NEW COMPOUNDS

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ABSTRACT

The present invention relates to the compounds of general formula I:

wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and X are defined as described hereinafter, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the medicaments containing the pharmacologically effective compounds, the preparation thereof and the use thereof.
NEW COMPOUNDS

[0001] The present invention relates to the compounds of general formula I:

\[
R_1 \begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{R}^1
\end{array}
\]

wherein n, R', R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and X are as defined hereinbelow, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the medicaments containing the pharmaceutically effective compounds, the preparation thereof and the use thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0002] In the above general formula I in one embodiment n denotes one of the numbers 0, 1 or 2,

[0003] R^1 denotes

[0005] (a) a C_{1-6}-alkyl group optionally substituted by a group R^{1,1},

[0006] (b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0007] (c) a substituted C_{2-6}-cycloalkyl group optionally substituted by a group R^{1,1} wherein a —CH=— unit may be replaced by a —C(O)— group,

[0008] (d) an aryl-C_{2-6}-alkyl group optionally substituted by 1, 2 or 3 groups R^{1,1},

[0009] (e) a five-membered heteroaryl-C_{2-5}-alkyl group optionally substituted by 1, 2 or 3 groups R^{1,1}, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,

[0010] (f) a six-membered heteroaryl-C_{2-6}-alkyl group optionally substituted by 1 or 2 groups R^{1,1}, which contains one, two or three N-atoms and which may additionally be benzo-condensed,

[0011] (g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R^{1,1}, which contains one, two or three N-atoms, or

[0012] (h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R^{1,1}, in which a —CH=— unit may be replaced by a —C(O)— group,

[0013] (i) O—R^{1,1,1},

[0014] (j) NR^{1,1,1}, R^{1,1,1},

[0015] (k) C(=NR^{1,1,1})—CN,

[0016] R^{1,1} denotes halogen, —NO_2, —CN, C_{3-6}-cycloalkyl, —OR^{1,1,1}, —SR^{1,1,1}, —C(O)R^{1,1,1}, —S(O)_2R^{1,1,1}, —O—S(O)—R^{1,1,1}, —CO_2R^{1,1,1}, —O—C(O)—R^{1,1,1}, —NR^{1,1,1}, —NR^{1,1,1}, C(O)—R^{1,1,1}, —NR^{1,1,1}, C(O)—R^{1,1,1}, —NR^{1,1,1}, C(O)—R^{1,1,1}, —NR^{1,1,1}, C(O)—R^{1,1,1}, or C(O)—NR^{1,1,1},

[0017] R^{1,1,1} denotes

[0018] (a) H,

[0019] (b) C_{1-4}-alkyl,

[0020] (c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0021] (d) a phenyl group optionally substituted by 1, 2 or 3 groups R^{1,1,1},

[0022] (e) C_{3-6}-cycloalkyl or

[0023] (f) a pyridyl group optionally substituted by 1, 2 or 3 groups R^{1,1,1},

[0024] R^{1,1,1} optionally independently of one another denote

[0025] (a) halogen, —NO_2, —CN, —OH, —O—C_{1-4}-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkyl or

[0026] (b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0027] R^{1,1,1,2} independently of one another denote halogen or C_{1-4}-alkyl,

[0028] R^{1,1,1,2} denotes

[0029] (a) C_{1-4}-alkyl,

[0030] (b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0031] (c) —O—C_{1-4}-alkyl or

[0032] (d) a phenyl group optionally substituted by 1, 2 or 3 groups R^{1,1,1,1} substituted,

[0033] R^{1,1,1,3},

[0034] R^{1,1,1,4} independently of one another denote

[0035] (a) H,

[0036] (b) a C_{1-4}-alkyl group optionally substituted by 1, 2 or 3 groups R^{1,1,1,1},

[0037] (c) a phenyl group optionally substituted by 1, 2 or 3 groups R^{1,1,1,1},

[0038] (d) C_{3-6}-cycloalkyl, or

[0039] R^{1,1,3} and R^{1,1,4} together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O or S, or

[0040] R^{1,1,3} and R^{1,1,4} together with the N atom to which they are attached, form a cyclic imide,

[0041] R^{1,1,4} independently of one another halogen denote —NH_2, —NH(C_{1-4}-alkyl), —N(C_{1-4}-alkyl), or

[0042] R^{1,2} denotes halogen, —NO_2, —CN, —OH, —O—CH_3 or phenyl,

[0043] R^{1,3} denotes

[0044] (a) halogen, —NO_2, —CN, —OR^{1,1,1}, —SR^{1,1,1}, —CO_2R^{1,1,1}, —C(O)R^{1,1,1}, —C_{1-4}-alkyl or

[0045] (b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0046] R^{1,4} independently of one another denote

[0047] (a) halogen, —NO_2, —CN, —OR^{1,1,1}, —SR^{1,1,1}, —S(O)_2R^{1,1,1}, —S(O)R^{1,1,1}, —NR^{1,1,3}R^{1,1,4}, —N(R^{1,4}), —C(O)—C_{1-4}-alkyl, C_{1-4}-alkyl,
(a) C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or
(c) an oxo group,
R¹¬² denotes H or C₃₋₅-alkyl,
R¹¬² denotes —OH or —O—C₃₋₅-alkyl,
R² denotes H,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl-C(O)—
R² and R¹ together with the carbon atom to which they are bound denote a C₃₋₅-cycloalkyl group optionally substituted by a group R³ wherein a —CH₂— unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO₂,
R³ denotes H, —OH,
R³ denotes H,
(a) H,
(b) C₃₋₅-alkyl,
(c) a C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R² independently of one another denote
(a) H, halogen, —CN, —OH, C₃₋₅-alkyl, C₃₋₅-cycloalkyl, —O—C₃₋₅-alkyl, —O—CF₃, —O—C₃₋₅-cycloalkyl, —N(C₃₋₅-alkyl)₂, —C(O)—NH₂, —SO₂—C₃₋₅-alkyl, or
(b) a C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes H, —CN, —OH,
(a) H, halogen, —CN, —OH, —C₃₋₅-alkyl,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl or —O—C₃₋₅-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes —O—C₃₋₅-alkyl,
R² denotes H, —CN, —OH, —C₃₋₅-alkyl,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl or —O—C₃₋₅-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes —O—C₃₋₅-alkyl, —O—CF₃, —O—C₃₋₅-cycloalkyl, —N(C₃₋₅-alkyl)₂, —C(O)—NH₂, —SO₂—C₃₋₅-alkyl, or
(b) a C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes H, —CN, —OH, —C₃₋₅-alkyl,
(a) H, halogen, —CN, —OH, —C₃₋₅-alkyl,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl or —O—C₃₋₅-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes H, —CN, —OH, —C₃₋₅-alkyl,
(a) H, halogen, —CN, —OH, —C₃₋₅-alkyl,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl or —O—C₃₋₅-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes —O—C₃₋₅-alkyl, —O—CF₃, —O—C₃₋₅-cycloalkyl, —N(C₃₋₅-alkyl)₂, —C(O)—NH₂, —SO₂—C₃₋₅-alkyl, or
(b) a C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R³ denotes H, —CN, —OH, —C₃₋₅-alkyl,
(a) H, halogen, —CN, —OH, —C₃₋₅-alkyl,
(b) C₃₋₅-alkyl,
(c) C₃₋₅-alkyl or —O—C₃₋₅-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
[0113] (b) a C₃₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
[0114] (c) a C₃₋₅-cycloalkyl group optionally substituted by a benzene group optionally substituted with a nitro group, wherein a —CH₂— unit may be replaced by a —CN— group,
[0115] (d) a phenyl group optionally substituted by 1, 2 or 3 groups R₊₁₋₃,
[0116] (e) a 5-membered heterocyclic group optionally substituted by 1, 2 or 3 groups R₊₁₋₃, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,
[0117] (f) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which contains one, two or three N-atoms,
[0118] (g) a nine- or ten-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which contains one, two or three N-atoms,
[0119] (h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which contains one, two or three N-atoms,
[0120] (i) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, in which a —CH₂— unit may be replaced by a —CN— group,
[0121] (j) —OR₊₁₋₃ or —OR₊₂₋₄,
[0122] (k) —NR₊₁₋₃ or —OR₊₂₋₄,
[0123] R₊₁₋₃ represents —CN, C₃₋₅-cycloalkyl, —OR₊₁₋₃, —NR₊₁₋₃ or —NR₊₂₋₄,
[0124] R₊₁₋₄ represents 
[0125] (a) H, 
[0126] (b) C₅₋₇-alkyl,
[0127] (c) a C₅₋₇-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
[0128] R₊₁₋₅ represents 
[0129] R₊₁₋₆ represents independently of one another one or more of 
[0130] (a) H, 
[0131] (b) C₅₋₇-alkyl,
[0132] (c) C₅₋₇-cycloalkyl, or 
[0133] R₊₁₋₇ and R₊₂₋₇ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or
[0134] R₊₁₋₈ represents halogen, —NO₂, —CN, —OH, —O—CH₃ or phenyl,
[0135] R₊₂₋₈ represents independently of one another one or more of 
[0136] (a) halogen, —NO₂, —CN, C₅₋₇-alkyl or 
[0137] (b) a C₅₋₇-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
[0138] R₊₃₋₈ represents independently of one another one or more of 
[0139] (a) halogen, —NO₂, —CN, —OR₊₁₋₃, —OR₊₂₋₄, —NR₊₁₋₃, —NR₊₂₋₄, —N(R₊₁₋₃), —C(O)—C₅₋₇-alkyl, C₅₋₇-cycloalkyl, or 
[0140] (b) a C₅₋₇-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
[0141] R₊₆₋₈ represents H or C₅₋₇-alkyl, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.
[0142] An embodiment 3 of the present invention comprises the compounds of the above general formula I, wherein
[0143] R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹₀, R¹₁, n and X are defined as mentioned hereinbefore in embodiment 1 and
[0144] R³ represents 
[0145] (a) a C₅₋₇-alkyl group optionally substituted by a group R₊₁₋₃,
[0146] (b) a phenyl group optionally substituted by 1, 2 or 3 groups R₊₁₋₃,
[0147] (c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups R₊₁₋₄, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,
[0148] (d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which contains one, two or three N-atoms,
[0149] (e) a nine- or ten-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which contains one, two or three N-atoms,
[0150] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, in which a —CH₂— unit may be replaced by a —CN— group,
[0151] R₊₁₋₃ represents independently of one another one or more of 
[0152] (a) F, Cl, Br, —OH, —OCH₃, C₅₋₇-alkyl or 
[0153] (b) a C₅₋₇-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
[0154] R₊₂₋₄ represents independently of one another one or more of 
[0155] (a) F, Cl, Br, —OH, —OCH₃, —NH₂, —NHCH₃, —N(CH₃)₂, —N(C₅₋₇-alkyl), —NH—C(O)—C₅₋₇-Alkyl, C₅₋₇-alkyl, or 
[0156] (b) a C₅₋₇-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.
[0157] An embodiment 4 of the present invention comprises the compounds of the above general formula I, wherein
R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹₀, R¹₁, n and X are defined as mentioned hereinbefore in embodiment 1 and
[0158] R³ represents 
[0159] (a) a C₅₋₇-alkyl group optionally substituted by a group R₊₁₋₃,
[0160] (b) a phenyl group optionally substituted by 1, 2 or 3 groups R₊₁₋₃,
[0161] (c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups R₊₁₋₄,
[0162] R₊₁₋₄, which is selected from among
[0163] (d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R₊₁₋₄, which is selected from among
[0164] (e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups R<sup>1</sup>–<sup>4</sup>, which is selected from among

[0165] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R<sup>1</sup>–<sup>4</sup>, which is selected from among

[0166] R<sup>1</sup>–<sup>4</sup> denotes —CN, cyclopropyl, —OH, —OCH<sub>3</sub>, —NH<sub>2</sub>, —NHCH<sub>3</sub>, —N(CH<sub>3</sub>)<sub>2</sub>.

[0167] R<sup>1</sup>–<sup>4</sup> independently of one another denotes

[0168] (a) F, Cl, Br, —OH, —OCH<sub>3</sub>, —OCF<sub>3</sub>, C<sub>1</sub>–<sub>4</sub> alkyl or

[0169] (b) a C<sub>1</sub>–<sub>4</sub> alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

[0170] R<sup>1</sup>–<sup>4</sup> independently of one another denotes

[0171] (a) F, Cl, Br, —OH, —OCH<sub>3</sub>, —OCF<sub>3</sub>, —NH<sub>2</sub>, —NH—C<sub>1</sub>–<sub>4</sub> alkyl, —N(C<sub>1</sub>–<sub>4</sub> alkyl)<sub>2</sub>, —NH—C(O)—C<sub>1</sub>–<sub>4</sub> alkyl, —C<sub>1</sub>–<sub>4</sub> alkyl, or

[0172] (b) a C<sub>1</sub>–<sub>4</sub> alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0173] An embodiment 5 of the present invention comprises the compounds of the above general formula I, wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup>, R<sup>e</sup>, R<sup>11</sup>, n and X are defined as mentioned hereinbefore in embodiment 1 and
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0175] An embodiment 6 of the present invention comprises the compounds of the above general formula I, wherein R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, n and X are defined as mentioned hereinbefore in embodiment 1 and

[0176] R¹ is selected from among
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

0177) An embodiment 7 of the present invention consists of the compounds of the above general formula I, wherein R^1 is defined as mentioned hereinbefore under embodiment 1, 2, 3, 4, 5 or 6 and

0178) n denotes one of the numbers 0, 1 or 2,
0179) R^2 denotes
0180) (a) H,
0181) (b) C\(_{1,4}\)-alkyl,
0182) R^3 and R^4 together with the carbon atom to which they are bound denote a C\(_{3,5}\)-cycloalkylene group optionally substituted by a group R^7 wherein a —CH\(_{2}\) unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO\(_{2}\),
0183) R^3,4 denotes H, —OH,
0184) R^5 denotes
0185) (a) H,
0186) (b) C\(_{1,4}\)-alkyl,
0187) (c) a C\(_{1,3}\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
0188) R^6 independently of one another denotes
0189) (a) H, halogen, —CN, —OH, C\(_{1,4}\)-alkyl, C\(_{3,5}\)-cycloalkyl, —O—C\(_{1,4}\)-alkyl, —O—CF\(_3\), —O—C\(_{3,6}\)-cycloalkyl, —N(C\(_{1,3}\)-alkyl)\(_2\), —C(O)—NH\(_2\), —(SO\(_2\))\(_2\)NH\(_2\), —SO\(_2\)—C\(_{3,5}\)-alkyl, or
0190) (b) a C\(_{1,3}\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
0191) R^7 denotes
0192) (a) H, halogen, —CN, —OH,
0193) (b) C\(_{1,4}\)-alkyl,
0194) (c) C\(_{1,3}\)-alkyl or —O—C\(_{1,3}\)-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
0195) (d) C\(_{3,5}\)-cycloalkyl,
0196) (e) —O—C\(_{1,4}\)-alkyl,
0197) (f) —O—C\(_{3,5}\)-cycloalkyl,
[0198] (g) \(-\text{NH}_2, \text{NH}(\text{C}_1,\text{a}-\text{alkyl}), -\text{N}(\text{C}_1,\text{a}-\text{alkyl})_2\),
[0199] (h) \(-\text{C}(\text{O})-\text{R}^{1,1}\),
[0200] (i) \(-\text{S}-\text{C}_1,\text{a}-\text{alkyl}\),
[0201] \text{R}^{1,1} \text{denotes} \ -\text{NH}_2, -\text{OH}, -\text{O}-\text{C}_1,\text{a}-\text{alkyl},
[0202] \text{R}^2 \text{denotes H, halogen, C}_1,\text{a}-\text{alkyl},
[0203] \text{R}^3 \text{denotes}
[0204] (a) H, halogen, -CN, -OH,
[0205] (b) C\text{g}-\text{alkyl},
[0206] (c) C\text{a}-\text{alkyl} or -O-C\text{a}-\text{alkyl}, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
[0207] (d) C\text{a}-\text{cycl alcanyl},
[0208] (e) C\text{g}-\text{alkyl},
[0209] (f) -O-C\text{a}-\text{alkyl},
[0210] (g) -O-C\text{g}-\text{cycl alcanyl},
[0211] (h) -NH\text{a}-\text{NH}(C\text{a}-\text{alkyl}), -N(C\text{a}-\text{alkyl})_2,
[0212] (i) \(-\text{C}(\text{O})-\text{R}^{1,1}\),
[0213] (j) \(-\text{S}-\text{C}_1,\text{a}-\text{alkyl}, \text{SO}_2-\text{C}_1,\text{a}-\text{alkyl}, \text{SO}_2\text{-C}_1,\text{a}-\text{alkyl},
[0214] \text{R}^{1,1} \text{denotes} \ -\text{NH}_2, -\text{OH}, -\text{O}-\text{C}_1,\text{a}-\text{alkyl},
[0215] \text{R}^3 \text{denotes H, halogen, C}_1,\text{a}-\text{alkyl},
[0216] \text{R}^3 \text{denotes}
[0217] (a) H, halogen, -CN, -OH,
[0218] (b) C\text{g}-\text{alkyl},
[0219] (c) C\text{a}-\text{alkyl} or -O-C\text{a}-\text{alkyl}, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
[0220] (d) C\text{a}-\text{cycl alcanyl},
[0221] (e) -O-C\text{a}-\text{alkyl},
[0222] (f) -O-C\text{g}-\text{cycl alcanyl},
[0223] (g) -NH\text{a}-\text{NH}(C\text{a}-\text{alkyl}), -N(C\text{a}-\text{alkyl})_2,
[0224] (h) \(-\text{C}(\text{O})-\text{R}^{1,1}\),
[0225] (i) \(-\text{S}-\text{C}_1,\text{a}-\text{alkyl},
[0226] \text{R}^{1,1} \text{denotes} \ -\text{NH}_2, -\text{OH}, -\text{O}-\text{C}_1,\text{a}-\text{alkyl}, and
[0227] \text{X independently of one another represent C-R^2 or N},
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0231] An embodiment 10 of the present invention comprises the compounds of the above general formula I, wherein \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{n and X} \text{are defined as mentioned hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8 or 9 and}
\text{R}^2 \text{and R}^4 \text{together with the carbon atom to which they are bonded denote a C}_5,\text{g}-\text{cycl alcanyl group wherein a -CH}_2- \text{unit may be replaced by an oxygen atom, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.}

[0232] An embodiment 11 of the present invention comprises the compounds of the above general formula I, wherein \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{n and X} \text{are defined as mentioned hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8 or 9 and}
\text{R}^2 \text{and R}^4 \text{together with the carbon atom to which they are bonded denote a group selected from}

\begin{align*}
&\text{R}^{1,1} \text{denotes} \ -\text{NH}_2, -\text{OH}, -\text{O}-\text{C}_1,\text{a}-\text{alkyl}, and
&\text{X independently of one another represent C-R^2 or N},
\end{align*}
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0233] An embodiment 12 of the present invention comprises the compounds of the above general formula I, wherein \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{n and X} \text{are defined as mentioned hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 and}
\text{R}^2 \text{denotes H or CH}_2,}
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0234] An embodiment 13 of the present invention comprises the compounds of the above general formula I, wherein \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}, \text{R}^{11}, \text{n and X} \text{are defined as mentioned hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 and}
\text{R}^2 \text{denotes H, F, Cl or methyl,}
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0235] An embodiment 14 of the present invention comprises the compounds of the above general formula I, wherein \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{n and X} \text{are defined as mentioned hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 and}
\text{R}^4 \text{denotes H, F, Cl or Br,}
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.
[0241] An embodiment 15 of the present invention comprises the compounds of general formula Ia

\[
\begin{align*}
R^1 & \quad R^2 \\
R^3 & \quad R^4 \\
R^5 & \quad R^6 \\
R^7 & \quad R^8 \\
R^9 & \quad R^10
\end{align*}
\]

wherein

[0242] \( R^1 \) denotes

[0243] (a) a \( C_{1-6} \)-alkyl group optionally substituted by a group \( R^{1-2} \),

[0244] (b) a phenyl group optionally substituted by 1, 2 or 3 groups \( R^{1-3} \),

[0245] (c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups \( R^{1-4} \), which contains at least one N, O or S atom and optionally additionally contains one, two or three further N-atoms,

[0246] (d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups \( R^{1-4} \), which contains one, two or three N-atoms,

[0247] (e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups \( R^{1-4} \), which contains one, two or three N-atoms,

[0248] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1-4} \), in which a \(-\text{CH}_2-\) unit may be replaced by a \(-\text{C}(\text{O})-\) group,

[0249] \( R^{1-2} \) denotes \(-\text{CN}, \ -\text{C}_{3-6}\text{-cycloalkyl}, \ -\text{OH}, \ -\text{OCH}_3, \ -\text{NH}_2, \ -\text{NHCH}_3, \ -\text{N}(\text{CH}_3)_2, \)

[0250] \( R^{1-4} \) independently of one another denotes

[0251] (a) F, Cl, Br, \(-\text{OH}, \ -\text{OCH}_3, \ -\text{NH}_2\) or

[0252] (b) a \( C_{1-6} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluoride atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms

[0253] \( R^{1-4} \) independently of one another denotes

[0254] (a) F, Cl, Br, \(-\text{OH}, \ -\text{OCH}_3, \ -\text{NH}_2, \ -\text{NHCH}_3, \ -\text{N}(\text{CH}_3)_2, \ -\text{NH}-\text{C}(\text{O})-\text{C}_{1-4}\text{-alkyl}, \ -\text{C}_{1-4}\text{-alkyl}, \)

[0255] (b) a \( C_{1-6} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluoride atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms

[0256] \( R^2 \) denotes H or CH₃.

