with the proviso that s + t = 0, 1, 2 or 3,

wherein the abovementioned radicals C<sub>1-6</sub>-alkyl, C<sub>1-3</sub>-alkylene, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl.

11. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein R<sup>13</sup> represents H or C<sub>1-6</sub>-alkyl or denotes a phenyl bonded via a C<sub>1-3</sub>-alkylene group.

12. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein

m and n independently of one another each represent 0, 1 or 2;  
p represents 0, 1 or 2;

Q represents a single bond, -CH<sub>2</sub>- or -O-;

X represents N, NR<sup>5</sup>, O, S or CR<sup>8</sup>;

Y represents N, NR<sup>6</sup>, O, S or CR<sup>9</sup>;

Z represents N, NR<sup>7</sup>, O, S or CR<sup>10</sup>;

R<sup>1</sup> represents CH(phenyl)<sub>2</sub>, phenyl, naphthyl, indolyl, benzofuranyl, benzothiophenyl (benzothieryl), benzoxazolyl, benzoxadiazolyl, pyrrolyl, furanyl, thienyl, thiazolyl, imidazolyl, oxazolyl, quinazolyl, quinoliny, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazothiazolyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl (dibenzothieryl), benzyl or 2-phenylethyl, in each case unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, -C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

R<sup>2</sup> represents H, C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl, or a C<sub>3-6</sub>-cycloalkyl, 8- to 10-membered benzo-fused cycloalkyl, CH(phenyl)<sub>2</sub>, aryl or heteroaryl bonded via a C<sub>1-6</sub>-alkylene group, C<sub>2-6</sub>-alkenylene group or C<sub>2-6</sub>-alkynylene group, wherein the radicals C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkylene, C<sub>2-6</sub>-alkenylene, C<sub>2-6</sub>-alkynylene and aryl are in each case unsubstituted or substituted once or several times, wherein aryl in particular is unsubstituted or substituted once or several times by identical or different radicals which are chosen independently of one another from the group consisting of -CH<sub>2</sub>-O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-O-CH<sub>2</sub>-, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl-O-, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH and SH;

R<sup>3</sup> represents H, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C(=O)-OR<sup>13</sup>, C<sub>1-6</sub>-alkyl, aryl or heteroaryl, wherein the radicals C<sub>1-6</sub>-alkyl, aryl and heteroaryl are in each case unsubstituted or substituted once or several times, wherein the aryl and heteroaryl in particular is unsubstituted or substituted once or several times by identical or different radicals chosen independently of one another from the group consisting of C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl-O-, F, Cl, Br, I, CF<sub>3</sub>, OCF<sub>3</sub>, OH and SH, wherein R<sup>2</sup> and R<sup>3</sup> do not both represent H; or

R<sup>2</sup> and R<sup>3</sup> together with the -N-(CH)- group joining them form a 4-, 5-, 6- or 7-membered, unsubstituted or mono- or polysubstituted heterocyclic ring, which may contain an oxygen atom as a ring-member and which can be fused with one or two 6-membered aromatic ring(s) (benzo group);

R<sup>4</sup> and R<sup>4a</sup> independently of one another each represent H, C<sub>1-6</sub>-alkyl, C<sub>3-8</sub>-cycloalkyl, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-3</sub>-alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times by identical or different substituents, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently of one another each represent H, C<sub>1-4</sub>-alkyl or phenyl;

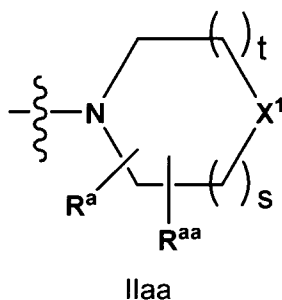
R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> independently of one another each represent H, -CF<sub>3</sub>, -C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-C(=O)-NR<sup>11</sup>R<sup>12</sup>, -C<sub>1-6</sub>-alkylene-NR<sup>11</sup>R<sup>12</sup>, phenyl, naphthyl, furyl, thienyl or pyridinyl or a phenyl, naphthyl, furyl, thienyl or pyridinyl bonded via a C<sub>1-6</sub>-alkylene group, wherein the phenyl, naphthyl, furyl, thienyl or pyridinyl is unsubstituted or substituted once or several times in an identical or different manner, wherein the substituents are preferably chosen independently of one another from the group consisting of -O-C<sub>1-3</sub>-alkyl, C<sub>1-6</sub>-alkyl, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OCF<sub>3</sub>, -OH, -SH, phenyl, naphthyl, furyl, thienyl and pyridinyl;

wherein at least one of the radicals R<sup>4</sup>, R<sup>4a</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> does not represent H,