[0257] \( R^3 \) and \( R^4 \) together with the carbon atom to which they are bonded denote a \( C_{3-6}\)-cycloalkylene group wherein a \(-\text{CH}_2-\) unit may be replaced by an oxygen atom.

[0258] \( R^3 \) denotes H or \( C_{1-4}\)-alkyl.

[0259] \( R^4 \) denotes H, F, Cl, Br or \( C_{1-4}\)-alkyl.

[0260] \( R^5 \) denotes H, F, Cl, Br, \(-\text{CN}, \ -\text{C}_{1-4}\text{-alkyl}, \ -\text{CF}_3, \ -\text{CHF}_2, \)

[0261] \( R^6 \) denotes F, Cl, Br, \(-\text{CN}, \ -\text{C}_{1-4}\text{-alkyl}, \ -\text{CF}_3, \ -\text{CHF}_2, \)

[0262] \( R^7 \) denotes F, Cl, Br, \(-\text{CN}, \ -\text{C}_{1-4}\text{-alkyl}, \ -\text{CF}_3, \ -\text{CHF}_2, \)

and

[0263] X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0264] An embodiment 16 of the present invention comprises the compounds of general formula Ib, wherein

[0265] \( R^4 \) denotes

[0266] (a) a \( C_{1-4}\)-alkyl group optionally substituted by a group \( R^{1-1} \),

[0267] (b) a phenyl group optionally substituted by 1, 2 or 3 groups \( R^{1-3} \),

[0268] (c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups

[0269] \( R^{1-4} \), which is selected from among

[0270] (d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups \( R^{1-4} \), which is selected from among

[0271] (e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups \( R^{1-4} \), which is selected from among

[0272] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1-4} \), which is selected from among

[0273] \( R^{1-1} \) denotes \(-\text{CN}, \ -\text{cyclopropyl}, \ -\text{OH}, \ -\text{OCH}_3, \ -\text{NH}_2, \ -\text{NHCH}_3, \ -\text{N}(\text{CH}_3)_2, \)

[0274] \( R^{1-4} \) denotes independently of one another

[0275] (a) F, Cl, Br, \(-\text{OH}, \ -\text{OCH}_3, \ -\text{OCF}_3, \ -\text{C}_{1-4}\text{-alkyl} \) or
[0276] (b) a C_{1-a}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

[0277] \( R^1, R^2 \) denote independently of one another

[0278] (a) F, Cl, Br, —OH, —OCH₃, —OCF₃, —NH₂, —NH—C₁₋₄-alkyl, —NH¹₋₄-alkyl, —NH—C(O)—C₁₋₄-alkyl, C₁₋₄-alkyl, or

[0279] (b) a C₁₋₄-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0280] \( R^2 \) denotes H or CH₃,

[0281] \( R^3 \) and \( R^4 \) together with the carbon atom to which they are bonded denote a C₁₋₄-cycloalkyl group wherein a —CH₂ unit may be replaced by an oxygen atom,

[0282] \( R^5 \) denotes H or CH₃,

[0283] \( R^6 \) denotes H, F, Cl or methyl,

[0284] \( R^7 \) denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,

[0285] \( R^8 \) denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl,

[0286] \( R^{11} \) denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and

[0287] X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0288] An embodiment 17 of the present invention comprises the compounds of general formula Ia, wherein

[0289] \( R^2 \) denotes a group selected from

![Chemical structures and diagrams]
[0290] R² denotes H or CH₃.
[0291] R³ and R⁴ together with the carbon atom to which they are bonded denote a C₃₋₆-cycloalkylene group wherein a —CH₂ unit may be replaced by an oxygen atom.

[0292] R³ denotes H or CH₃.
[0293] R⁴ denotes H, F, Cl or methyl.
[0294] R⁴ denotes H, F, Cl, Br, —CN, C₁₋₃-alkyl, CF₃, CHF₂.
[0295] R⁴ denotes F, Cl, Br, C₁₋₃-alkyl, —O—C₁₋₃-alkyl, —S—C₁₋₃-alkyl,

[0296] R¹⁻ denotes F, Cl, Br, —CN, C₁₋₃-alkyl, CF₃, CHF₂.

[0297] X denotes CH or N,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0298] An embodiment of the present invention comprises the compounds of general formula (Ia) wherein

[0299] R¹ denotes a group selected from
[0302] \( R^2 \) denotes H or CH₃,

[0303] \( R^5 \) denotes H, F, Cl or methyl.

[0304] \( R^7 \) denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and

[0305] \( R^9 \) denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl,

[0306] \( R^{11} \) denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and

[0307] X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0308] An embodiment 19 of the present invention comprises the compounds of general formula 1b

wherein

[0309] \( R^1 \) denotes

[0310] (a) a C₁₋₄-alkyl group optionally substituted by a group R₁₋₄,

[0311] (b) a phenyl group optionally substituted by 1, 2 or 3 groups R₁₋₄,

[0312] (c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups R₁₋₄, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

[0313] (d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₋₄, which contains one, two or three N-atoms,

[0314] (e) a nine- or ten-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₋₄, which contains one, two or three N-atoms,

[0315] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₋₄, in which a —CH₂— unit may be replaced by a —C(O)— group,

[0316] \( R^{1-4} \) denotes —CN, C₁₋₄-cycloalkyl, —OH, —OCH₃, —NH₂, —NHCH₃, —N(CH₃)₂,

[0317] \( R^{1-3} \) denotes independently of one another

[0318] (a) F, Cl, Br, —OH, —OCH₃, C₁₋₄-alkyl or

[0319] (b) a C₁₋₄-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

[0320] \( R^{1-4} \) denotes independently of one another

[0321] (a) F, Cl, Br, —OH, —OCH₃, —NH₂, —NHCH₃, —N(CH₃)₂, —NH—C(O)—C₁₋₄-alkyl, C₁₋₄-alkyl or

[0322] (b) a C₁₋₄-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
Continued

[0338] \( R^{3,4} \) denotes —CN, cyclopropyl, —OH, —OCH₃, —NH₂, —NHCH₃, —N(CH₃)₂.
[0339] \( R^{1,2} \) denotes independently of one another

[0340] (a) F, Cl, Br, —OH, —OCH₃, —OCF₃, \( C_{1-4} \)-alkyl or

[0341] (b) a \( C_{1-3} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

[0342] \( R^{1,4} \) denotes independently of one another

[0343] (a) F, Cl, Br, —OH, —OCH₃, —OCF₃, —NH₂, —NH—\( C_{1-4} \)-alkyl, —N(\( C_{1-4} \)-alkyl)₂, —NH—C(O)—\( C_{1-4} \)-alkyl, \( C_{1-4} \)-alkyl, \( C_{1-4} \)-alkyl, or

[0344] (b) a \( C_{1-3} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0345] \( R^2 \) denotes H or CH₃,
[0346] \( R^3 \) denotes H or CH₃,
[0347] \( R^4 \) denotes H, F, Cl or methyl,
[0348] \( R^7 \) denotes H, F, Cl, Br, —CN, \( C_{1-4} \)-alkyl, CF₃, CHF₂,
[0349] \( R^8 \) denotes F, Cl, Br, \( C_{1-4} \)-alkyl, —O—\( C_{1-4} \)-alkyl, —S—\( C_{1-4} \)-alkyl,
[0350] \( R^{11} \) denotes F, Cl, Br, —CN, \( C_{1-4} \)-alkyl, CF₃, CHF₂,

[0351] \( X \) denotes CH or N,

[0352] An embodiment 21 of the present invention comprises the compounds of general formula 1b, wherein

[0353] \( R^1 \) denotes a group selected from

Continued
[0354] R² denotes H or CH₃.
[0355] R³ denotes H or CH₃.
[0356] R⁴ denotes H, F, Cl or methyl,
[0357] R⁵ denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
[0358] R⁶ denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl,
—S—C₁₋₄-alkyl,
[0359] R¹¹ denotes F, Cl, Br,—CN, C₁₋₄-alkyl, CF₃, CHF₂, and
[0360] X denotes CH or N,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0361] An embodiment 22 of the present invention comprises the compounds of general formula Ib, wherein

[0362] R¹ denotes a group selected from
[0363] \( R^2 \) denotes H, or CH$_2$.
[0364] \( R^2 \) denotes H or CH$_3$.
[0365] \( R^2 \) denotes H, or CI or methyl.
[0366] \( R^2 \) denotes H, or CI or methyl.
[0367] \( R^2 \) denotes H, or CI or methyl.
[0368] \( R^2 \) denotes H, or CI or methyl.
and
[0369] \( R^2 \) denotes H, or CI or methyl.

An embodiment 23 of the present invention comprises the compounds of general formula 1c:

\[
\text{[0370]} \quad \text{wherein}
\]

[0371] \( R^1 \) denotes
[0372] (a) a \( C_1 \)-alkyl group optionally substituted by a group \( R^{1,1} \),
[0373] (b) a phenyl group optionally substituted by 1, 2 or 3 groups \( R^{1,3} \),
[0374] (c) a five-membered heterocyclic group optionally substituted by at least one \( N \), O or \( S \) atom and which optionally additionally contains one, two or three \( N \)-atoms,
[0375] (d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1,3} \), which contains one, two or three \( N \)-atoms,
[0376] (e) a nine- or ten-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1,3} \), which contains one, two or three \( N \)-atoms,
[0377] (f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1,3} \), wherein a —CH$_2$— unit may be replaced by a —C(O)— group,
[0378] \( R^{11} \) denotes —CN, \( C_1 \)-alkyl, —OH, —OCH$_3$, —NH$_2$, —NHCH$_3$, or —N(CH$_3$)$_2$.

[0379] \( R^{1,3} \) independently of one another denote
[0380] (a) CF, Cl, Br, —OH, —OCH$_3$, \( C_1 \)-alkyl or
[0381] (b) a \( C_1 \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and
[0382] \( R^{1,4} \) independently of one another denote
[0383] (a) \( F, \) Cl, Br, —OH, —OCH$_3$, —NH$_2$, —NHCH$_3$, —N(CH$_3$)$_2$, —NH—C(O)—\( C_1 \)-alkyl, \( C_1 \)-alkyl, or
[0384] (b) a \( C_1 \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
[0385] \( R^2 \) denotes H or CH$_3$.
[0386] \( R^2 \) denotes H or \( C_1 \)-alkyl.
[0387] \( R^2 \) denotes H, F, CI, Br or \( C_1 \)-alkyl.
[0388] \( R^2 \) denotes H, F, CI, Br, —CN, \( C_1 \)-alkyl, CF$_3$, CHF$_2$.
[0389] \( R^2 \) denotes H, F, CI, Br, —CN, \( C_1 \)-alkyl, CF$_3$, CHF$_2$ and
[0390] \( R^2 \) denotes H, F, CI, Br, —CN, \( C_1 \)-alkyl, CF$_3$, CHF$_2$,
and
[0391] \( X \) denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment 24 of the present invention comprises the compounds of general formula 1c, wherein

[0393] \( R^1 \) denotes
[0394] (a) a \( C_1 \)-alkyl group optionally substituted by a group \( R^{1,1} \),
[0395] (b) a phenyl group optionally substituted by 1, 2 or 3 groups \( R^{1,3} \),
[0396] (c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups \( R^{1,3} \), which is selected from among

[0397] (d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1,3} \), which is selected from among

[0398] (e) a nine-membered heterocyclic group optionally substituted by 1 or 2 groups \( R^{1,3} \), which is selected from among
(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R₁⁻², which is selected from among

[0403] (a) F, Cl, Br, —OH, —OCH₃, —OCF₃, C₁₋₄ alkyl or
(b) a C₁₋₄ alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms, and

[0404] R₁₋₄ independently of one another denote
(a) F, Cl, Br, —OH, —OCH₃, —OCF₃, —NH₂, —NH—C₁₋₄ alkyl, —N(C₁₋₄ alkyl)₂, —NH—C(O)—C₁₋₄ alkyl, C₁₋₄ alkyl, or
(b) a C₁₋₄ alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,

[0407] R² denotes H or CH₃,
[0408] R³ denotes H or CH₃,
[0409] R⁴ denotes H, F, Cl or methyl,
[0410] R⁵ denotes H, F, Cl, Br, —CN, C₁₋₄ alkyl, CF₃, CHF₂,
[0411] R⁶ denotes F, Cl, Br, C₁₋₄ alkyl, —O—C₁₋₄ alkyl, —S—C₁₋₄ alkyl,
[0412] R¹⁻¹ denotes F, Cl, Br, —CN, C₁₋₄ alkyl, CF₃, CHF₂, and

[0413] X denotes CH or N,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0414] An embodiment 25 of the present invention comprises the compounds of general formula Ic, wherein
[0415] R¹ denotes a group selected from
[0416] R² denotes H or CH₃,
[0417] R³ denotes H or CH₃,
[0418] R⁴ denotes H, F, Cl or methyl,
[0419] R⁵ denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
[0420] R⁶ denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl,
[0421] R¹⁵ denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and
[0422] X denotes CH or N,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0423] An embodiment 26 of the present invention comprises the compounds of general formula Ic, wherein

[0424] R¹ denotes a group selected from
[0425] R^2 denotes H or CH₃.
[0426] R^3 denotes H or CH₃.
[0427] R^4 denotes H, F, Cl, or methyl.
[0428] R^5 denotes H, F, Cl, Br, —CN, C₈₋₁₄-alkyl, CF₃, CHF₂-

[0429] R^6 denotes F, Cl, Br, C₈₋₁₄-alkyl, —O—C₁₋₄-alkyl, —S—C₈₋₁₄-alkyl,

[0430] R^7 denotes F, Cl, Br, —CN, C₈₋₁₄-alkyl, CF₃, CHF₂-

and

[0431] X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0432] An embodiment 27 of the present invention comprises the compounds of general formula 1d.

![Chemical Structure](image)

wherein

[0433] R^1 denotes a group selected from

![Chemical Structure](image)
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0439] An embodiment 28 of the present invention comprises the compounds of general formula I, Ia, Ib, Ic or Id, wherein n, R¹, R², R³, R⁴, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and X are defined as described hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 and

[0440] R⁷ denotes H, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0441] The following are mentioned as examples of most particularly preferred compounds of the above general formula I:

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**Structure**

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the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

**A further embodiment of the present invention comprises the compounds of general formula II**

![Chemical structure](image)

wherein

- **(0443)** \( n \) denotes one of the numbers 0, 1 or 2,
- **(0444)** \( R^2 \) denotes
  - (a) H,
  - (b) \( C_{1-4} \)-alkyl,
  - (c) \( C_{1-4} \)-alkyl-C(O)—,
- **(0448)** \( R^3 \) denotes
  - (a) H,
  - (b) \( C_{1-4} \)-alkyl,
  - (c) \( C_{1-3} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
  - (d) \( C_{1-2} \)-cyanoalkyl,
  - (e) \( O—C_{1-4} \)-alkyl,
  - (f) \( O—C_{1-4} \)-cyanoalkyl,
  - (g) \( NH_2—NH(C_{1-3} \)-alkyl), \(-N(C_{1-3} \)-alkyl),
  - (h) \( C(O)—R'^1 \),
  - (i) \( S—C_{1-4} \)-alkyl, \(-SO_2—R'^2 \),
  - (j) \( R^3 \) independently of one another denotes
  - (a) H, halogen, —CN, —OH, —O—C_{1-4} \)-alkyl, —O—CF₃, —O—C_{3-7} \)-cyanoalkyl, —N(C_{1-3} \)-alkyl)₂, —C(O)—NH₂, —(SO₂)NH₂, —SO₂—C_{1-3} \)-alkyl, or
  - (b) a \( C_{1-3} \)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
  - (c) \( C_{1-3} \)-alkyl or —O—C_{1-3} \)-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
  - (d) \( C_{1-2} \)-cyanoalkyl,
  - (e) —O—C_{1-4} \)-alkyl,
  - (f) —O—C_{3-7} \)-cyanoalkyl,
  - (g) —NH₂—NH(C_{1-3} \)-alkyl), —N(C_{1-3} \)-alkyl),
  - (h) —C(O)—R'^1,
  - (i) —S—C_{1-4} \)-alkyl, —SO₂—R'^2,
(j) a five-membered heteroaryl group optionally substituted by one or two C_{1,3-alkyl} groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1,3-alkyl} groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl.

R_{1,2}^{2,1} denotes —NH_{2}, —NH(C_{1,2-alkyl}), —N(C_{1,2-alkyl})_2, N-acetidinyl, N-pyrrolidinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C_{1,3-alkyl} or —O—C_{1,3-7-cycloalkyl},

R_{1,2}^{2,3} denotes —NH_{2}, —NH(C_{1,2-alkyl}), —N(C_{1,2-alkyl})_2, N-acetidinyl, N-pyrrolidinyl, N-piperidinyl or N-morpholinyl

R_{1,2}^{2,4} denotes H, halogen, C_{1,4-alkyl},

R_{1,2}^{2,0} denotes H

(a) H, halogen, —CN, —OH,
(b) C_{1,0-alkyl},
(c) C_{1,3-alkyl} or —O—C_{1,3-alkyl}, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_{1,7-cycloalkyl},
(e) C_{1,2-alkynyl},
(f) —O—C_{1,2-alkyl},
(g) —O—C_{1,2-alkyl},
(h) —NH_{2}, —NH(C_{1,2-alkyl}), —N(C_{1,2-alkyl})_2,
(i) —Cl —R_{0}^{1,2},
(j) —SO_{2} —C_{1,4-alkyl}, —SO_{2} —C_{1,4-alkyl}, —SO_{2} —C_{1,4-alkyl}, —SO_{2} —C_{1,4-alkyl}, —SO_{2} —C_{1,4-alkyl}, —SO_{2} —C_{1,4-alkyl},

R_{1,2}^{1,0} denotes —NH_{2}, —NH(C_{1,2-alkyl}), —N(C_{1,2-alkyl})_2, N-acetidinyl, N-pyrrolidinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C_{1,4-alkyl} or —O—C_{1,7-cycloalkyl},

R_{1,2}^{1,1} denotes —NH_{2}, —NH(C_{1,2-alkyl}), —N(C_{1,2-alkyl})_2, N-acetidinyl, N-pyrrolidinyl, N-piperidinyl or N-morpholinyl

X independently of another denotes C—R_{0}^{2} or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of the above general formula II, wherein

n denotes one of the numbers 0, 1 or 2,

R_{2}^{2} denotes H or CH_{3},

R_{3}^{2} denotes H or CH_{3},

R_{4}^{2} denotes H, F or methyl,

R_{5}^{2} denotes H, F, Cl or methyl,

R_{6}^{2} denotes H, F, Cl or methyl,

R_{7}^{2} denotes F, Cl, Br, —CN, CF_{3}, CHF_{2},

R_{8}^{2} denotes H,

R_{9}^{2} denotes F, Cl, Br, —CN, C_{1,4-alkyl}, CF_{3}, CHF_{2},

and

X independently of another represent C—R_{0}^{2} or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

The following compounds are mentioned as examples of particularly preferred compounds of the above general formula II:

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| (1.1) | ![H2N3NCH3](image)
| (1.2) | ![H2N3NCH3](image)
| (1.3) | ![H2N3NCH3](image) |
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

[0510] A further embodiment of the present application relates to the use of the compounds of general formula II, wherein \( R^2, R^3, R^4, R^7, R^8, R^9, R^{10} \) and \( R^{11} \) are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases for preparing compounds of general formula I, which have B1-antagonistic properties.
wherein

- **[0512]** R₁ denotes
- **[0513]** (a) a C₁₋₅-alkyl group optionally substituted by a group R¹₁
- **[0514]** (b) a C₁₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
- **[0515]** (c) a C₅₋₁₀-cycloalkyl group optionally substituted by a group R₁₁ wherein a —CH₂— unit may be replaced by a —C(O)— group.
- **[0516]** (d) an aryl-C₆₋₁₅-alkyl group optionally substituted by 1, 2 or 3 groups R¹₅
- **[0517]** (e) a five-membered heteroaryl-C₆₋₁₀-alkyl group optionally substituted by 1, 2 or 3 groups R¹₅, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,
- **[0518]** (f) a six-membered heteroaryl-C₆₋₁₀-alkyl group optionally substituted by 1 or 2 groups R¹₅, which contains one, two or three N-atoms and which may additionally be benzo-condensed,
- **[0519]** (g) a nine or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R¹₅, which contains one, two or three N-atoms,
- **[0520]** (h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₅, wherein a —CH₂— unit may be replaced by a —C(O)— group,
- **[0521]** (i) —O—R¹₁₅
- **[0522]** (j) —NR¹₁₅
- **[0523]** (k) —C(=NR¹₁₅)—CN,
- **[0526]** (a) H,
- **[0527]** (b) C₆₋₁₀-alkyl,
- **[0528]** (c) a C₆₋₁₀-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
- **[0529]** (d) a phenyl group optionally substituted by 1, 2 or 3 groups R¹₁₅
- **[0530]** (e) C₆₋₁₀-cycloalkyl or
- **[0531]** (f) a pyridyl group optionally substituted by 1, 2 or 3 groups R¹₁₅
- **[0532]** R¹₁₅, independently of one another denotes
- **[0533]** (a) halogen, —NO₂, —CN, —OH, —O—C₆₋₁₀-alkyl, C₆₋₁₀-cycloalkyl, C₆₋₁₀-alkyl or
- **[0534]** (b) a C₅₋₁₀-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
- **[0535]** R¹₁₅, independently of one another denotes halogen or C₁₋₅-alkyl,
- **[0536]** R¹₁₅, independently of one another denotes
- **[0537]** (a) C₁₋₅-alkyl,
- **[0538]** (b) a C₁₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
- **[0539]** (c) —O—C₁₋₅-alkyl or
- **[0540]** (d) a phenyl group optionally substituted by 1, 2 or 3 groups R¹₁₅,
- **[0541]** R¹₁₅,
- **[0542]** R¹₁₅, independently of one another denote
- **[0543]** (a) H,
- **[0544]** (b) C₆₋₁₀-alkyl group optionally substituted by 1, 2 or 3 groups R¹₁₅
- **[0545]** (c) a phenyl group optionally substituted by 1, 2 or 3 groups R¹₁₅,
- **[0546]** (d) C₆₋₁₀-cycloalkyl, or
- **[0547]** R¹₁₅ and R¹₁₄ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or
- **[0548]** R¹₁₅ and R¹₁₄ together with the N atom to which they are attached, form a cyclic imide,
- **[0549]** R¹₁₄, independently of one another denote halogen, —NH₂, —NH(C₁₋₅-alkyl), —N(C₁₋₅-alkyl)₂ or —SO₂—R¹₁₄,
- **[0550]** R¹₁₅ denotes halogen, —NO₂, —CN, —OH, —O—CH₃ or phenyl,
- **[0551]** R¹₁₅ denotes halogen, —NO₂, —CN, —OR¹₁₅, —SR¹₁₅, —C(O)R¹₁₅, C₁₋₅-alkyl or
- **[0552]** (b) a C₁₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
- **[0553]** R¹₁₄, independently of one another denotes halogen, —NO₂, —CN, —OR¹₁₄, —SR¹₁₄, —C(O)R¹₁₄, R¹₁₄—R¹₁₄, R¹₁₄—O—C(O)R¹₁₄, R¹₁₄—NR¹₁₄—C(O)R¹₁₄ or C(O)—NR¹₁₄
- **[0554]** R¹₁₄, independently of one another denotes
- **[0555]** (a) halogen, —NO₂, —CN, —OR¹₁₄, —SR¹₁₄, —C(O)R¹₁₄, R¹₁₄—R¹₁₄, R¹₁₄—O—C(O)R¹₁₄, R¹₁₄—NR¹₁₄—C(O)R¹₁₄ or C(O)—NR¹₁₄
- **[0556]** (a) a C₁₋₅-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms, or
- **[0557]** (c) an oxo group,
- **[0558]** R¹₄, R¹₄ denotes H or C₁₋₅-alkyl,
- **[0559]** R¹₅ denotes —OH or —O—C₁₋₅-alkyl,
- **[0560]** R² denotes
- **[0561]** (a) H,
- **[0562]** (b) C₁₋₅-alkyl,
- **[0563]** (c) C₁₋₅-alkyl, or
- **[0564]** R² and R⁴ together with the carbon atom to which they are attached denote a C₅₋₁₀-cycloalkyl group optionally substituted by a group R¹¹ wherein a —CH₂— unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO₂, and
R^{3,1} denotes H or OH.

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of the above general formula III, wherein

R^3 is selected from among

-continued
[0568] $R^2$ denotes H or CH$_3$.
[0569] $R^3$ and $R^4$ together with the carbon atom to which they are attached denote a $C_{3,4}$-cycloalkylene group optionally substituted by a group $R^{3,4}$ wherein $a -- CH_2 --$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO$_2$, and $R^{3,4}$ denotes H, $-- OH$,
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.
[0571] The following compounds are mentioned as examples of most particularly preferred compounds of the above general formula III:

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2.1)</td>
<td><img src="image1" alt="Structure Image" /></td>
</tr>
<tr>
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<td><img src="image2" alt="Structure Image" /></td>
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<tr>
<td>(2.4)</td>
<td><img src="image4" alt="Structure Image" /></td>
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</table>

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.
[0572] A further embodiment of the present application relates to the use of the compounds of general formula III, wherein $R^2$, $R^3$, and $R^4$ are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or
organic acids or bases for preparing compounds of general formula I which have B1-antagonistic properties.

[0573] A further embodiment of the present invention comprises the compounds of general formula IV

![Chemical Structure](image)

wherein

[0574] n denotes one of the numbers 0, 1 or 2,

[0575] R^1 denotes

[0576] (a) H,

[0577] (b) C_{1-4}-alkyl,

[0578] (c) C_{1-4}-alkyl-C(O)-

[0579] R^2 and R^3 together with the carbon atom to which they are attached denote a C_{3-5}-cycloalkylene group optionally substituted by a group R^{3,1} wherein a —CH=— unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_{2},

[0580] R^{3,1} denotes H, —OH,

[0581] R^4 denotes

[0582] (a) H,

[0583] (b) C_{1-4}-alkyl,

[0584] (c) a C_{1-4}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0585] R^5 independently of one another denote

[0586] (a) H, halogen, —CN, —OH, C_{1-4}-alkyl, C_{3-7} cycloalkyl, —O—C_{1-4}-alkyl, —O—CF_3, —O—C_{1-4}-alkyl, —N(C_1-C_4-alkyl), —C(O)—NH_2, —SO_2—C_{1-4}-alkyl, or

[0587] (b) a C_{1-4}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0588] R^6 denotes

[0589] (a) H, halogen, —CN, —OH,

[0590] (b) C_{1-4}-alkyl,

[0591] (c) C_{1-4}-alkyl or —O—C_{1-4}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0592] (d) C_{3-7} cycloalkyl,

[0593] (e) —O—C_{1-4}-alkyl,

[0594] (f) —O—C_{1-4}-cycloalkyl,

[0595] (g) —NH_2, —NH(C_1-C_4-alkyl), —N(C_1-C_4-alkyl),

[0596] (h) C(O)—R^{1,1},

[0597] (i) —S—C_{1-4}-alkyl, —SO_2—R^{1,2},

[0598] (j) a five-membered heteroaryl group optionally substituted by one or two C_{1-4}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiaooxazolyl, triazolyl, pyrazolyl, triazinyl and tetrazolyl, or

[0599] (k) a six-membered heteroaryl group optionally substituted by one or two C_{1-4}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

[0600] R^{3,1} denotes —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl), N-acetidinyl, N-pyridinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C_{1-4}-alkyl or —O—C_{3-7} cycloalkyl,

[0601] R^{3,1} denotes —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl), N-acetidinyl, N-pyridinyl, N-piperidinyl or N-morpholinyl and

[0602] R^8 denotes H, halogen, C_{1-4}-alkyl,

[0603] R^9 denotes

[0604] (a) H, halogen, —CN, —OH,

[0605] (b) C_{1-4}-alkyl,

[0606] (c) C_{1-4}-alkyl or —O—C_{1-4}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0607] (d) C_{3-7} cycloalkyl,

[0608] (e) C_{1-4}-alkynyl,

[0609] (f) —O—C_{1-4}-alkyl,

[0610] (g) —O—C_{3-7} cycloalkyl,

[0611] (h) —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl),

[0612] (i) —O—R^{1,1},

[0613] (j) —S—C_{1-4}-alkyl, —SO_2—C_{1-4}-alkyl,

[0614] (k) a five-membered heteroaryl group optionally substituted by one or two C_{1-4}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

[0615] R^10 denotes H, halogen, C_{1-4}-alkyl,

[0616] (a) H, halogen, —CN, —OH,

[0617] (b) C_{1-4}-alkyl,

[0618] (c) C_{1-4}-alkyl or —O—C_{1-4}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

[0619] (d) C_{3-7} cycloalkyl,

[0620] (e) —O—C_{1-4}-alkyl,

[0621] (f) —O—C_{3-7} cycloalkyl,

[0622] (g) —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl),

[0623] (h) C(O)—R^{1,1},

[0624] (i) —S—C_{1-4}-alkyl, —SO_2—R^{1,2},

[0625] (j) a five-membered heteroaryl group optionally substituted by one or two C_{1-4}-alkyl groups which is selected from among pyrryl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiaooxazolyl, thiaooxazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

[0626] (k) a six-membered heteroaryl group optionally substituted by one or two C_{1-4}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

[0627] R^{1,1} denotes —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl), N-acetidinyl, N-pyridinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C_{1-4}-alkyl or —O—C_{3-7} cycloalkyl,

[0628] R^{1,1} denotes —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl), N-acetidinyl, N-pyridinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C_{1-4}-alkyl or —O—C_{3-7} cycloalkyl,

[0629] R^{1,1} denotes —NH_2, —NH(C_{1-4}-alkyl), —N(C_1-C_4-alkyl), N-acetidinyl, N-pyridinyl, N-piperidinyl or N-morpholinyl and

[0630] X independently of one another denotes C—R^6 or N.
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of the above general formula IV, wherein

- \( n \) denotes one of the numbers 0, 1 or 2,
- \( R^2 \) denotes H or CH\(_3\),
- \( R^3 \) and \( R^4 \) together with the carbon atom to which they are attached denote a C\(_{3-6}\)-cycloalkylene group optionally substituted by a group R\(^{3,4}\) wherein a \(-\text{CH}_3\) unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO\(_2\),
- \( R^{3,4} \) denotes H, —OH,
- \( R^5 \) denotes H or CH\(_3\),
- \( R^6 \) denotes H, F, Cl or methyl,
- \( R^7 \) denotes H, F, Cl, Br, —CN, C\(_1-4\)-alkyl, CF\(_3\), CHF\(_2\),
- \( R^8 \) denotes H, F, Cl, Br, —CN, C\(_1-4\)-alkyl, CF\(_3\), CHF\(_2\),
- \( R^9 \) denotes F, Cl, Br, C\(_1-4\)-alkyl, —O—C\(_1-4\)-alkyl, —S—C\(_1-4\)-alkyl,
- \( R^{10} \) denotes H,
- \( R^{11} \) denotes F, Cl, Br, —CN, C\(_1-4\)-alkyl, CF\(_3\), CHF\(_2\), and
- \( X \) independently of one another denotes C—R\(^8\) or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

The following compounds are mentioned as examples of most particularly preferred compounds of the above general formula IV:

<table>
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</table>
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present application relates to the use of the compounds of general formula IV, wherein R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases for preparing compounds of general formula I which have B1-antagonistic properties.

Terms and Definitions Used

Unless otherwise stated, all the substituents are independent of one another. If for example there are a plurality of C₄₋₅-alkyl groups as substituents in one group, in the case of three substituents C₄₋₅-alkyl, one may represent methyl, one n-propyl and one tert-butyl.

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

Also included in the subject matter of this invention are the compounds according to the invention, including the salts thereof, in which one or more hydrogen atoms, for example one, two, three, four or five hydrogen atoms, are replaced by deuterium.

By the term “C₁₋₂-alkyl” (including those that are part of other groups) are meant alkyl groups with 1 to 3 carbon atoms, by the term “C₂₋₅-alkyl” are meant branched and unbranched alkyl groups with 1 to 24 carbon atoms, by the term “C₆₋₁₀-alkyl” are meant branched and unbranched alkyl groups with 1 to 8 carbon atoms. Examples include: methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, n-heptyl and n-octyl. The abbreviations Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, etc. May optionally also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec-butyl and tert-butyl.

Moreover the definitions mentioned previously also include those groups wherein each methylene group may be substituted by up to two of each methyl group may be substituted by up to three fluorne atoms.

By the term “C₄₋₂-alkylene” are meant branched and unbranched alkylene groups with 0 to 2 carbon atoms, while a C₉₋₁₀-alkylene group denotes a bond. Examples include: methylene, ethylene and ethane-1,1-diyld. Moreover the definitions mentioned previously also include those groups wherein each methylene group may be substituted by up to two fluorne atoms.

By the term “C₆₋₅-cycloalkyl” (including those that are part of other groups) are meant cyclic alkyl groups with 3 to 7 carbon atoms and by the term “C₆₋₅-cycloalkyl” are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Unless otherwise stated, the cyclic alkylene groups may be substituted by one or more groups selected from among methyl, ethyl, iso-propyl, tert-butyl, hydroxy, fluorne, chlorin, bromine and iodine.

By the term “C₆₋₅-cycloalkylene” (including those that are part of other groups) are meant cyclic alkylene groups with 3 to 6 carbon atoms. Examples include: cyclopropylene, cyclobutenylene, cyclopentylene or cyclohexylene. Unless otherwise stated, the cyclic alkylene groups may be substituted by one or more groups selected from among methyl, ethyl, iso-propyl, tert-butyl, hydroxy, fluorne, chlorin, bromine and iodine.

By the term “C₂₋₄-alkynyl” (including those that are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples include: ethynyl, propynyl or butynyl. Unless stated otherwise, the definitions propynyl and butynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1-butynyl, 2-butynyl and 3-butynyl etc.

“Halogen” within the scope of the present invention denotes fluorne, chlorin, bromine or iodine. Unless stated to the contrary, fluorne, chlorin and bromine are regarded as preferred halogens.

By the term “heterocyclic rings” or “heterocyclic group” are meant stable 5- or 6-membered monocyclic ring systems, which may be both saturated and mono- or di-un-saturated and besides carbon atoms may carry one or two heteroatoms, which are selected from among nitrogen, oxygen and sulphur. Both nitrogen and sulphur heteroatoms may optionally be oxidised. The previously mentioned heterocycles may be attached to the rest of the molecule via a carbon atom or a nitrogen atom. The following compounds are mentioned as examples:
“Cyclic imides” includes for example succinimides, maleimide and phthalimide.

By the term “aryl” (including those that are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples of these are phenyl, 1-naphthyl or 2-naphthyl; the preferred aryl group is phenyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, n-propyl, iso-propyl, tert-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different.

By the term “heteroaryl” are meant five- or six-membered heterocyclic aromatic groups, which may contain one, two, three or four heteroatoms, selected from among oxygen, sulphur and nitrogen, and additionally contain so many conjugated double bonds that an aromatic system is formed. These heteroaryl may additionally be benzo-condensed with a phenyl ring, so as to form nine- or ten-membered bicyclic heteroaryl.

The following are examples of five- or six-membered heteroaromatic groups:

Unless otherwise stated, the heteroaryl mentioned previously may be substituted by one or more groups selected from among methyl, ethyl, n-propyl, iso-propyl, tert-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different.

In addition, any nitrogen atom present in the heteroaryl group may be oxidised, thereby forming an N-oxide.

By the term “oxo group” is meant an oxygen substituent at a carbon atom, which leads to the formation of a carbonyl group —C(=O)—. The introduction of an oxo group as substituent at a non-aromatic carbon atom leads to a conversion of a —CH2— group into a —C(=O)— group. The introduction of an oxo group at an aromatic carbon atom leads to the conversion of a —CH— group into a —C(=O)— group and may result in the loss of aromaticity.

If they contain suitable basic functions, for example amino groups, compounds of general formula I may be converted, particularly for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of inorganic acids for this purpose include hydrobromic acid, phosphoric acid, nitric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or p-toluene sulphonic acid, while organic acids that may be used include malic acid, succinic acid, acetic acid, fumaric acid, maleic acid, mandelic acid, lactic acid, tartaric acid or citric acid.

In addition, the compounds of general formula I, if they contain suitable carboxylic acid functions, may be converted into the physiologically acceptable salts thereof with inorganic or organic bases, particularly for pharmaceutical applications. Examples of inorganic bases include alkalai or alkaline earth metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, or carbonates, ammonia, zinc or ammonium hydroxides; examples of organic amines include diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, cyclamoxaline or diethylene oxalic acid.

The compounds according to the invention may be present as racemates, provided that they have only one chiral element, but may also be obtained as pure enantiomers, i.e. in the (R) or (S) form.

However, the application also includes the individual diastereomeric pairs of enantiomers or mixtures thereof,
which are obtained if there is more than one chiral element in the compounds of general formula I, as well as the individual optically active enantiomers of which the above-mentioned racemates are made up.

[0669] Compounds with a carbon double bond may be present in both the E and Z form.