R<sup>11</sup> and R<sup>12</sup> independently of one another each represent H, substituted or unsubstituted C<sub>1-6</sub>-alkyl or C<sub>3-8</sub>-cycloalkyl;

or

the group  $-NR^{11}R^{12}$  represents the heterocyclic ring of the type according to the general formula IIaa



wherein

$X^1$  represents O, S,  $NR^{18}$ ,  $CH_2$ ,  $C(H)(\text{halogen})$  or  $C(\text{halogen})_2$ , wherein halogen preferably denotes F, Cl or Br,  $R^{18}$  represents H;  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl; aryl, preferably phenyl or naphthyl; or heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl; or  $R^{18}$  represents a  $C_{3-8}$ -cycloalkyl bonded via a  $C_{1-3}$ -alkylene group, an aryl, preferably phenyl or naphthyl, bonded via a  $C_{1-3}$ -alkylene group; or a heteroaryl, preferably a 5- to 6-membered heteroaryl having 1 or 2 N hetero atoms, in particular pyridinyl, bonded via a  $C_{1-3}$ -alkylene group, wherein the abovementioned radicals  $C_{1-6}$ -alkyl,  $C_{3-8}$ -cycloalkyl,  $C_{1-3}$ -alkylene, aryl and heteroaryl can in each case be unsubstituted or substituted once or several times by identical or different radicals, wherein the substituents are preferably chosen independently of one another from the group consisting of  $-O-C_{1-3}$ -alkyl,  $-C_{1-6}$ -alkyl,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-CF_3$ ,  $-OCF_3$ ,  $-OH$ ,  $-SH$ , phenyl, naphthyl, furyl, thienyl and pyridinyl,

$R^a$  and  $R^{aa}$  independently of one another each represent H, methyl, ethyl, F, Cl or Br, and

s and t independently of one another each represent 0, 1 or 2, with the proviso that  $s + t = 0, 1, 2$  or 3,

R<sup>13</sup> represents H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, benzyl or phenethyl.

13. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein

X represents CR<sup>8</sup>,  
Y represents CR<sup>9</sup> and  
Z represents S,

or

X represents S,  
Y represents CR<sup>9</sup> and  
Z represents N,

or

X represents CR<sup>8</sup>,  
Y represents N and  
Z represents O,

or

X represents CR<sup>8</sup>,  
Y represents CR<sup>9</sup> and  
Z represents NR<sup>7</sup>,

or

X represents S,  
Y represents CR<sup>9</sup> and  
Z represents CR<sup>10</sup>

or

X represents N,  
Y represents CR<sup>9</sup> and  
Z represents NR<sup>7</sup>

or

X represents O,  
Y represents CR<sup>9</sup> and  
Z represents N

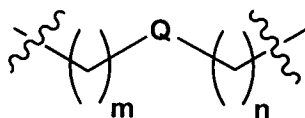
or

X represents NR<sup>5</sup>,  
Y represents N and  
Z represents CR<sup>10</sup>

or

X represents CR<sup>8</sup>,  
Y represents N and  
Z represents NR<sup>7</sup>.

14. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein m, n and Q in the part structure



are chosen such that this part structure is chosen from the group consisting of a single bond,  $-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)_3-$ ;  $-(\text{CH}_2)-\text{O}-(\text{CH}_2)-$ ;  $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)-$ ;  $-(\text{CH}_2)-\text{O}-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$  and  $-(\text{CH}_2)-\text{O}-$ .

15. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein p represents 0 or 1, preferably 1.

16. Substituted sulfonamide derivatives according to one or more of the preceding claims, wherein the sulfonamide derivative is chosen from the group consisting of

- 1 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 2 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 3 (R)-N-(3-oxo-1-phenyl-3-(3-(pyridin-4-yl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 4 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(piperidine-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 5 1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-(1-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethanone
- 6 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propan-1-one
- 7 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-p-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 8 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-m-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 9 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 10 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-m-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one