[0670] If a compound is present in different tautomeric forms, the compound prepared is not limited to one tautomeric form but includes all the tautomeric forms. This also applies particularly to nitrogen-containing heteroaryls:

\[
\begin{align*}
\text{N} & \equiv \text{N} \\
\text{N} & \equiv \text{N}
\end{align*}
\]

Preparation Methods

[0671] According to the invention the compounds of general formula I are obtained by methods known per se, for example by the following methods:

(A) Amide Coupling:

\[
\begin{align*}
\text{R}^5 & \equiv \text{N} \\
\text{R}^5 & \equiv \text{N}
\end{align*}
\]

[0672] An alternative method of preparing compounds of general formula I consists in linking carboxylic acids of general formula V, wherein all the groups are as hereinbefore defined, with amines of general formula IV, wherein all the groups are as hereinbefore defined.

[0673] The linking of carboxylic acids of general formula II as shown, wherein all the groups are as hereinbefore defined, with amines of general formula III, wherein all the groups are as hereinbefore defined, to form carboxylic acid amides of general formula I wherein all the groups are as hereinbefore defined, may be carried out by conventional methods of amide formation.

[0674] The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carboimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)-N,
The reaction of an aniline of general formula VIII, wherein all the groups are as hereinbefore defined, with a nitrile of general formula VII, wherein X, R₈, and n are as hereinbefore defined, and Hal denotes a fluorine, chlorine or bromine atom, is carried out using known methods, for example in a solvent such as tetrahydrofuran, dimethylformamide or dimethylsulphoxide and conveniently in the presence of a base such as triethylamine, sodium hydroxide solution or potassium carbonate at a temperature of 20° C. to 160° C. If the aniline of general formula VIII is liquid, the reaction may also be carried out without a solvent and additional base.

An alternative method of preparing compounds of general formula VI is the palladium-catalysed reaction of a nitrile of general formula VII, wherein Hal denotes bromine or chlorine, with an aniline of general formula VIII. Reaction conditions for this reaction, which is also known as a Buchwald-Hartwig reaction, are known from the literature.

Description of the Method of Binding the cyoBK1-Receptor

CHO cells that express the cyonologous BK1-receptor are cultivated in “HAM’S F-12 Medium”. The medium is removed from confluent cultures, the cells are washed with PBS buffer, scraped off or detached using Versene and isolated by centrifuging. Then the cells are homogenised in suspension, the homogenate is centrifuged and resuspended. After the protein content has been determined 200 μL of the homogenate (50 to 250 μg protein/assay) are incubated for 60-180 minutes at ambient temperature with 0.5 to 5.0 nM kallidin (DesArg10,Leu9), [3,4-Prolyl-3,4H(N)] y and increasing concentrations of the test substance in a total volume of 250 μL. The incubation is stopped by rapid filtration through GF/B glass fibre filters that have been pre-treated with polyethyleneimine (0.3%). The radioactivity bound to the protein is measured with a TopCount NXT. The radioactivity bound in the presence of 1.0 μM kallidin (DesArg10) is defined as non-specific binding. The concentration binding curve may be analysed using computer-aided non-linear curve fitting to determine the corresponding Kᵢ value for the test substance.

Test results of the cyoBK1-receptor binding assay:

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<th>Kᵢ [nM]</th>
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<td>K_i [nM]</td>
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### Indications

[0688] In view of their pharmacological properties, the novel compounds and their physiologically acceptable salts are suitable for treating diseases and symptoms of diseases caused at least to some extent by stimulation of bradykinin-B₁ receptors, or in which antagonisation of the bradykinin-B₁ receptor can bring about an improvement in symptoms.

[0689] In a further aspect the present invention encompasses the compounds of the above-mentioned general formula I according to the invention for use as medicaments.

[0690] In view of their pharmacological effect the substances are suitable for the treatment of:

(a) acute pain such as for example toothache, peri- and post-operative pain, traumatic pain, muscle pain, the pain caused by burns, sunburn, trigeminal neuralgia, pain caused by colic, as well as spasms of the gastro-intestinal tract or uterus;

(b) visceral pain such as for example chronic pelvic pain, gynaecological pain, pain before and during menstruation, pain caused by pancreatitis, peptic ulcers, interstitial cystitis, renal colic, cholecystitis, prostatitis, angina pectoris, pain caused by irritable bowel, non-ulcerative dyspepsia and gastritis, prostatitis, non-cardiac thoracic pain and pain caused by myocardial ischaemia and cardiac infarct;

(c) neuropathic pain such as for example painful neuropathies, pain of diabetic neuropathy, AIDS-associated neuropathic pain non-herpes-associated neuralgia, post-herpetic neuralgia, nerve damage, cerebro-cranial trauma, pain of nerve damage caused by toxins or chemotherapy, phantom pain, pain of multiple sclerosis, nerve root tears and painful traumatically-caused damage to individual nerves, and central pain such as for example pain after stroke, spinal injuries or tumours;

(d) inflammatory/pain receptor-mediated pain in connection with diseases such as for example osteoarthritis, rheumatoid arthritis, rheumatic fever, tendo-synovitis, bursitis, tenosynovitis, gout and gout-arthritis, traumatic arthritis, vulvodynia, damage to and diseases of the muscles and fascia, juvenile arthritis, spondylitis, psoriasis-arthritis, myositis, dental disease, influenza and other viral infections such as colds, systemic lupus erythematoses or pain caused by burns;

(e) tumour pain associated with cancers such as lymphomas, myeloid leukaemia, Hodgkin's disease, non-Hodgkin's lymphomas, lymphogranulomatosis, lymphosarcoma, solid malignant tumours and extensive metastases;

(f) headache diseases of various origins, such as for example cluster headaches, migraine (with or without aura) and tension headaches;

(g) painful conditions of mixed origin, such as for example chronic back pain including lumbar, or fibromyalgia.

[0691] The compounds are also suitable for treating:

(h) inflammatory complaints or phenomena caused by sunburn and burns, inflammation of the gums, oedema after burns trauma, cerebral oedema and angio-oedema, intestinal complaints including Crohn’s disease and ulcerative colitis.
irritable bowel syndrome, pancreatitis, nephritis, cystitis (interstitial cystitis), uveitis; inflammatory skin diseases (such as psoriasis and eczema), vascular diseases of the connective tissue, sprains and fracture, and musculoskeletal diseases with inflammatory symptoms such as acute rheumatic fever, polymyalgia rheumatica, reactive arthritis, rheumatoid arthritis, spondylarthritides, and also osteoarthritis, and inflammation of the connective tissue of other origins, and collagenoses of all origins such as systemic lupus erythematoses, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still's disease or Felty syndrome;

(i) inflammatory changes connected with diseases of the airways such as bronchial asthma, including allergic asthma (atopic and non-atopic) as well as bronchospasm on exertion, occupationally induced asthma, viral or bacterial exacerbation of an existing asthma and other non-allergically induced asthmatic diseases;

(j) chronic bronchitis and chronic obstructive pulmonary disease (COPD) including pulmonary emphysema, viral or bacterial exacerbation of chronic bronchitis or chronic obstructive bronchitis, acute adult respiratory distress syndrome (ARDS), bronchitis, lung inflammation, allergic rhinitis (seasonal and all year round) vasomotor rhinitis and diseases caused by dust in the lungs such as aluminosis, anthracosis, asbestosis, chalciosis, siderosis, silicosis, tabaicosis and byssinosis, exogenous allergic alveolitis, cystic fibrosis, bronchiectasis, pulmonary diseases in alpha-1-antitrypsin deficiency and cough;

(k) diabetes mellitus and its effects (such as e.g. diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy) and diabetic symptoms in insulin (for example hyperglycaemia, diuresis, proteinuria and increased renal excretion of nitrite and kaliurein);

(l) sepsis and septic shock after bacterial infections or after trauma;

(m) syndromes that cause itching and allergic skin reactions;

(n) damage to the central nervous system;

(o) wounds and tissue damage;

(p) benign prostatic hyperplasia and hyperactive bladder;

(q) neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease;

(m) osteoporosis;

(e) epilepsy;

(q) vascular diseases such as panarteritis nodosa, polyarthritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner’s granulomatosis, giant cell arteritis, arteriosclerosis and erythema nodosum;

inflammation of the gums;

(r) disorders of the motility or spasms of respiratory, genito-urinary, gastro-intestinal including biliary or vascular structures and organs;

(s) post-operative fever;

(l) for the treatment and prevention of cardiovascular diseases such as high blood pressure and related complaints;

(u) for the treatment and prevention of cancer and related complaints;

(v) for the treatment and prevention of psychiatric diseases such as depression;

(w) for the treatment and prevention of urinary incontinence and related complaints;

(x) for the treatment and prevention of morbid obesity and related complaints;

(y) for the treatment and prevention of atherosclerosis and related complaints.

(2) for the treatment and prevention of epilepsy.

The substances are suitable for causal treatment in the sense of slowing down or stopping the progress of chronically progressive diseases, particularly osteoarthritis, rheumatoid arthritis and spondylarthritides.

In another aspect the present invention encompasses the use of the compounds of the above-mentioned general formula I according to the invention for preparing a medicament for therapeutic use in the above-mentioned indications.

Preferably, the compounds of general formula I according to the invention are used for the treatment of osteoarthritis, rheumatoid arthritis or COPD.

The term “treatment” or “therapy” refers to a therapeutic treatment of patients with a manifest, acute or chronic indication, including on the one hand symptomatic (pollutive) treatment to relieve the symptoms of the disease and on the other hand causal or curative treatment of the indication with the aim of ending the pathological condition, reducing the severity of the pathological condition or delaying the progression of the pathological condition, depending on the nature or gravity of the indication.

The present invention further relates to the use of a compound of general formula I for preparing a medicament for the acute and prophylactic treatment of acute pain, visceral pain, neuropathic pain, inflammatory/pain receptor-mediated pain, tumour pain, headache pain and pain of mixed causes and other diseases as mentioned above. This use is characterised in that it comprises administering an effective amount of a compound of general formula I or a pharmaceutically acceptable salt thereof to a patient requiring such treatment.

The term “patient” preferably refers to a human being.

In addition to their suitability as therapeutic drugs for humans, these substances are also useful in the veterinary medical treatment of domestic pets, exotic animals and farmed animals.

Combinations

For treating pain, it may be advantageous to combine the compounds according to the invention with stimulating substances such as caffeine or other pain-alleviating active compounds. If active compounds suitable for treating the cause of the pain are available, these can be combined with the compounds according to the invention.

The following compounds may be used for combination therapy, for example:

Non-steroidal antiinflammatory drugs (NSAR) such as for example propionic acid derivatives which may be selected from among alminoprofen, bucloc acid, ciproprofen, fenoprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, piroprofen, piroprofan and tiaprofenic acid; acetic acid derivatives which may be selected from among indomethacin, acemetacin, aclonofenac, isoxepac, sulindac and tolmetin; fenamic derivatives which may be selected from among meclofenamic acid, mefenamic acid and tolenamic acid; biphensylcarboxylic acid derivatives; oxizics which may be selected from among meloxicam, piroxicam and tenoxicam; salicylic acid derivatives which may be selected from among aminopyrine and fenesprofen; and corkins which may be selected from among celecoxib and ertori-coxib).
[0702] Opiate receptor agonists which may for example be selected from among morphine, Darvon, tramadol and buprenorphine; cannabinoid agonists such as for example GW-1000; Sodium channel blockers which may for example be selected from among carbamazepine, mexiletin, pregabalin, tectin and ralniamide.

[0703] N-type calcium channel blockers such as for example lercanidipine.

[0704] Serotonergic and noradrenergic modulators which may be selected from among for example duloxetine and amitriptyline.

[0705] Corticosteroids which may be selected from among for example betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone.

[0706] Histamine H1-receptor antagonists which may for example be selected from among brompheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenpyraliline, tripelennamine, hydroxyzine, mexitizoline, promethazine, trimetazine azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine.

[0707] Leukotriene antagonists and 5-lipoxygenase inhibitors which may for example be selected from among zafirlukast, montelukast, pranlukast and zileuton.

[0708] Local anaesthetics which may for example be selected from among amboxol and lidocaine.

[0709] TRPV1 antagonists which may for example be selected from among AZD-1386, JTS-653 and PHE-377.

[0710] Nicotine receptor agonists such for example A-366833.

[0711] P2X3-receptor antagonists such as e.g. A-317491.

[0712] anti-NF antibodies and NGF antagonists which may for example be selected from among JN-42160443 and PPH 207.

[0713] NK1 and NK2 antagonists such as e.g. CP-728663.

[0714] NMDA antagonists which may for example be selected from among CNS-5161, AZ-756 and V-3381.

[0715] Potassium channel modulators such as e.g. CL-888.

[0716] GABA modulators such as e.g. baclofen.

[0717] Anti-migraine drugs such as e.g. sumatriptan, zolmitriptan, naratriptan and eletriptan.

[0718] For treating one or more of the above-mentioned respiratory complaints it may be advantageous to combine the compounds of general formula I according to the invention with other active substances for treating respiratory complaints. If suitable active substances for treating the cause of the respiratory complaints are available, these may be combined with the compounds according to the invention.

[0719] The compounds of general formula I may optionally also be used in conjunction with other pharmacologically active substances. It is preferable to use active substances of the type selected from among the betametanides, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-receptor (Cy5.1,T1, Cy5.1,T2, Cy5.1,T3) antagonists, inhibitors of MAP 2 kinases such as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, LTD4-receptor (BlT1, BlT2) antagonists, EGF-receptor-inhibitors, H1-receptor antagonists, antihista-mines, H4-receptor antagonists, PAF-antagonists and PI3-kine inhibitors CXCR1 and/or CXCR2 receptor antagonists and anti-tussives.

[0720] The compounds of general formula I may also be used in the form of double or triple combinations thereof, such as for example combinations of compounds of formula I with one or two compounds selected from among betamimetics, corticosteroids, PDE4-inhibitors, EGF-receptor and LTD4-antagonists, anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors, EGF-receptor and LTD4-antagonists, PDE4-inhibitors, corticosteroids, EGF-receptor and LTD4-antagonists, EGF-receptor and LTD4-antagonists, EGF-receptor and LTD4-antagonists, EGF-receptor and LTD4-antagonists.

[0721] CCR3-inhibitors, INOS-inhibitors (inducible nitric oxide synthase-inhibitors), 6R-1-erythro-5,6,7-8-tetrahydrobiphenyl (hereinafter referred to as "BH4") and the derivatives thereof which are mentioned in WO 2006/120176, and SYK-inhibitors (spleen tyrosine kinase inhibitors).

[0722] anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors and MRP4-inhibitors.

[0723] Combinations of three active substances of one of the above mentioned categories of compounds are also covered by the invention.

[0724] Betamimetics used according to the invention are preferably compounds selected from among arformoterol, carmoterol, formoterol, indacaterol, salmeterol, albuterol, bumberal, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, hexoprenal, ibuterol, isethiostin, isopenral, levosalbutamol, mabuterol, meludrin, metaproterenol, milvetor, orciprenal, pirbuterol, procaterol, reproterol, rimeterol, riocinid, salmeterol, soterenol, sulphenoterol, terbutalin, tiamid, tolbuterol and zileuton or

[0725] 6-hydroxy-8-[1-hydroxy-2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl) 4H-benzo[d][1,4]oxazin-3-one, or

[0726] 8-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl)-6-hydroxy-4H-benzo[d][1,4]oxazin-3-one, or

[0727] 8-[2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl)-6-hydroxy-4H-benzo[d][1,4]oxazin-3-one, or

[0728] 8-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl)-6-hydroxy-4H-benzo[d][1,4]oxazin-3-one, or

[0729] 8-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl)-6-hydroxy-4H-benzo[d][1,4]oxazin-3-one, or

[0730] N-(5-[2-[3-(4,4-diethyl-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0731] N-(5-[2-[3-(4,4-diethyl-6-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0732] N-(5-[2-[3-(4,4-diethyl-1-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0733] N-(5-[2-[1,1-dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0734] N-(5-[2-[1,1-dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0735] N-(5-[2-[3-(4,4-diethyl-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0736] N-(5-[2-[3-(4,4-diethyl-6-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0737] N-(5-[2-[3-(4,4-diethyl-1-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide, or

[0738] N-(5-[2-[1,1-dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl]-2-hydroxy-phenyl)methanesulphonamide,
phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluene sulphonate, while the chloride, bromide, iodide, sulphate, methanesulphonate or p-toluene sulphonate are preferred as counter-ions. Of all the salts the chlorides, bromides, iodides and methanesulphonates are particularly preferred.

[0776] Other anticholinergics may be selected from among
tropanol 2,2-di(phenylpropionate)methobromide, trope
cine 2,2-di(p phenylpropionate)methobromide,
tropanol 2-fluoro-2,2-diphenylacetate methobromide,
tropanol 3,3',4,4'-tetrafluorobenzilate methobromide,
tropanol 4,4'-difluorobenzilate methobromide,
tropanol 9-hydroxy-fluorene-9-carboxylate methobromide,
tropanol 9-fluoro-fluorene-9-carboxylate methobromide,
tropanol 9-hydroxy-fluorene-9-carboxylate metho
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[0824] 4-(1-[3-(4-bis[difluoromethoxy]phenyl)-2-(3-methyl-1-oxido-4-pyridinyl)ethyl]alpha, alpha-bis[trifluoromethyl]-benzenemethanol (L-826141),
[0825] N-3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide,
[0826] (4-[4AR*,4BS*]-9-ethoxy-1,2,3,4,4a,10b-hexahydro-s-6-methoxy-2-methylbenzo]-[1,6]naphthyridin-6-yl]-N-13-disopropylbenzamide,
[0827] (R)-(+)-1-(4-bromobenzyl)-4-(3-cyclopropylxyloxy)-4-methoxyphenyl]-2-pyrrolidone,
[0828] 3-cyclopropylxyloxy-4-methoxyphenyl]-1-(4-N-[N-2-cyano-S-methyl-isothioureido]-benzyl)-2-pyrrolidone,
[0829] cis-[4-cyano-4-(3-cyclopropylxoy)-4-methoxyphenyl]-1-carboxylic acid,
[0830] 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-cyclohexan-1-one,
[0831] cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl]-cyclohexan-1-ol],
[0832] (R)-(4-ethyl)-4-(3-cyclopropylxyloxy-4-methoxyphenyl)-pyrroloidin-2-ylidene]acetate,
[0833] (S)-(4-ethyl)-4-(3-cyclopropylxyloxy-4-methoxyphenyl)-pyrroloidin-2-ylidene]acetate,
[0834] 9-cyclopropyl-1,5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrrozol-3,4-c]-1,2,4-triazolo-[4,3-a]pyridine and
[0835] 9-cyclopropyl-1,5,6-dihydro-7-ethyl-3-(3-tet-buty)-9H-pyrrozol-3,4-c]-1,2,4-triazolo-[4,3-a]pyridine, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodide, hydro sulphate, hydrophosphate, hydrothiocarboxylic acid, hydrothionate, hydrogenacetate, hydroacetate, hydroxacetate, hydroximate, hydroxyacetate, hydroxosuccinate, hydroxobenzene and hydro-π-thiolenesulphonate.
[0836] EGF-R inhibitors used according to the invention are preferably compounds selected from among cetuximab, trastuzumab, panitumumab (=ABX_EGF), Mab ICR-62, gefitinib, cangemibib and erlotinib or
[0837] 4-(3-chloro-4-fluorophenyl]amine]-6-[4-(mor phonol-4-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0838] 4-(3-chloro-4-fluorophenyl]amine]-6-[4-(N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0839] 4-(3-chloro-4-fluorophenyl]amine]-6-[4-(N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0840] 4-[4-(1-carboxyethyl]amino]-6-[4-(mor phonol-4-yl]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0841] 4-(3-chloro-4-fluoro-phenyl]amine]-6-[4-(R)-6-methyl-2-oxo-morpholin-4-yl]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0842] 4-(3-chloro-4-fluoro-phenyl]amine]-6-[4-(R)-6-methyl-2-oxo-morpholin-4-yl]-2-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0843] 4-(3-chloro-4-fluoro-phenyl]amine]-6-[4-(R)-2-methoxymethyl-6-oxo-morpholin-4-yl]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0844] 4-(3-chloro-4-fluoro-phenyl]amine]-6-[2-(SS)-6-methyl-2-oxo-morpholin-4-yl]ethoxy]-7-methoxyquinazoline,
[0845] 4-(3-chloro-4-fluorophenyl]amine]-6-[4-[N-(2-methoxy-ethyl]-N-methylamino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0846] 4-(3-chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0847] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-[N,N-bis-(2-methoxy-ethyl]-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0848] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-[N,N-bis-(2-methoxy-ethyl]-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0849] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-[N,N-bis-(2-methoxy-ethyl]-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0850] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-[N,N-bis-(2-methoxy-ethyl]-amino]-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline,
[0851] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(R)-tetrahydrofururan-3-ylxoyquinazoline,
[0852] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(S)-tetrahydrofururan-3-ylxoyquinazoline,
[0853] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(R)-tetrahydrofururan-3-ylxoyquinazoline,
[0854] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(S)-tetrahydrofururan-3-ylxoyquinazoline,
[0855] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(R)-tetrahydrofururan-2-ylmethoxyquinazoline,
[0856] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-(S)-tetrahydrofururan-2-ylmethoxyquinazoline,
[0857] 4-[4(chloro-4-fluorophenyl]amine]-6-[6,7-bis-(2-methoxy-ethyl)-quinazoline,
[0858] 4-[4(chloro-4-fluorophenyl]amine]-7-[3-(mor phonol-4-yl]propoxy]-6-[4-vinylcarbonyl]amino]-quinazoline,
[0859] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-(hydroxy-phe ny)-7H-pyrrolo-[2,3-d]pyrimidine,
[0860] 3-cyano-4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-dimethylaminol]-1-oxo-2-buten-1-yl]amino]-7-ethoxyquinazoline,
[0861] 4-[4(chloro-4-fluorophenyl]amine]-6-[5-[4,7-methanesulphonyl-ethyl]amino]-6-methyl]-furran-2-yl]quinazoline,
[0862] 4-[4(R)-[1-phenyl-ethyl]amino]-6-[4-[R]-6-methyl-2-oxo-morpholin-4-yl]-1-oxo-2-buten-1-yl]amino]-7-methoxyquinazoline,
[0863] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-(morpholino-4-yl)-1-oxo-2-buten-1-yl]amino]-7-(tetrahydrofururan-2-yl]methoxyquinazoline,
[0864] 4-[4(chloro-4-fluorophenyl]amine]-6-[4-[N,N-bis-(2-methoxy-ethyl]amino]-1-oxo-2-buten-1-yl]amino]-7-(tetrahydrofururan-2-yl]methoxyquinazoline,
[0865] 4-[4(ethynyl-phenyl]amine]-6-[4-[5.5-dimethyl-2-oxo-morpholin-4-yl]-1-oxo-2-buten-1-yl]amino]-quinazoline,
[0866] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(2,2-dimethyl-6-oxo-morpholin-4-yl)ethoxy-7-methoxy-quinazoline,
[0867] 4-[3-chloro-4-fluoro-phenyl]amino]-6-[2,2-dimethyl-6-oxo-morpholin-4-yl]ethoxy-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
[0868] 4-[3-chloro-4-fluoro-phenyl]amino]-7-[2,2-dimethyl-6-oxo-morpholin-4-yl]ethoxy-6-{(S)-(tetrahydrofuran-2-yl)methoxy}-quinazoline,
[0869] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{2-[4-(2-oxo-morpholin-4-yl)piperidin-1-yl]ethoxy}-7-methoxy-quinazoline,
[0870] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[(tert-butyloxycarbonyl)piperidin-4-yl]oxy}-7-methoxy-quinazoline,
[0871] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(trans-4-amino-cyclohexane-1-yl)-7-methoxy-quinazoline,
[0872] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(4-methanesulphonylamino-cyclohexane-1-yl)-7-methoxy-quinazoline,
[0873] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(tetrahydropyran-3-yl)-7-methoxy-quinazoline,
[0874] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[methyl-piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0875] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[morphpolin-4-yl]carbonyl)piperidin-4-yl]-7-methoxy-quinazoline,
[0876] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[methylmethylcarbonyl)piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0877] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{piperidin-3-yl)-oxy}-7-methoxy-quinazoline,
[0878] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[2-acetylaminio-ethyl)piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0879] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(tetrahydropyran-4-yl)-7-ethoxy-quinazoline,
[0880] 4-[3-chloro-4-fluoro-phenyl]amino]-6-[(S)-(tetrahydrofuran-3-yl)-oxy]-7-hydroxy-quinazoline,
[0881] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(trans-4-[dimethylamino]sulphonylamino)-7-(2-methoxy-ethoxy)-quinazoline,
[0882] 4-[3-chloro-4-fluoro-phenyl]amino]-6-[trans-4-[(dimethylamino)sulphonylamino]cyclohexane-1-yl)-oxy]-7-methoxy-quinazoline,
[0883] 4-[3-chloro-4-fluoro-phenyl]amino]-6-[trans-4-[(morpholin-4-yl)carbonylamino]cyclohexane-1-yl)-oxy]-7-methoxy-quinazoline,
[0884] 4-[3-chloro-4-fluoro-phenyl]amino]-6-[trans-4-[(morpholin-4-yl)sulphonylamino]cyclohexane-1-yl)-oxy]-7-methoxy-quinazoline,
[0885] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(tetrahydropyran-4-yl)-7-(2-acetamidino-ethoxy)-quinazoline,
[0886] 4-[3-chloro-4-fluoro-phenyl]amino]-6-(tetrahydropyran-4-yl)-7-(2-methanesulphonylamino-ethoxy)-quinazoline,
[0887] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-[piperidin-1-yl]carbonyl)piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0888] 4-[3-chloro-4-fluoro-phenyl]amino]-6-{1-aminocarbonylmethyl-piperidin-4-yl)-oxy}-7-methoxy-quinazoline,
[0889] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(tetrahydropyran-4-yl)carbonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0890] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(morpholin-4-yl)carbonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0891] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(morpholin-4-yl)sulphonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0892] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexane-1-yl)-oxy)-7-methoxy-quinazoline,
[0893] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(1-methanesulphonyl)piperidin-4-yl)-oxy}-7-ethoxy-quinazoline,
[0894] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(1-methanesulphonyl)piperidin-4-yl]-oxy}-7-(2-methoxy-ethoxy)-quinazoline,
[0895] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{1-(2-methoxy-acetyl)piperidin-4-yl]-oxy}-7-(2-methoxy-ethoxy)-quinazoline,
[0896] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-acetamido-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0897] 4-{(3-ethylmethylphenyl)amino]-6-{1-[(tert-butyloxycarbonyl)piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0898] 4-{(3-ethylmethylphenyl)amino]-6-{(tetrahydropyran-4-yl)-oxy}-7-methoxy-quinazoline,
[0899] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(piperidin-1-yl)carbonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0899] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(4-methyl-piperazin-1-yl)carbonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0900] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(4-methyl-piperazin-1-yl)carbonyl]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0901] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0902] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-oxopyrrolidin-1-yl]ethyl)piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0903] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl)piperidin-4-yl]-oxy}-7-(2-methoxy-ethoxy)-quinazoline,
[0904] 4-{(3-ethyl-phenyl)amino]-6-1-acetyl-piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0905] 4-{(3-ethylmethylphenyl)amino]-6-{1-ethyl-methyl-piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0906] 4-{(3-ethylmethylphenyl)amino]-6-{1-methanesulphonylpiperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0907] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{1-methyl-piperidin-4-yl]-oxy}(7-2-methoxy-ethoxy)-quinazoline,
[0908] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{1-isopropyloxycarbonylpiperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0909] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-methylamino-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0910] 4-{(3-chloro-4-fluoro-phenyl)amino]-6-{(cis-4-[N-(2-methoxy-acetyl)]N-methyl-amin)-cyclohexane-1-yl)-oxy}-7-methoxy-quinazoline,
[0911] 4-{(3-ethyl-phenyl)amino]-6-{piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0912] 4-{(3-ethyl-phenyl)amino]-6-{[1-(2-methoxy-acetyl)]piperidin-4-yl]-oxy}-7-methoxy-quinazoline,
[0913] 4-{(3-ethylphenoxy)aminol-6-[-1-[(morpholin-4-y1)carbonyl]piperidin-4-ylxoy]-7-methoxy-quinazoline,
[0914] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-cis-2, 6-dimethylmorpholin-4-y1]carbonyl]piperidin-4-ylxoy]-7-methoxy-quinazoline,
[0915] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-[(2-methylmorpholin-4-y1)carbonyl]piperidin-4-ylxoy]-7-
methoxy-quinazoline,
[0916] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-(S,S)-
(2-oxa-5-aza-bicyclo[2,2,1]hept-5-y1)carbonyl]piperidin-4-ylxoy]-7-methoxy-quinazoline,
[0917] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-(N-methyl-N'-methoxyethylaminocarbonyl]piperidin-4-ylxoy]-7-methoxy-quinazoline,
[0918] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-(ethyl-
piperidin-4-ylxoy)]-7-methoxy-quinazoline,
[0919] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-[(2-
methoxyethyl)carbonyl]piperidin-4-ylxoy]-7-methoxy-
quinazoline,
[0920] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-[(3-
methoxypropylamino)carbonyl]piperidin-4-ylxoy]-7-
methoxy-quinazoline,
[0921] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-cis-(N-
methanesulphonyl-N-methyl-amino)cylohexane-1-y1oxy]-7-methoxy-quinazoline,
[0922] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-cis-(N-
acetyl-N-methyl-amino)cylohexane-1-y1oxy]-7-methoxy-
quinazoline,
[0923] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-trans-4-
methylamino-cyclohexane-1-y1oxy]-7-methoxy-quinazoline,
[0924] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-trans-4-
(N-methanesulphonyl-N-methyl-amino)cylohexane-1-y1oxy]-7-methoxy-quinazoline,
[0925] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-trans-4-
(dimethylamino-cyclohexane-1-y1oxy]-7-methoxy-
quinazoline,
[0926] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-trans-4-
(N-{[(morpholin-4-y1)carbonyl]-N-methyl-amino)cylohexane-1-y1oxy]-7-methoxy-quinazoline,
[0927] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-2(2,2-
dimethyl-6-oxo-morpholin-4-y1)ethoxy]-7-(S)-(tetrahy-
drofuran-2-yl)ethoxy]-7-methoxy-quinazoline,
[0928] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-meth-
anesulphonyl-piperidin-4-ylxoy]-7-methoxy-quinazoline,
[0929] 4-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-1-(cyano-
piperidin-4-ylxoy)]-7-methoxy-quinazoline,
[0930] 3-cyano-{(3-chloro-4-fluoro-phenoxy)aminol-6-[-
4(N,N-dimethylamino)1-oxo-2-buten-1-y1amino]-7-
ethoxy-quinoline,
[0931] 4-{[3-chloro-4-fluorophenyl]aminol-6-{-14-(ho-
momorpholin-4-y1)1-oxo-2-buten-1-y1amino]-7-[(S)-
tetrahydrofuran-3-y1]oxy]-7-methoxy-quinazoline,
[0932] 4-{(3-chloro-4-fluorophenyl)aminol-7-[-2-(2,4-
(2-oxa-5-azas-bicyclo[2,2,1]hept-5-y1)carbonyl]piperazin-1-y1]-
ethoxy]-6-{(vinylcarbonyl)amino]-quinazoline,
[0933] 4-{(3-chloro-4-fluorophenyl)aminol-7-[2-(S)-6-
methyl-2-oxo-morpholin-4-y1]ethoxy]-6-{(vinylcarbonyl)amino]-quinazoline,
[0934] 4-{(3-chloro-4-fluorophenyl)aminol-7-[4-(R)-6-
methyl-2-oxo-morpholin-4-y1]butyloxy]-6-{(vinylcarbonyl)amino]-quinazoline,
[0935] 4-{(3-chloro-4-fluorophenyl)aminol-7-[4-(S)-6-
methyl-2-oxo-morpholin-4-y1]butyloxy]-6-{(vinylcarbonyl)amino]-quinazoline,
[0936] 4-{(3-chloro-4-fluorophenyl)aminol-6-[-14-{[2-
(ethoxy carbonyl)]ethyl]-N-{[ethoxy carbonyl]methyl}amino]-1-oxo-2-buten-1-y1amino]-7-cyclopropyl-
methoxy-quinazoline,

optionally in the form of their racemates, enantiomers or diastereomers, optionally in the form of the pharmaceutically acceptable acid addition salts, solvates and/or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodicide, hydro sulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromalate, heaconsulphate, hydroacetate, hydrochloride, hydrofluoride, hydroartrate, hydroxalite, hydrosuccinate, hydrobenzoxide and hydro-p-phthlenesulphonate.

[0937] LDTD4-receptor antagonists used according to the invention are preferably compounds selected from among montelukast, pranlukast and zafirlukast, or (S)-8-[2-{4-[4-(4-
fluorophenyl)butyloxy]phenyl][ethenyl]-2-(1H-tetrazol-5-y1)-
4H-1-benzopyran-4-one (MEN-91507),
[0938] 4-{6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenyl)thio]propoxypropyl]2-propylenoxy]butyric acid (MNN-001),
[0939] 1-(R)-(3-2,6-difluoro-2-quinolinyl)ethenyl]phenyl]-3-[(2-oxo-2-propylphényl]thio)methylcyco-
propene-acetic acid,
[0940] 1-[[I](R)-3-(2,2,3-dichlorothieno[3,2-b]pyri-
din-5-y1)E-ethyl]phenyl]-3-[(2-1-hydroxy-1-methyl-
ethyl]phenyl]propyl]thio)methylcyclopropeneaacetic acid and
[0941] 2-{[2-2-(4-tet-buty-2-thiazolyl)-5-nitrobenzoyl]oxymethyl]phenyl}acetic acid,

optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodicide, hydro sulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromalate, heaconsolate, hydroacetate, hydrochloride, hydrofluoride, hydroartrate, hydroxalite, hydrosuccinate, hydrobenzoxide and hydro-p-phthlenesulphonate. By salts or derivatives which the LDTD4-receptor antagonists may optionally be capable of forming are, for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth salts, sulphbenzoxides, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivatates or furoates.

[0942] Histamine H1 receptor antagonists used according to the invention are preferably compounds selected from among epinastin, cetirizin, azelastin, fexofenadin, levocabastin, loradizin, nizolastin, ketotiifen, emedastin, dimetinden, clemastin, bamiqsin, ecechlorphenemr, pheninemr, doxylamine, chlorophenoxyamin, dimenhydrinat, diphenhydro, promethazin, ebautin, olopatadine, desloradin and mazel cen, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, the acid addition salts are selected from among hydrochloride, hydrobromide, hydriodicide, hydro sulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromalate,
hydroacetate, hydrocitrate, hydrofumarate, hydrogentartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluene-sulphonate.

[0943] Histamine H4 receptor antagonists used according to the invention are preferably compounds such as for example (5-chloro-1H-indol-2-yl)-(4-methyl-1-piperazinyl)-methanone (N3-7777120), optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, the acid addition salts selected from among hydrochloride, hydrobromide, hydroiodide, hydro sulphate, hydrophosphate, hydrotrihalomethanesulphonate, hydrotrifluoracetate, hydro malate, hydroacetate, hydrocitrate, hydrofumarate, hydrogentartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluene-sulphonate are used.

[0944] MAP Kinase inhibitors used according to the invention are preferably compounds selected from among:

[0945] Bentapamisol (AS-602801)

[0946] Dorozapimod

[0947] 5-carbamoylindole (SD-169).

[0948] 6-[aminocarbonyl](2,6-difluorophenyl)amino]-2-(2,4-difluorophenyl)-3-pyridinecarboxamide (VX-702).


[0950] 9,12-epoxy-1H-diindol[1,2,3-fg:2,1,3′-kl]pyrrolo[3,4-j][1,16]benzodiazepine-10-carboxylic acid (CEP-1347), and

[0951] 4-[3-(4-chlorophenyl)-5-(1-methyl-4-piperidinyl)-1H-pyrazol-4-yI]-pyrimidine (SC-409), optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

[0952] Neurokinin (NK1 or NK2) antagonists used according to the invention are preferably compounds selected from among: Suvodutum, Nepudutum and Egproptum; optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

[0953] Antiinvasive substances used according to the invention are preferably compounds selected from among hydrocodone, caramiphen, carbetapentane and dextramethorphine, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

[0954] Substances of preferred CXCR1 or CXCR2 antagonists used according to the invention are preferably compounds such as e.g. 3-[3-[dimethylamino]carbonyl]2-hydroxyphenyl]amino]-4-[(1H)-1-(5-methylthien-2-yl)pyrrol]amino]cyclobut-3-ene-1,2-dione (SCH-527123), optionally in the form of its racemates, enantiomers, diastereomers and optionally in the form of the pharmaceutically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

[0955] The dosage necessary for obtaining a pain-relieving effect is, in the case of intravenous administration, expecially from 0.01 to 3 mg/kg of body weight, preferably from 0.1 to 1 mg/kg, and, in the case of oral administration, from 0.1 to 8 mg/kg of body weight, preferably from 0.5 to 3 mg/kg, in each case to 1 to 3 times per day. The compounds prepared according to the invention can be administered intravenously, subcutaneously, intramuscularly, intrarectally, intranasally, by inhalation, transdermally or orally, aerosol formulations being particularly suitable for inhalation. They can be incorporated into customary pharmaceutical preparations, such as tablets, coated tablets, capsules, powders, suspensions, solutions, metered-dose aerosols or suppositories, if appropriate together with one or more customary inert carriers and/or diluents, for example with maize starch, lactose, cane sugar, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbital, water/ polyethylene glycol, propylene glycol, cetylstearyl alcohol, carbomethylecellulose or fatty substances, such as hardened fat, or suitable mixtures thereof.

EXPERIMENTAL SECTION

[0956] Generally, there are mass spectra and 1H-NMR spectra for the compounds that have been prepared. The ratios given for the eluents are in volume units of the solvents in question. For ammonia, the given volume units are based on a concentrated solution of ammonia in water.

[0957] Unless indicated otherwise, the acid, base and salt solutions used for working up the reaction solutions are aqueous systems having the stated concentrations.

[0958] For chromatographic purification, silica gel from Millipore (MATREX™, 35 to 70 μm) or Albox (E: Merck, Darmstadt, Alusina 90 standardized, 63 to 200 μm, article No. 1.01907.9050) is used.