- 11 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-o-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 12 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-o-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 13 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 14 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(piperidin-1-carbonyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 15 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-phenyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 16 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-phenyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 17 (R)-N-(3-oxo-1-phenyl-3-(3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 18 N-(2-(2-(4-ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)methoxy-N,2,6-trimethylbenzenesulfonamide
- 19 1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethanone
- 20 N-((1R)-3-oxo-1-phenyl-3-(4-p-tolyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 21 N-((1R)-3-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-oxo-1-phenylpropyl)naphthalene-2-sulfonamide
- 22 1-(4-(4-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 23 1-(4-ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)butan-1-one
- 24 1-(3-(4-chlorophenyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 25 1-(3-(4-fluorophenyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 26 (R)-N-(3-oxo-1-phenyl-3-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide

- 27 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 28 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(piperidin-1-ylmethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 29 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(3-(morpholinomethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)ethanone
- 30 4-methoxy-N,2,6-trimethyl-N-(2-(2-(3-(morpholinomethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)benzenesulfonamide
- 31 1-(3-((dimethylamino)methyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)ethanone
- 32 N-(2-(2-(3-((dimethylamino)methyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)-4-methoxy-N,2,6-trimethylbenzenesulfonamide
- 33 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(6-chloropyridin-3-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 34 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(3-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 35 3-(1-(4-chloro-2,5-dimethylphenylsulfonyl)piperidin-2-yl)-1-(4-(3-fluorophenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 36 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-(pyridin-4-yl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone
- 37 1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 38 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethan-1-one
- 39 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 40 1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 41 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propan-1-one

- 42 N-(3-oxo-1-phenyl-3-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propyl)naphthalene-2-sulfonamide
- 43 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-ylmethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)butan-1-one
- 44 1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-)-2-(1-(3-(trifluoromethyl)phenylsulfonyl)piperidin-2-yl)ethan-1-one
- 45 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one
- 46 N-(3-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-3-oxo-1-phenylpropyl)naphthalene-2-sulfonamide
- 47 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)butan-1-one
- 48 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethan-1-one
- 49 4-methoxy-N,2,6-trimethyl-N-(2-(2-oxo-2-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)ethoxy)ethyl)benzenesulfonamide
- 50 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethan-1-one
- 51 4-methoxy-N,2,6-trimethyl-N-(2-(2-(2-((4-methylpiperazin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-oxoethoxy)ethyl)benzenesulfonamide
- 52 3-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)propan-1-one
- 53 4-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)-1-(2-(pyridin-4-yl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)butan-1-one
- 54 1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-2-[1-[[3-(trifluoromethyl)phenyl]sulfonyl]-piperidin-2-yl]-ethanone
- 55 3-[1-[(4-chloro-2,5-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propan-1-one
- 56 N-[2-[2-[2-(azetidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-oxo-ethoxy]-ethyl]-2-chloro-N-cyclopropyl-6-methyl-benzenesulfonic acid amide

- 57 2-chloro-N-cyclopropyl-N-[2-[2-[(3,3-difluoro-azetidin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-6-methyl-benzenesulfonic acid amide
- 58 2-[[[(2S)-1-[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-5-yl]-ethanone
- 59 2-[[[(2S)-1-[2-chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 60 2-chloro-N-cyclopropyl-6-methyl-N-[2-[2-oxo-2-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethoxy]-ethyl]-benzenesulfonic acid amide
- 61 2-[[[(2S)-1-[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 62 2-[[[(2S)-1-[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-(pyrrolidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 63 2-[[[(2S)-1-[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-pyrrolidin-2-yl]-methoxy]-1-[2-(piperidin-1-yl-methyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 64 2-[[[(2S)-1-[4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-[(4-methyl-[1,4]diazepan-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 66 4-Methoxy-N,2,6-trimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 68 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-butan-1-one
- 69 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 71 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 73 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 74 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one

- 75 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 76 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butan-1-one
- 78 N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 81 N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 82 N-Benzyl-4-Methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 83 4-Methoxy-2,6-Dimethyl-N-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide
- 84 4-Methoxy-2,6-Dimethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-N-phenyl-benzenesulfonic acid amide
- 85 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 86 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydro-quinolin-2-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 87 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one
- 88 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-4-[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-butan-1-one
- 91 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone
- 92 2-[[4-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 93 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone

- 94 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[4-[[2-(trifluoromethyl)-phenyl]sulfonyl]-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-methoxy]-ethanone
- 95 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 96 4-Methoxy-N,2,3,6-tetramethyl-N-[2-[2-oxo-2-(4-phenyl-4,5,6,7-tetrahydro-1-imidazo[4,5-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 97 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone
- 98 1-(4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-2-[[1-[[2-(trifluoromethyl)-phenyl]sulfonyl]-piperidin-2-yl]-methoxy]-ethanone
- 99 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propan-1-one
- 100 3-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-propan-1-one
- 101 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-1-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]ethanone
- 102 2-[2-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-ethoxy]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 103 N-Methyl-N-[4-[2-[(4-methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-4-oxo-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide
- 104 N-Methyl-N-[4-Oxo-4-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-butyl]-3-(trifluoromethyl)-benzenesulfonic acid amide
- 105 1-[2-[(4-Methyl-piperazin-1-yl)-methyl]-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-[4-(naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-ethanone
- 106 2-[4-(Naphthalen-2-ylsulfonyl)-3,4-dihydro-2H-[1,4]benzoxazin-3-yl]-1-(4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-5-yl)-ethanone
- 107 4-Methoxy-N,2,6-trimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide

- 108 4-Methoxy-N,2,6-trimethyl-N-[2-[2-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-2-oxo-ethoxy]-ethyl]-benzenesulfonic acid amide
- 109 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethanone
- 110 2-[[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-methoxy]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-ethanone
- 111 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 112 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 113 4-[1-[(2-Chloro-6-methyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 114 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 115 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 116 4-[1-[(4-Methoxy-2,6-dimethyl-phenyl)sulfonyl]-piperidin-2-yl]-1-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-butan-1-one
- 117 4-[1-(Naphthalen-1-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 118 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-[1-(naphthalen-1-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 119 4-[1-(Naphthalen-2-ylsulfonyl)-piperidin-2-yl]-1-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-butan-1-one
- 120 1-[1-Methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-[1-(naphthalen-2-ylsulfonyl)-piperidin-2-yl]-butan-1-one
- 121 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-(2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl)-ethoxy]-ethyl]-benzenesulfonic acid amide
- 122 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-[1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-ethoxy]-ethyl]-benzenesulfonic acid amide

- 123 N-[(1-Ethyl-1H-imidazol-2-yl)-methyl]-4-methoxy-2,6-dimethyl-N-[2-[2-[1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrrolo[3,4-c]pyrazol-5-yl]-2-oxoethoxy]-ethyl]-benzenesulfonic acid amide
- 124 N-(4H-[1,3]Benzodioxin-7-yl-methyl)-4-methoxy-2,6-dimethyl-N-[2-[2-oxo-2-phenyl-4,5,6,7-tetrahydro-oxazolo[5,4-c]pyridin-5-yl]-ethoxy]-ethyl]-benzenesulfonic acid amide
- 125 2-[[[(2S)-1-[(4-methoxy-2,6-dimethyl-phenyl)sulfonyl]-1,2,3,4-tetrahydroquinolin-2-yl]-methoxy]-1-(3-pyridin-4-yl-4,5,6,7-tetrahydro-isoxazolo[4,5-c]pyridin-5-yl)-ethanone
- 126 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)piperidin-2-yl)methoxy)-1-(4-phenyl-3-(piperidin-1-ylmethyl)-6,7-dihydroisoxazolo[4,5-c]pyridin-5(4H-yl)ethanone

optionally in the form of their physiologically acceptable salts.

17. Medicaments containing at least one substituted sulfonamide derivative according to one or more of claims 1 to 16, optionally containing suitable additives and/or auxiliary substances and/or further active compounds.

18. Use of at least one substituted sulfonamide derivative according to one of claims 1 to 16 for the preparation of a medicament for treatment of pain, in particular acute, visceral, neuropathic, chronic pain or inflammatory pain, migraine, diabetes, diseases of the respiratory tract, inflammatory intestinal diseases, neurological diseases, inflammations of the skin, rheumatic diseases, septic shock, reperfusion syndrome, obesity and as an angiogenesis inhibitor.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2009/002608

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D495/04 C07D498/04 A61K31/4745 A61P25/04

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                             | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | WO 2007/140383 A (NEUROGEN CORP [US];<br>HODGETTS KEVIN J [US]; IHLE DAVID C [US];<br>LI GUIYI) 6 December 2007 (2007-12-06)<br>the whole document<br><p style="text-align: center;">-----</p> | 1-18                  |

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

Date of mailing of the international search report

17 June 2009

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/002608

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|----------------------------------------|------------------|-------------------------|------------------|
| WO 2007140383                          | A                | NONE                    |                  |