[0959] In the descriptions of the experiments, the following abbreviations are used: TLC thin layer chromatograph DIPEA disopropylethylamine DMA N,N-dimethylacetamide

[0960] DMAP 4-dimethylaminopyridine DIPEA N,N-dimethylformamide

[0961] DMSO dimethylsulphoxide HATU 0-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate RP reverse phase R retention time tert teritary TBTU 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate TEA triethylamine THF tetrahydrofuran

[0962] The following analytical HPLC methods were used:

[0963] Method 1: Column: Interchim Strategy C18, 5 μM, 4.6x20 mm

[0964] Detection: 220-320 nm

[0965] Eluant A: water(0.1%) trifluoroacetic acid

[0966] Eluant B: acetone

[0967] Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
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Method 2: Column: Merck Cromolith Flash RP18e, 4.6x25 mm

<table>
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<th>time in min</th>
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<th>flow rate in mL/min</th>
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<tr>
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<td>90.0</td>
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<td>1.6</td>
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</tbody>
</table>

[0968] Eluant A: water/0.1% formic acid
[0969] Eluant B: acetonitrile/0.1% formic acid
[0970] Gradient:

Method 3: Column: YMC-Pack ODS-AQ, 3 μM, 4.6x75 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
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</thead>
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<td>1.6</td>
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<td>90.0</td>
<td>10.0</td>
<td>1.6</td>
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</tbody>
</table>

[0971] Eluant A: water/0.15% formic acid
[0972] Eluant B: acetonitrile
[0973] Gradient:

Method 4: Column: Zorbax Stable Bond C18, 1.8 μM, 3x30 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
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<tbody>
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</tbody>
</table>

[0974] Eluant A: water/0.15% formic acid
[0975] Eluant B: acetonitrile
[0976] Gradient:

Method 5: Column: Sunfire C18, 3.5 μM, 4.6x50 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
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<td>2.6</td>
<td>95.0</td>
<td>5.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

[0977] Detection: 180-820 nm
[0978] Eluant A: water/0.1% trifluoroacetic acid
[0979] Eluant B: acetonitrile/0.1% trifluoroacetic acid
[0980] Temperature: 40° C.
[0981] Gradient:

Method 6: Column: Sunfire C18, 3.5 μM, 4.6x50 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
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<td>5.0</td>
<td>1.5</td>
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</tr>
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<td>1.5</td>
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</tbody>
</table>

[0982] Detection: 180-820 nm
[0983] Eluant A: water/0.1% trifluoroacetic acid
[0984] Eluant B: acetonitrile/0.1% trifluoroacetic acid
[0985] Temperature: 40° C.
[0986] Gradient:

Method 7: Column: YMC-Pack ODS-AQ, 3 μM, 4.6x75 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>95.0</td>
<td>5.0</td>
<td>1.6</td>
</tr>
<tr>
<td>4.5</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>5.0</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>5.5</td>
<td>90.0</td>
<td>10.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

[0987] Eluant A: water/0.15% formic acid
[0988] Eluant B: acetonitrile
[0989] Gradient:

Method 8: Column: Zorbax Stable Bond C18, 1.8 μM, 3x30 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2.00</td>
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<td>50.0</td>
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<tr>
<td>2.25</td>
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<td>1.6</td>
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<tr>
<td>2.50</td>
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<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>2.75</td>
<td>95.0</td>
<td>5.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

[0990] Eluant A: water/0.15% formic acid
[0991] Eluant B: acetonitrile
[0992] Gradient:

Method 9: Column: Zorbax Stable Bond C18, 1.8 μM, 3x30 mm

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
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<td>1.6</td>
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<tr>
<td>2.25</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>2.50</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>2.75</td>
<td>95.0</td>
<td>5.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

[0993] Eluant A: water/0.15% formic acid
[0994] Eluant B: acetonitrile
[0995] Gradient:
### Method 10: Column: Zorbax Stable Bond C18, 3.5 μM, 4.6×75 mm

**[0996]** Eluant A: water/0.15% formic acid  
**[0997]** Eluant B: acetonitrile  
**[0998]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>95.0</td>
<td>5.0</td>
<td>1.6</td>
</tr>
<tr>
<td>4.5</td>
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<td>90.0</td>
<td>1.6</td>
</tr>
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<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>5.5</td>
<td>90.0</td>
<td>10.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

### Method 11: Column: X Terra C18, 3.5 μM, 4.6×50 mm

**[0999]** Detection: 180-820 nm  
**[1000]** Eluant A: water/0.1% trifluoroacetic acid  
**[1001]** Eluant B: acetonitrile/0.1% trifluoroacetic acid  
**[1002]** Temperature: 40°C  
**[1003]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
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<tbody>
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<td>0.0</td>
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<tr>
<td>3.4</td>
<td>95.0</td>
<td>5.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Method 12: Column: Merck Cromolith Flash RP18e, 4.6×25 mm

**[1004]** Eluant A: water/0.1% formic acid  
**[1005]** Eluant B: acetonitrile/0.1% formic acid  
**[1006]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
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<td>0.0</td>
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<td>1.6</td>
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<tr>
<td>3.0</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
</tr>
<tr>
<td>3.3</td>
<td>95.0</td>
<td>5.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

### Method 13: Column: Merck Cromolith SpeedROD RP-18e, 4.6×50 mm

**[1007]** Eluant A: water/0.1% formic acid  
**[1008]** Eluant B: acetonitrile/0.1% formic acid  
**[1009]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
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<td>0.0</td>
<td>90.0</td>
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<td>10.0</td>
<td>90.0</td>
<td>1.5</td>
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<td>5.0</td>
<td>10.0</td>
<td>90.0</td>
<td>1.5</td>
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<tr>
<td>5.5</td>
<td>95.0</td>
<td>5.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Method 14: Column: Zorbax Stable Bond C18, 3.5 μM, 4.6×75 mm

**[1010]** Eluant A: water/0.15%/0% formic acid  
**[1011]** Eluant B: acetonitrile  
**[1012]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
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<td>1.6</td>
</tr>
<tr>
<td>2.0</td>
<td>10.0</td>
<td>90.0</td>
<td>1.6</td>
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<tr>
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<td>10.0</td>
<td>90.0</td>
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<tr>
<td>5.5</td>
<td>90.0</td>
<td>10.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

### Method 15: The following preparative methods were used for the reversed-phase chromatography:

### Method 1: Column: Atlantis C18, 5 μM, 100×30 mm

**[1014]** Detection: 210-500 nm  
**[1015]** Eluant A: water/0.1% trifluoroacetic acid  
**[1016]** Eluant B: acetonitrile  
**[1017]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
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</thead>
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<td>95.0</td>
<td>50</td>
</tr>
<tr>
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<td>95.0</td>
<td>5.0</td>
<td>50</td>
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<tr>
<td>10.1</td>
<td>95.0</td>
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<td>5</td>
</tr>
</tbody>
</table>

### Method 2: Column: Varian Pursuit 5 μM, 50×200 mm

**[1018]** Eluant A: water/0.1% trifluoroacetic acid  
**[1019]** Eluant B: acetonitrile/0.1% trifluoroacetic acid  
**[1020]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
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<td>98.0</td>
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<tr>
<td>15.3</td>
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<td>180</td>
</tr>
<tr>
<td>15.3</td>
<td>95.0</td>
<td>5.0</td>
<td>180</td>
</tr>
</tbody>
</table>

### Method 3: Column: YMC-Pack ODS-AQ 5 μM, 30×100 mm

**[1021]** Eluant A: water/0.15%/0% formic acid  
**[1022]** Eluant B: acetonitrile  
**[1023]** Gradient:

<table>
<thead>
<tr>
<th>time in min</th>
<th>% A</th>
<th>% B</th>
<th>flow rate in mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>95.0</td>
<td>5.0</td>
<td>50</td>
</tr>
<tr>
<td>2.0</td>
<td>95.0</td>
<td>5.0</td>
<td>50</td>
</tr>
<tr>
<td>6.0</td>
<td>10.0</td>
<td>90.0</td>
<td>50</td>
</tr>
</tbody>
</table>
Preparation of the Starting Compounds

The compounds of general formula I may be prepared from the following intermediates A, B and C:

AAV 1: Amide Coupling

A solution of the carboxylic acid component (1 mol-equivalent), triethylamine (2.5 mol-equivalents) and TBTU (1.1 mol-equivalents) in THF was stirred for 30 minutes at ambient temperature. Then the amine component (1.1 mol-equivalent as hydrochloride) was added and stirring was continued overnight. Then the mixture was evaporated down, mixed with water, made alkaline with dilute potassium carbonate solution and extracted with ethyl acetate. The product was isolated and purified by column chromatography or reversed phase chromatography.

AAV 2: Ester Hydrolysis

2N sodium hydroxide solution (2 mol-equivalents) was added to a solution of the ester (1 mol-equivalent) in methanol and the mixture was stirred for 1 to 5 hours at ambient temperature. Then it was acidified with acetic acid and the mixture was evaporated to dryness in vacuo. The crude product thus obtained was purified in the normal way by column chromatography on silica gel.

AAV 3: Cleaving the tert-Butyloxycarbonyl Protective Group

A solution of the tert-butoxycarbonyl-amine compound (1 mol-equivalent) in dichloromethane was combined with trifluoroacetic acid (3 to 10 mol-equivalents) and stirred at ambient temperature until the protective group had been cleaved completely. The reaction mixture was then evaporated to dryness and the crude product thus obtained was purified by chromatography.
A solution of the aniline component (1 mol-equivalent) and a strong base such as e.g. potassium-tert-butoxide (1 mol-equivalent) in DMSO was stirred for one hour at ambient temperature, then combined with the 4-fluoro-benzonitrile component (1 mol-equivalent) and stirred overnight at approx. 80°C. For working up the mixture was filtered through Alox and evaporated to dryness in vacuo.

The nitrile group of the diphenylamine intermediate product thus obtained was then reduced to the aminomethyl group with the addition of Raney nickel at 55°C and 3 bar excess hydrogen pressure and the product obtained was purified by chromatography. In order to prepare the intermediate A with an alpha-alkylbenzyl group (e.g. A1, A4, A5) the nitrile derivative (1 mol-equivalent) was dissolved in diethyl ether and at 0 to 5°C, it was added with stirring to a solution of alkylmagnesium bromide (4 mol-equivalents) in diethyl ether and then stirred for another 30 minutes approx. The reaction mixture was then stirred into 1M hydrochloric acid at -5°C and the alkylketone thus obtained was isolated and purified by chromatography in the usual way.

A solution of the ketone thus obtained (1 mol-equivalent) in acetonitrile was combined with triethylamine (2 mol-equivalents) and hydroxylamine hydrochloride (1.3 mol-equivalents) and refluxed for 4 hours. Then water was added and the mixture was extracted with dichloromethane. The resulting oxime was isolated from the organic phase and purified by conventional methods.

A solution of the oxime (1 mol-equivalent) in methanol was combined with methanolic hydrochloric acid (6.6 mol-equivalents). After the addition of zinc powder (1.4 mol-equivalents) the mixture was refluxed for 3 hours with stirring. After cooling the mixture was combined with water and extracted with dichloromethane. If necessary, the amine thus obtained was purified by chromatography.

Another possible way of reducing the oxime to the corresponding amine is by catalytic hydrogenation. For this, the oxime was hydrogenated in methanolic ammonia solution after the addition of Raney nickel at 50°C and at an excess hydrogen pressure of 50 psi until the uptake of hydrogen had ended. If necessary, the amine thus obtained was purified by chromatography.
Preparation of the Intermediates A

Intermediate A3

(6-aminomethyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

Intermediate A4

2-(6-(1-aminomethyl)-5-fluoro-pyridin-3-ylamino)-5-fluoro-benzonitrile

Intermediate A5

(6-(1-aminomethyl-pyridin-3-yl)-(4-isopropyl-2-trifluoromethyl-phenyl)-amine

HPLC: \( R_f = 1.95 \) minutes (method 2)

Mass spectrum (ESI): \([M+H]^+ = 310\)

HPLC: \( R_f = 1.92 \) minutes (method 2)
Intermediate A6
(4-aminomethyl-phenyl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[1050]

Intermediate A7
(6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[1053]

Intermediate A9
(6-aminomethyl-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine

[1058]

thin layer chromatogram (silica gel, CH₂Cl₂/ethanol 19:1): Rf = 0.16

[1051] [1052]

HPLC: Rf = 1.97 minutes (method 2)

[1059] [1060]

Intermediate A10
(6-aminomethyl-5-chloro-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine

[1061]

Intermediate A8
(6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[1062]

HPLC: Rf = 2.06 minutes (method 3)

[1054] [1055]

thin layer chromatogram (silica gel, CH₂Cl₂/ethanol 19:1): Rf = 0.08

[1064] [1065]
Intermediate A12
(4-aminomethyl-3-fluoro-phenyl)-(2-trifluoromethyl-phenyl)-amine

[1066]

Intermediate A13
(6-aminomethyl-5-chloro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine

[1068] thin layer chromatogram (silica gel, CH₂Cl₂/ethanol 19:1): Rᵢ=0.09

Intermediate A14
(6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[1071] thin layer chromatogram (silica gel, CH₂Cl₂/ethanol/NH₃OH 9:1:0.1): Rᵢ=0.58

Intermediate A15
(6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

[1075]

Intermediate A16
(6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine


Intermediate A17
(4-aminomethyl-phenyl)-(2-trifluoromethyl-phenyl)-amine

[1078] HPLC: Rᵢ=1.44 minutes (method 2)

Intermediate A18
(6-aminomethyl-5-chloro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

[1080] HPLC: Rᵢ=1.36 minutes (method 1)

Intermediate A19
(6-aminomethyl-5-chloro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

[1082]

Intermediate A20
(4-aminomethyl-phenyl)-(2-trifluoromethyl-phenyl)-amine

[1083] HPLC: Rᵢ=2.05 minutes (method 2)
Intermediate A19
(4-aminomethyl-3-fluoro-phenyl)-(6-fluoro-2-trifluoromethyl-phenyl)-amine

[1084]

thin layer chromatogram (silica gel, CH$_2$Cl$_2$/ethanol 9:1): $R_f=0.18$

Intermediate A20
2-(6-aminomethyl-5-fluoro-pyridin-3-ylamino)-benzonitrile

[1086]

HPLC: $R_f=1.14$ minutes (method 2)
Mass spectrum (ESI): [M+H]+243

Intermediate A21
(6-aminomethyl-5-methyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[1089]

HPLC: $R_f=1.87$ minutes (method 2)
Mass spectrum (ESI): [M+H]+330

Intermediate A24
(6-aminomethyl-pyridin-3-yl)-(4-bromo-2-chloro-6-fluorophenyl)-amine

[1096]

HPLC: $R_f=2.18$ minutes (method 2)
Intermediate A26
(6-aminomethyl-5-methyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

[1102]

Intermmediate A27
(6-aminomethyl-5-methyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine

[1104]

HPLC: R_f=2.33 minutes (method 2)

[1103]

Intermediate A28
(6-aminomethyl-pyridin-3-yl)-(4-chloro-2-difluoromethyl-phenyl)-amine

[1106]

HPLC: R_f=1.66 minutes (method 2)

[1107]

Mass spectrum (ESI): [M+H]+=282

[1105]

Intermediate A29
(4-aminomethyl-3-fluoro-phenyl)-(4-chloro-2-trifluoromethyl-phenyl)-amine

[1109]

HPLC: R_f=1.83 minutes (method 2)

[1110]

Intermediate A30
2-(4-aminomethyl-3-fluoro-phenylamino)-benzonitrile

[1111]

HPLC: R_f=1.38 minutes (method 2)

[1112]

Intermediate A31
(4-aminomethyl-phenyl)-(4-bromo-2-trifluoromethyl-phenyl)amine

[1113]

HPLC: R_f=1.81 minutes (method 2)

[1114]

Preparation of the Intermediates B

[1115]

[1116] The following intermediates B1 to B11 were prepared by amide coupling according to general working
method AAV1 and subsequent ester saponification according to general working method AAV2:

Intermediate B1
1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid

Intermediate B4
1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylic acid

Mass spectrum (ESI): [M+H]+=222

Intermediate B5
(S)-3-[(3H-imidazolo[4,5-b]pyridin-6-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

Mass spectrum (ESI): [M+H]=−275

Intermediate B6
(S)-3-[(2-methylamino-pyrimidine-5-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

HPLC: Rf=1.49 minutes (method 3)

Intermediate B7
(S)-3-[(2-methyl-pyrimidine-5-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

HPLC: Rf=0.47 minutes (method 2)

Mass spectrum (ESI): [M+H]+=267

**Intermediate B8**

(S)-3-[[5-hydroxy-pyridine-3-carbonyl]-amino]-
tetrahydrofuran-3-carboxylic acid

[1135]

**Intermediate B11**

1-[(2-methyl-pyrimidine-5-carbonyl)-amino]-cyclo-
propane-carboxylic acid

[1144]


[1146] The following intermediates B12 to B15 may be prepared analogously:

**Intermediate B12**:

[1147]

**Intermediate B13**:

[1148]

**Intermediate B14**:

[1149]

**Intermediate B15**:

[1149]

[1136] HPLC: Rₜ = 0.48 minutes (method 2)


**Intermediate B9**

(S)-3-[[6-aminopyridine-3-carbonyl]-amino]-tet-
rahdrofuran-3-carboxylic acid

[1138]

**Intermediate B10**

(S)-3-[[6-oxo-1,6-dihydropyridazine-4-carbonyl]-
amino]-tetrahydro-furan-3-carboxylic acid

[1141]

[1139] HPLC: Rₜ = 0.33 minutes (method 2)


**Intermediate B14**

[1149]

[1142] HPLC: Rₜ = 0.33 minutes (method 2)

Preparation of the Intermediates C

[1150]

Intermediate C1
1-amino-cyclopropane carboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1152]

Intermediate C2
1-amino-cyclopropane carboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1153] HPLC: R_f=1.55 minutes (method 13)

[1155]

Intermediate C3
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(1-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1158]

Intermediate C4
1-amino-cyclopropane carboxylic acid-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1160]

Intermediate C5
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1163]

[1156] HPLC: R_f=2.33 minutes (method 7)

Intermediate C6
(S)-3-amo nitro heterocycle 3-carboxylic acid-3-fl uoro-5-(4-fl uoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl methyl-amide

[1165]

(b) 3-benzylamino-oxetan-3-carboxylic acid

[1173] A solution of 3-benzylamino-oxetan-3-carbonitrile (370 mg, 1.33 mmol) and 5 mL 4M sodium hydroxide solution in 20 mL ethanol was refluxed overnight, then neutralised with 1M hydrochloric acid neutralised and evaporated to dryness. The crude product thus obtained was purified by chromatography.

[1174] C_{14}H_{22}NO_{3} (297.35)


(c) 3-benzylamino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1176] Prepared from 3-benzylamino-oxetan-3-carboxylic acid and 4-(2-trifluoromethyl-phenylamino)-benzylamine by amide coupling according to general working method AAV.

[1177] C_{22}H_{25}F_{3}N_{2}O_{2} (545.59)


(d) 3-amino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1179] 3-benzylamino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide (32.0 mg, 0.059 mmol) was dissolved in 10 mL methanol, combined with 20 mg Pd charcoal (10%) and debenzylated at ambient temperature under 3 bar hydrogen pressure.

[1180] C_{22}H_{25}F_{3}N_{2}O_{2} (365.35)

[1181] HPLC: R_t = 1.93 minutes (method 5)


Intermediate C9
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide

[1183]

HPLC: R_t = 1.50 minutes (method 2)

Intermediate C8
3-amino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1169]

Intermediate C10
1-amino-cyclopropanecarboxylic acid-2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide

[1185]

(a) 3-benzylamino-oxetan-3-carbonitrile

[1170] A solution of 3-oxetanone (908 mg, 12.6 mmol), dibenzylamine (6.08 mL, 31.6 mmol) and trimethylsilyleamine (2.00 mL, 15.8 mmol) in 20 mL concentrated acetic acid was stirred overnight at 60°C. After cooling it was adjusted to pH 10 with concentrated ammonia and the solution was extracted with chloroform. After evaporation, the crude product was obtained, which was purified by chromatography through silica gel.

[1171] C_{14}H_{19}N_{2}O (278.35)


Intermediate C10

Intermediate C11
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylamide

Intermediate C14
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide

[1187]

Mass spectrum (ESI): [M+H]+ = 416

Intermediate C12
1-amino-cyclopropanecarboxylic acid-2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylamide

Intermediate C15
1-amino-cyclopropanecarboxylic acid-[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1189]


Intermediate C13
1-amino-cyclopropanecarboxylic acid-[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

Intermediate C16
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1191]


Intermediate C17

[1193]

[1194] HPLC: Rf = 1.99 minutes (method 2)


Intermediate C18

[1196]


Intermediate C19

[1198]

[1199] HPLC: Rf = 1.34 minutes (method 2)

Intermediate C17
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-amide

[1201]

Intermediate C20
1-amino-cyclopropanecarboxylic acid-[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1208]

HPLC: R$_f$=2.35 minutes (method 2)

[1202]

Intermediate C18
(S)-3-amino-tetrahydrofuran-3-carboxylic acid-4-[4-chloro-2-trifluoromethyl-phenylamino]-benzylamide

[1203]

Mass spectrum (ESI): [M+H]$^+$=365

[1209]

HPLC: R$_f$=1.30 minutes (method 2)

Intermediate C21
1-amino-cyclopropanecarboxylic acid-[5-(4-chloro-2-difluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[1210]

[1211]

HPLC: R$_f$=2.41 minutes (method 2)

Intermediate C19
1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-amide

[1204]

Mass spectrum (ESI): [M+H]$^+$=367

[1212]

HPLC: R$_f$=1.48 minutes (method 2)

Intermediate C22
(S)-3-amino-tetrahydrofuran-3-carboxylic acid 2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1205]

[1213]

[1214]

HPLC: R$_f$=1.24 minutes (method 2)

Mass spectrum (ESI): [M+H]$^+$=383

[1206]

[1207]

Mass spectrum (ESI): [M+H]$^+$=398

[1215]
The following intermediates C23 to C25 may be prepared analogously:

Intermediate C23:

Intermediate C24:

Intermediate C25:

Preparation of the End Compounds:

Example 1

Pyrimidine-5-carboxylic acid N-(1-(4-(2,3-dichlorophenyl)-amino)benzyl-carbamoyl)cyclopropylamide

1a) ethyl 1-[(pyrimidine-5-carbonyl)-aminol-cyclopropanecarboxylate

1b) 1-[(pyrimidine-5-carbonyl)-aminol-cyclopropanecarboxylic acid

1c) N-(4-aminomethyl)phenyl)-2,3-dichloroaniline-trifluoroacetate

1d) pyrimidine-5-carboxylic acid N-(1-(4-(2,3-dichlorophenyl)-amino)benzyl-carbamoyl)cyclopropylamide

A solution of 15.74 g (126.9 mmol) pyrimidine-5-carboxylic acid, 43.57 mL (312.6 mmol) triethylamine and 44.61 g (138.9 mmol) TBTU in 460 mL THF was stirred for 30 minutes at ambient temperature. Then 9.11 g (127.3 mmol) ethyl 1-aminocyclopropane-carboxylate hydrochloride were added and the mixture was stirred further overnight. Then the mixture was evaporated down and the residue was combined with 200 mL water, made alkaline with dilute potassium carbonate solution and extracted with ethyl acetate. The intermediate product was purified by column chromatography (silica gel, dichloromethane+4-4% methanol);

Yield: 95% of theory

C_{13}H_{11}N_5O_5 (355.24)

R_f=1.23 min. method 1

28.39 mL of a 2N sodium hydroxide solution were added to a solution of 13.36 g (56.79 mmol) ethyl 1-[(pyrimidine-5-carbonyl)-aminol-cyclopropane-carboxylate in 240 mL methanol and the mixture was stirred for one hour at ambient temperature. Then it was acidified with concentrated acetic acid and evaporated to dryness in vacuo. The crude product thus obtained was purified by column chromatography (silica gel, dichloromethane+5-30% 10% acetic acid in methanol).

Yield: 100% of theory

C_{13}H_{21}N_5O_7 (207.19)

R_f=1.23 min. method 1

A solution of 32 mg (0.2 mmol) 2,3-dichloroaniline and 22 mg (0.2 mmol) potassium tert-butoxide in 9 mL DMSO was stirred for one hour at ambient temperature, then combined with 24 mg (0.2 mmol) 4-fluorobenzonitrile and stirred further overnight at 80°C. For working up the reaction mixture was filtered through Alox B, washed with DMF and evaporated to dryness in vacuo. The residue was hydrogenated in 100 mL methylallic ammonia solution with 20 mg Roney nickel as catalyst at 55°C under a hydrogen pressure of 3 bar for 5 hours. Then the catalyst was filtered off, the filtrate was freed from the solvent and the crude product was purified by HPLC (method 1).

Yield: 47% of theory

C_{13}H_{23}Cl_2N_5 (267.15)

0.5 mL (3.6 mmol) triethylamine, 433 mg (1.35 mmol) TBTU and 326 mg (1.2 mmol) N-(4-aminomethyl)phenyl)-2,3-dichloroaniline-trifluoroacetate (from 1c) were added to a solution of 250 mg (1.2 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b) in 15 mL tetrahydrofuran. The mixture was stirred overnight at ambient temperature, then evaporated to dryness and purified by HPLC (method 1).

Yield: 16% of theory

C_{23}H_{20}Cl_2N_7O_5 (456.32)

R_f=2.1 min. method 5
Example 2
Pyrimidine-5-carboxylic acid-N-(1-(4-(2-chlorophenylamino)benzyl)carbamoyl)cyclopropylamide

2a) N-(4-(aminomethyl)phenyl)-2-chloroaniline

[1237] Analogously to method (1c) the title compound was prepared starting from 2-chloroaniline, 4-fluorobenzonitrile and Raney nickel.

[1238] C_{13}H_{14}ClN_{2} (228.68)

2b) pyrimidine-5-carboxylic acid-N-(1-(4-(2-chlorophenylamino)benzyl)carbamoyl)cyclopropyl)amide

[1239] Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-2-chloroaniline (from 2a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropane-1-carboxylic acid (from 1b).

[1240] C_{25}H_{20}ClN_{3}O_{2} (421.88)

[1241] R_{f}=2.13 min. method 6

Example 3
Pyrimidine-5-carboxylic acid-N-(1-(4-(phenylamino)benzyl)carbamoyl)cyclopropylamide

[1242] 3a) 4-(aminomethyl)-N-phenylaniline

[1243] Analogously to method (1c) the title compound was prepared starting from aniline, 4-fluorobenzonitrile and Raney nickel.

[1244] C_{11}H_{13}N_{2} (199.26)

3b) pyrimidine-5-carboxylic acid-N-(1-(4-(phenylamino)benzyl)carbamoyl)cyclopropyl)amide

[1245] Analogously to method (1d) the title compound was prepared starting from 4-(aminomethyl)-N-phenylamine (from 3a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropane-1-carboxylic acid (from 1b).

[1246] C_{22}H_{20}ClN_{2}O_{2} (421.88)

[1247] R_{f}=1.82 min. method 5

Example 4
Pyrimidine-5-carboxylic acid-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropyl)amide

[1248] 4a) N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline

[1249] Analogously to method (1c) the title compound was prepared starting from 2-(trifluoromethyl)aniline, 4-fluorobenzonitrile and Raney nickel.

[1250] C_{13}H_{13}F_{2}N_{2} (266.26)

4b) pyrimidine-5-carboxylic acid-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropyl)amide

[1251] Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropane-1-carboxylic acid (from 1b).

[1252] C_{23}H_{20}F_{2}N_{2}O_{2} (455.43)

[1253] R_{f}=2.27 min. method 6

Example 5
5-oxo-pyrrrolidine-2-carboxylic acid-[1-(4-(2-trifluoromethyl)-phenylamino)-benzyl]carbamoyl]-cyclopropyl)amide

[1254] 5a) 1-amine-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropane-1-carboxamide

[1255] A solution of 376 mg (1.87 mmol) 1-(tert-butoxy-carbonylamino)cyclopropane-1-carboxylic acid in 20 mL DMF was combined with 0.4 mL (2.85 mmol) triethylamine and
600 mg (1.87 mmol) TBHTU and stirred for 5 minutes at ambient temperature. Then 500 mg N-(4-aminoethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) were added and the mixture was stirred at ambient temperature over the weekend. The mixture was then filtered through [1256] Alox B, washed with DMF/methanol=9:1 and evaporated to dryness in vacuo. The residue was combined with a 1:1 mixture of dichloromethane and trifluoroacetic acid and stirred for one hour at ambient temperature. The reaction mixture was evaporated to dryness in vacuo and the crude product was purified by column chromatography (silica gel, dichloromethane+2-8% methanol:ammonia=9:1).

[1257] Yield: 10% of theory

[1258] C$_{22}$H$_{15}$Cl$_2$N$_2$O$_5$ (456.32)

5b) 5-oxo-pyrrolidine-2-carboxylic acid-[1-(4-(2-
trifluoromethyl-phenylamino)-benzylcarbamoyl]-
cyclopropyl]-amide

[1259] Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and 5-oxopyrrolidine-2-carboxylic acid.

[1260] C$_{23}$H$_{25}$F$_2$N$_2$O$_5$ (480.46)

[1261] R$_f$=1.89 min. method 5

[1262] Examples 6 to 22 that follow were prepared analogously to method (1d) from 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide and the corresponding acids:

Example 6
1-(4-dimethylamino-butyrylamino)-cyclopropanecar-
boxylic acid-4-(2-trifluoromethyl-phenylamino)-
benzylamide

[1263]

[1264] C$_{24}$H$_{27}$F$_2$N$_2$O$_5$ (462.5)

[1265] R$_f$=1.67 min. method 5

Example 7
1-(3,3,3-trifluoro-propionylamino)-cyclopropanecar-
boxylic acid-4-(2-trifluoromethyl-phenylamino)-
benzylamide

[1266]

[1267] C$_{21}$H$_{19}$F$_2$N$_2$O$_5$ (459.4)

[1268] R$_f$=2.21 min. method 5

Example 8
1-(3-dimethylamino-propionylamino)-cyclopropan-
carboxylic acid-4-(2-trifluoromethyl-phenylamino)-
benzylamide

[1269]

[1270] C$_{23}$H$_{25}$F$_2$N$_2$O$_4$ (448.5)

[1271] R$_f$=1.67 min. method 5

Example 9
2,4-dihydroxy-pyrimidine-5-carboxylic acid-[1-[4-
(2-trifluoromethyl-phenylamino)benzylcarbam-
oyl]-cyclopropyl]-amide

[1272]

[1273] C$_{24}$H$_{27}$F$_2$N$_2$O$_4$ (487.4)

[1274] R$_f$=1.93 min. method 5

Example 10
1-(5-dimethylamino-pentanoylamino)-cyclopropan-
carboxylic acid-4-(2-tri-fluoromethyl-phenyl-
amino)-benzylamide

[1275]

[1276] C$_{23}$H$_{25}$F$_2$N$_2$O$_4$ (476.5)

[1277] R$_f$=1.69 min. method 5
Example 11
N-[1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-nicotinamide

Example 14
1-(2-methoxy-acetamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

Example 12
1-(2-dimethylamino-acetamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

Example 15
1-(cyclopropanecarbonyl-amino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

Example 13
1-propionylamino-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenyl-amino)-benzylamide

Example 16
1-pentanoylamino-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenyl-amino)-benzylamide
Example 17
1-methyl-1H-imidazol-4-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

Example 20
N-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-benzamide

Example 18
1-methyl-4H-imidazole-2-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

Example 21
Pyridine-2-carboxylic acid {1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

Example 19
1-(2-cyclopropyl-acetylamino)-cyclopropane-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

Example 22
1-methyl-piperidine-4-carboxylic acid {1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

C_{23}H_{24}F_{3}N_{4}O_{2} (457.5) method 5
R_f=1.88 min. method 5

C_{23}H_{24}F_{3}N_{4}O_{2} (454.4)
R_f=2.20 min. method 5

C_{23}H_{24}F_{3}N_{4}O_{2} (431.5)
R_f=2.18 min. method 5

C_{23}H_{24}F_{3}N_{4}O_{2} (474.5)
R_f=1.68 min. method 5
Example 23

1-(2,2,4-trifluorocyclohexyl)-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)-cyclopropanecarboxamide

[1312]

Example 24

N-[(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropyl]-isoxazole-5-carboxamide

[1316]

Example 25

Pyrimidine-5-carboxylic acid N-[(1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethylcarbamoyl)cyclopropyl]amide

[1321] 25a) 1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone

[1322] The reaction is carried out under protective gas (argon). A mixture of 2.39 g (12 mmol) 1-(4-bromophenyl)ethanone, 0.99 mL (8 mmol) 4-(difluoromethoxy)aniline, 2.21 g (16 mmol) potassium carbonate, 150 mg (0.8 mmol) copper iodide and 180 mg (1.6 mmol) 1-proline in 12 mL DMSO was stirred for 72 hours at 95°C. The reaction mixture was added to water, mixed with a little ammonia extracted twice with tert-butyl-methyl ether. The combined organic phases were dried on sodium sulphate and evaporated to dryness in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/30% ethyl acetate). The product was further reacted directly.

[1323] Yield: 33% of theory

[1324] C₁₆H₁₄F₂N₂O (277.27)

[1325] Rₓ=1.98 min. method 1

25b) (Z)-1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone-oxime

[1326] A mixture of 1.08 g (3.9 mmol) 1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone and 0.92 mL (15.58 mmol) aqueous 50% hydroxylamine solution in 10 mL ethanol was stirred for 3 hours at 100°C. The reaction mixture was evaporated to dryness in vacuo and the residue was purified by preparative HPLC (method 2).

[1327] Yield: 19% of theory

[1328] C₁₆H₁₄F₂N₂O₂ (292.28)

[1329] Rₓ=1.96 min. method 1

[1330] 25c) 4-(1-aminooethyl)-N-(4-(difluoromethoxy)phenyl)aniline

[1331] 0.22 g (0.75 mmol) (Z)-1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone-oxime in 20 mL methanolic ammonia solution were hydrogenated with the addition of 50 mg Raney nickel at 50°C at a hydrogen pressure of 50 psi for 5 hours. The catalyst was filtered off and the filtrate was evaporated to dryness. The crude product thus obtained was further reacted directly.

[1332] C₁₆H₁₄F₂N₂O (278.3)

[1333] Rₓ=1.37 min. method 1

[1334] 25d) pyrimidine-5-carboxylic acid N-(1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethylcarbamoyl)cyclopropyl]amide

[1335] Analogously to method (1d) the title compound was prepared starting from 4-(1-aminooethyl)-N-(4-(difluoromethoxy)phenyl)aniline (from 25c) and 1-(pyrimidine-5-carboxyl)-aminocyclopropanecarboxylic acid (from 1b).

[1336] C₁₆H₁₄F₂N₂O₂ (467.47)

[1337] Rₓ=1.78 min. method 1

Example 26

5-(trifluoromethyl)-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropyl]nicotinamide

[1338]
26a) 5-(trifluoromethyl)nicotinic acid

[1339] A solution of 1.5 g 3-bromo-5-(trifluoromethyl)pyridine in 50 ml of toluene was added dropwise at 75°C to a mixture of 0.96 ml (15.9 mmol) 1.6 molar butylthiium solution in hexane and 3.98 ml (8 mmol) 2 molar butylmagnesium chloride solution in diethyl ether and 10 ml THF. After 20 minutes 20 g (454 mmol) dry ice were added and the mixture was again stirred for 20 minutes at 75°C and for 3 hours at RT. The reaction mixture was combined with 50 ml 1 molar sodium hydroxide solution and extracted twice with diethyl ether. The aqueous phase was acidified with 4 molar hydrochloric acid and extracted three times with diethyl ether. The combined organic phases were dried on sodium sulphate and evaporated to dryness in vacuo. The residue was mixed with dichloromethane and the precipitate formed was suction filtered and dried in the circulating air dryer at 55°C.

[1340] Yield: 9% of theory

[1341] C₇H₆F₃NO₂ (191.11)

26b) 5-(trifluoromethyl)-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)nictinamide

[1342] Analogously to method (1d) the title compound was prepared starting from 1-amine-N-(4-(4-(2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropene carboxamide (from 2a) and 5-(trifluoromethyl)nictinimic acid (from 26a).

[1343] C₂₂H₂₂F₂N₂O₄ (459.42)

[1344] Rₚ=2.41 min. method 6

Example 27
5-methyl-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)-1,3,4-oxadiazole-2-carboxamide

[1345]

27a) 5-methyl-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)-1,3,4-oxadiazole-2-carboxamide

[1346] Analogously to method (1d) the title compound was prepared starting from 1-amine-N-(4-(4-(2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropene carboxamide (from 2a) and 5-methyl-1,3,4-oxadiazole-2-carboxylic acid.

[1347] C₂₂H₂₀F₂N₂O₄ (459.42)

[1348] Rₚ=1.66 min. method 6

Example 28
Pyrimidine-5-carboxylic acid-N-(1-(4-(4-(methylthio)-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide

[1349]

28a) N-(4-(aminomethyl)phenyl)-4-(methylthio)-2-(trifluoromethyl)aniline

[1350] Analogously to method (1c) the title compound was prepared starting from 4-(methylthio)-2-(trifluoromethyl)aniline and 4-fluorobenzonitrile.

[1351] C₁₄H₁₁F₃N₂S (312.35)

[1352] Rₚ=1.88 min. method 2

28b) pyrimidine-5-carboxylic acid-N-(1-(4-(4-(methylthio)-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide

[1353] Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-4-(methylthio)-2-(trifluoromethyl)aniline (from 28a) and 1-[pyrimidine-5-carboxylic]-amino-cyclopropene carboxylic acid (from 1b).

[1354] C₂₂H₂₂F₂N₂O₂S (501.53)

[1355] Rₚ=2.33 min. method 2

Example 29
N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)-cyclopropyl)thiazole-5-carboxamide

[1356]

29a) N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline

[1357] Analogously to method (1c) the title compound was prepared starting from 2-trifluoromethyl-4-fluorobenzonitrile and 4-fluorobenzonitrile.

[1358] C₁₄H₁₁F₃N₂S (280.22)

[1359] Rₚ=0.38 min. method 4

29b) tert-butyl 1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)-cyclopropylcarbamate

[1360] 0.98 mL (7.04 mmol) triethylamine and 1.24 g (3.87 mmol) TBDU were added to a solution of 710 mg (3.52
mmol) 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid in 60 mL DMF and the mixture was stirred for 30 minutes at ambient temperature. Then 1 g N-(4-aminomethyl)phenyl)-2-(trifluoromethyl)aniline was added and the mixture was stirred for 1 hour at ambient temperature. The reaction mixture was evacuated to dryness in vacuo. The residue was taken up in ethyl acetate and washed twice with 5% sodium carbonate solution. The organic phase was dried on sodium sulphate and evaporated to dryness in vacuo.

Yield: 96% of theory  
C₂₃H₂₅F₃N₂O₂ (467.46)  
R₇=1.50 min. method 4

29c) 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide

1.57 g (3.36 mmol) tert-butyl 1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)-carbamoylcyclopropylcarbamate in 10 mL diethyl ether were combined with 20 mL 4 molar hydrogen chloride in dioxane and stirred for 10 minutes at ambient temperature. The reaction mixture was combined with ethyl acetate and made alkaline with saturated potassium carbonate solution. The organic phase was dried on sodium sulphate and evaporated to dryness in vacuo.

Yield: 101% of theory  
C₂₃H₂₃F₃N₂O (367.34)  
R₇=1.33 min. method 4

29d) N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)carbamoyl)cyclopropyl-1-thiazole-5-carboxamide

Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and thiazole-5-carboxylic acid.

R₇=2.76 min. method 3

Example 30  
N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)-1-(3,3,3-trifluoropropanamido)cyclopropanecarboxamide

R₇=2.76 min. method 3

Example 30  
N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)-1-(3,3,3-trifluoropropanamido)cyclopropanecarboxamide

30a) N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)-1-(3,3,3-trifluoropropionyl)chloride

34 mg (0.2 mmol) 3-chloroper oxybenzoic acid were added to 66 mg (0.13 mmol) pyrimidine-5-carboxylic acid-N-(1-(4-(4-methylthio)-2-(trifluoromethyl)-phenylamino)benzyl)carbamoylcyclopropylamide (from 28b), dissolved in 5 mL dichloromethane, and the mixture was left at ambient temperature overnight with stirring. Then the mixture was added to saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic phase was dried through a phase separation cartridge and the filtrate was evaporated to dryness in vacuo.

Yield: 40% of theory  
C₁₄H₁₂F₄N₂O₃S (533.52)  
R₇=1.34 min. method 2
Example 33
Pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide

[1385]

1-[2-(pyrimidin-5-yl)acetic acid]-N-(4-(2-(trifluoromethyl)phenylamino)-benzyl)cyclopropene-carboxamide

[1386]

Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropene-carboxamide (from 29c) and pyrimidine-5-carboxylic acid.

[1387] C_{13}H_{13}F_{2}N_{2}O_{4} (473.42)

[1388] R_{f}=2.09 min. method 2

Example 34
1-(2-(pyrimidin-5-yl)acetic acid)-N-(4-(2-(trifluoromethyl)phenylamino)-benzyl)cyclopropene-carboxamide

[1389]

Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropene-carboxamide (from 29c) and pyrimidine-5-carboxylic acid.

[1390] C_{13}H_{13}F_{2}N_{2}O_{4} (469.46)

[1391] R_{f}=2.21 min. method 6

Example 35
Pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyano-phenylamino)benzylcarbamoyl)cyclopropyl)amide

[1393]

[1394] 35a) tert-butyl-4-aminobenzylcarbamate

92.65 g (424.5 mmol) di-tert-butyl-dicarbonate were added to 61.85 g (424.4 mmol) 4-aminomethyl-aniline dissolved in 850 mL chloroform and the mixture was stirred at ambient temperature until no more exudate was present. The mixture was evaporated to dryness in vacuo and the residue was recrystallised from ethyl acetate/hexane (approx. 3 mL/g).

[1395] Yield: 66% of theory

[1396] C_{13}H_{13}N_{2}O_{4} (222.26)

[1397] R_{f}=0.49 hexane/ethyl acetate (1/1)

35b) tert-butyl-(2-(2-cyanophenylamino)benzylcarbamate

[1398] The reaction was carried out under protective gas (nitrogen), 8 mg (0.01 mmol) of tris(dibenzilylideneacetone) dipalladium and 17 mg (0.04 mmol) Xantphos were added to 100 mg (0.45 mmol) tert-butyl-4-aminobenzylcarbamate, 138 mg (0.63 mmol) potassium sulphate and 98 mg (0.54 mmol) 2-bromobenzenitrile in 5 mL toluene. The mixture was stirred overnight at 110 °C and then the inorganic salts were filtered off. The filtrate was evaporated to dryness in vacuo and the residue was purified through an RP column with a solvent gradient (water/acetonitrile+0.1% trifluoroacetic acid).

[1399] Yield: 82% of theory

[1400] C_{13}H_{13}N_{2}O_{4} (323.39)

[1401] R_{f}=2.57 min. method 2

35c) 2-(4-(aminomethyl)phenylamino)benzonitrile-2,2,2-trifluoroacetate

119 mg (0.37 mmol) tert-butyl 4-(2-cyanophenylamino)benzylcarbamate were dissolved in 5 mL dichloromethane and combined with 1 mL (13.06 mmol) trifluoroacetic acid. The reaction was stirred overnight at ambient temperature and then evaporated to dryness in vacuo.

[1402] Yield: 99% of theory

[1403] C_{13}H_{13}N_{2}O_{4} (337.3)

[1404] R_{f}=1.30 min. method 2

35d) pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyanophenylamino)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 2-(4-(aminomethyl)phenylamino)benzonitrile 2,2,2-trifluoroacetate (from 35c) and 1-(pyrimidine-5-carboxyl)-amino)cyclopropene-carboxylic acid (from 1b).

[1406]

[1407] C_{13}H_{13}N_{2}O_{4} (412.44)

[1408] R_{f}=1.84 min. method 2

Example 36
Pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyano-4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide

[1409]
36a) Tert-butyl-4-(2-cyano-4-fluorophenylamino) benzylcarbamate

[1410] Analogously to method (35b) the title compound was prepared starting from tert-butyl-4-aminobenzylcarbamate (from 35a), potassium sulphate, 2-bromo-5-fluorobenzonitrile, tris(dibenzylideneacetone)dipalladium and Xantphos.

[1411] C_{13}H_{16}FN_3O_2 (341.38)

[1412] R = 2.61 min. method 2

36b) 2-(4-(aminomethyl)phenylamino)-5-fluorobenzonitrile 2,2,2-trifluoroacetate

[1413] Analogously to method (35c) the title compound was prepared starting from tert-butyl-4-(2-cyano-4-fluorophenylamino)benzylcarbamate and trifluoroacetic acid.

[1414] C_{14}H_{15}FN_3O_2 (329.30)

[1415] R = 1.39 min. method 2

36c) pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyano-4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide

[1416] Analogously to method (1b) the title compound was prepared from 2-(4-(aminomethyl)phenylamino)-5-fluorobenzonitrile, 2,2,2-trifluoroacetate (from 36b) and 1-[(pyrimidine-5-carbonyl)amino]-cyclopropanecarboxylic acid (from 1b).

[1417] C_{13}H_{14}FN_3O_2 (430.43)

[1418] R = 1.91 min. method 2

Example 37

Pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide

[1419]

37a) 4-(aminomethyl)-N-(4-fluorophenyl)aniline

[1420] Analogously to method (1c) the title compound was prepared starting from 2-bromo-4-fluoro-aniline, 4-fluorobenzonitrile and Raney nickel.

[1421] C_{13}H_{13}FN_2 (216.25)

37b) pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide

[1422] Analogously to method (1d) the title compound was prepared from 4-(aminomethyl)-N-(4-fluorophenyl)aniline (from 37a) and 1-[(pyrimidine-5-carbonyl)amino]-cyclopropanecarboxylic acid (from 1b).

[1423] C_{21}H_{15}FN_3O_2 (405.43)

[1424] mass spectroscopy [M+H]^+ = 406

Example 38

Pyrimidine-5-carboxylic acid-N-(1-((5-(2-chlorophenylamino)-3-fluoropyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1425]

38a) 6-(aminomethyl)-N-(2-chlorophenyl)-5-fluoropyridin-3-amine

[1426] Analogously to method (1c) the title compound was prepared starting from 2-chloro-aniline, 2-cyano-3,5-difluoropyridine and Raney nickel.

[1427] C_{13}H_{12}FN_3 (251.69)

[1428] R = 1.295 min. method 1

38b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-chlorophenylamino)-3-fluoropyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1429] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2-chlorophenyl)-5-fluoropyridin-3-amine (from 38a) and 1-[(pyrimidine-5-carbonyl)amino]-cyclopropanecarboxylic acid (from 1b).

[1430] C_{21}H_{14}FN_3O_2 (440.86)

[1431] R = 1.75 min. method 1

Example 39

Pyrimidine-5-carboxylic acid-N-(1-((5-(2-trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1432]

39a) 6-(aminomethyl)-N-(2-(trifluoromethyl)phenyl) pyridin-3-amine

[1433] Analogously to method (1c) the title compound was prepared starting from 2-(trifluoromethyl)aniline, 5-fluoropicolinic acid nitrile and Raney nickel.

[1434] C_{14}H_{13}FN_2 (267.25)

[1435] R = 1.29 min. method 1

39b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1436] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine (from 39a) and 1-[(pyrimidine-5-carbonyl)amino]-cyclopropanecarboxylic acid (from 1b).

[1437] C_{21}H_{14}FN_3O_2 (456.42)

[1438] R = 1.39 min. method 1
Example 40

Pyrimidine-5-carboxylic acid-N-(1-((5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethyl)carbamoyl)cyclopropylamide

[1439]

40a) 5-(2-(trifluoromethyl)phenylamino)picolinic acid nitride

[1440] 820 mg (6.72 mmol) 5-fluoropicolinic acid nitride and 0.84 mL (6.72 mmol) 2-(trifluoromethyl)aniline in 10 mL DMSO were combined with 1.51 g (13.43 mmol) potassium tert-butoxide and stirred for 2 hours at ambient temperature. The mixture was poured onto an aqueous sodium chloride solution and extracted with tert-butyl methyl ether. The organic phase was evaporated to dryness in vacuo and the crude product thus obtained was purified by HPLC (method 2).

[1441] Yield: 54% of theory

[1442] C15H13F2N2O (263.22)

40b) 1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone

[1443] The reaction was carried out under protective gas (nitrogen). 860 mg (3.27 mmol) 5-(2-(trifluoromethyl)phenylamino)picolinic acid nitride in 5 mL diethyl ether at -10°C were added dropwise to 9.34 mL (15.07 mmol) of a 1.4 molar solution of methylmagnesium bromide in toluene/THF (3:1) and the mixture was left for 15 minutes at this temperature with stirring. The reaction mixture was combined with saturated ammonium chloride solution, neutralised with 1 molar aqueous hydrochloric acid at -5°C and extracted with tert-butyl methyl ether. The organic phase was evaporated to dryness in vacuo.

[1444] Yield: 96% of theory

[1445] C15H13F2N2O (280.25)

[1446] Rf=1.97 min. method 1

40c) (Z)-1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime

[1447] 0.73 mL (12.42 mmol) of a 50% aqueous hydroxylamine solution were added to 870 mg (3.1 mmol) 1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone in 5 mL ethanol. The mixture was stirred for 2 hours at 100°C and then the solvents were distilled off.

[1448] Yield: 98% of theory

[1449] C15H13F2N2O (295.26)

[1450] Rf=1.75 min. method 1

40d) 6-(1-aminoethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine

[1451] 900 mg (3.05 mmol) (Z)-1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime and 100 mg Raney nickel in 25 mL methanolic ammonia were hydrogenated for 1.5 days at ambient temperature and 50 psi hydrogen pressure. The reaction mixture was filtered, evaporated to dryness and then further reacted directly.

[1452] Yield: 96% of theory

[1453] C14H12F2N2O (281.28)

[1454] Rf=1.33 min. method 1

40e) pyrimidine-5-carboxylic acid-N-(1-((5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethyl)carbamoyl)cyclopropylamide

[1455] Analogously to method (1d) the title compound was prepared from 6-(1-aminoethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine (from 40d) and 1-(pyrimidine-5-carbonyl)-amino)cyclopropanecarboxylic acid (from 1b).

[1456] C27H23F2N3O2 (470.45)

[1457] Rf=1.46 min. method 1

Example 41

Pyrimidine-5-carboxylic acid-N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1458]

41a) 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine

[1459] Analogously to method (1c) the title compound was prepared starting from 2-trifluoromethyl-4-fluoro-aniline, 2-cyano-5-fluoropyridine and Raney nickel.

[1460] C14H12F2N2O (285.24)

[1461] Rf=1.50 min. method 9

41b) pyrimidine-5-carboxylic acid-N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1462] Analogously to Example (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and 1-(pyrimidine-5-carbonyl)-amino)cyclopropanecarboxylic acid (from 1b).

[1463] C27H23F2N3O2 (474.41)

[1464] Rf=2.96 min. method 7
Example 42

Pyrimidine-5-carboxylic acid-N-(1-((5-(5-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarboxamoyl)cyclopropyl)amide

[1465]

42a) 6-(aminomethyl)-N-(5-fluoro-2-trifluoromethyl)phenyl)pyridin-3-amine

[1466] Analogously to method (1c) the title compound was prepared starting from 2-fluoro-6-(trifluoromethyl)aniline, 2-cyano-5-fluoropyridine and Raney nickel.

[1467] C_{17}H_{13}F_{4}N_{3} (281.24)

[1468] R_f=1.95 min. method 8

42b) pyrimidine-5-carboxylic acid-N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarboxamoyl)cyclopropyl)amide

[1469] Analogously to method (1d) the title compound was prepared starting from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 1b).

[1470] C_{18}H_{14}F_{5}N_{3}O_{2} (474.41)

[1471] R_f=3.10 min. method 7

Example 43

(S)-pyrimidine-5-carboxylic acid-N-(3-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarboxamoyl)tetrahydrofuran-3-yl)amide

[1472]

43a) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate

[1473] 19.37 g (50 mmol) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate (S)-2-hydroxy-2-phenylacetate were suspended in 75 mL THF and 75 mL water, combined with 6.3 g (75 mmol) sodium hydrogen carbonate and stirred for 3 hours at ambient temperature.

[1474] The mixture was extracted twice with dichloromethane. The organic phases were washed with 14% sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained was further reacted directly.

[1475] Yield: 85% of theory

[1476] C_{17}H_{13}F_{3}N_{3}O_{3} (473.26)

[1477] R_f=1.19 min. method 1

43b) (S)-phenethyl-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylate

[1478] 4.43 mL (40.3 mmol) N-methylmorpholine and 5.69 g (17.7 mmol) 18-TBu were added to a solution of 2 g (16.1 mmol) pyrimidine-5-carboxylic acid in 50 mL DMF.

The mixture was left for 30 minutes at ambient temperature with stirring and then combined with 3.8 g (16.16 mmol) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate. The mixture was stirred overnight at ambient temperature and then evaporated to dryness. The crude product thus obtained was purified by HPLC (method 2).

[1479] Yield: 93% of theory

[1480] C_{17}H_{13}F_{3}N_{3}O_{3} (441.36)

[1481] R_f=1.60 min. method 1

43c) (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid

[1482] 30.74 mL (30.24 mmol) of a 1 molar sodium hydroxide solution were added to a solution of 5.14 g (15.1 mmol) (S)-phenethyl-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylate in 97 mL ethanol. The mixture was stirred for 1 hour at ambient temperature and then acidified with 4 molar hydrochloric acid. The purification was carried out by HPLC (method 2).

[1483] Yield: 93% of theory

[1484] C_{17}H_{13}F_{3}N_{3}O_{3} (473.21)

[1485] R_f=0.87 min. method 1

43d) pyrimidine-5-carboxylic acid-(S)—N-(3-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarboxamoyl)tetrahydrofuran-3-yl)amide

[1486] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

[1487] C_{18}H_{15}F_{5}N_{3}O_{3} (504.44)

[1488] R_f=2.86 min. method 7

Example 44

Pyrimidine-5-carboxylic acid-N-(1-((5-(2-fluoro-6-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarboxamoyl)cyclopropyl)amide

[1489]
44a) 6-(aminomethyl)-N-(2-fluoro-6-(trifluoromethyl)phenyl)pyridin-3-amine

45a) 5-(4-fluoro-2-(trifluoromethyl)phenylamino)picolinic acid nitrile

45b) 1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethaneone

45c) (E)-1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime

45d) 6-(1-aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine

45e) pyrimidine-5-carboxylic acid-N-(1-1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropylamide

45f) pyridazine-5-carboxylic acid-N-(3-3-(5-(2-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-ylamide

The compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine. 

The compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine. 

The compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine.

The compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine.

Example 45

Pyrimidine-5-carboxylic acid-N-(1-1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropylamide

Example 46

(S)-pyrimidine-5-carboxylic acid-N-(3-3-(5-(2-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-ylamide

Example 47

(S)-pyrimidine-5-carboxylic acid-N-(3-3-(5-(2-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-ylamide
[1518] Analogously to method (1d) the title compound was prepared from 6-(1-((aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 45d) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

[1519] C_{24}H_{22}F_{2}N_{6}O_{3} (518.46)

[1520] R_f=3.00 min. method 7

Example 48
(S)-pyrimidine-5-carboxylic acid-N-(3-(5-(5-fluoro-2-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl]tetrahydrofuran-3-y]amide

[1521]

[1522] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(5-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 42a) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

[1523] C_{24}H_{22}F_{2}N_{6}O_{3} (504.44)

[1524] R_f=3.15 min. method 7

Example 49
Pyridine-5-carboxylic acid-N-(1-((5-(2-methyl-6-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1525]

[1526] Analogously to method (1c) the title compound was prepared from 2-methyl-6-(trifluoromethyl)aniline and 2-cyano-5-fluoropyridine with Raney nickel as catalyst.

[1527] C_{14}H_{14}F_{2}N_{4} (281.28)

[1528] R_f=1.52 min. method 2

Example 50a
6-(aminomethyl)-N-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-amine

[1529] Analogously to method (1c) the title compound was prepared from 6-(aminomethyl)-N-(2-methyl-6-(trifluoromethyl)phenyl)pyridin-3-amine (from 49a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxylic acid (from 1b).

[1530] C_{22}H_{24}F_{2}N_{5}O_{2} (470.45)

[1531] R_f=1.57 min. method 2

Example 50
Pyridine-5-carboxylic acid-N-(1-((5-(4-methoxy-2-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1532]

[1533] Analogously to method (1c) the title compound was prepared from 2-amino-5-methoxybenzotri fluoride and 2-cyano-5-fluoropyridine with Raney nickel as catalyst.

[1534] C_{14}H_{14}F_{2}N_{4} (297.28)

[1535] R_f=0.21 ethyl acetate/methanol/ammonia=9:1:0.1

50b) pyridine-5-carboxylic acid-N-1-((5-(4-methoxy-2-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1536] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 50a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxylic acid (from 1b).

[1537] C_{22}H_{24}F_{2}N_{5}O_{2} (486.45)

[1538] R_f=2.82 min. method 7

Example 51
Pyridine-5-carboxylic acid-N-(1-((5-(4-methyl-2-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

[1539]

[1540] 49b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-methyl-6-(trifluoromethyl)phenyl)amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide
51a 6-(aminomethyl)-N-(4-methyl-2-trifluoromethyl)phenyl)pyridin-3-amine

[1540] Analogously to method (1c) the title compound was prepared from 2-amino-5-methylbenzotriazole and 2-cyano-5-fluoropyridine using Raney nickel.

[1541] C₂₁H₁₈F₅N₅ (281.28)

[1542] Rₜ=1.63 min. method 2

51b pyrimidine-5-carboxylic acid-N-(1-((5-(4-methyl-2-trifluoromethyl)phenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1543] 0.1 ml (0.56 mmol) DIPEA and 87 mg (0.27 mmol) O-[ethoxycarbonyl]cyanomethyleneamine)-N,N,N,N-tetramethyluronium tetrafluoroborate, dissolved in 0.5 ml DMF, were added to a solution of 50 mg (0.24 mmol) 1-[(pyrimidine-5-carboxy)-amino]-cyclopropene carboxylic acid (from 1b) in 2 ml THF. The mixture was left for 15 minutes at ambient temperature with stirring and then 82 mg (0.29 mmol) of 6-(aminomethyl)-N-(4-methyl-2-trifluoromethyl)phenyl)pyridin-3-amine (from 51a) in 0.5 ml DMF were added. The mixture was stirred overnight at ambient temperature and then purified by HPLC (Microsorb C18, 4.6 x 250 mm with acetonitrile/water/trifluoroacetic acid = 100/0/0.1 = 100/0/0.1).

[1544] Yield: 33% of theory

[1545] C₂₁H₁₈F₅N₅O₂ (470.45)

[1546] Rₜ=1.63 min. method 2

Example 52
Pyrimidine-5-carboxylic acid-N-1-((5-(2,4-bis(trifluoromethyl)phenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1547]

52a 6-(aminomethyl)-N-(2,4-bis(trifluoromethyl)phenyl)pyridin-3-amine

[1548] Analogously to method (1c) the title compound was prepared from 2,4-bis(trifluoromethyl)aniline and 2-cyano-5-fluoropyridine using Raney nickel.

[1549] C₃₀H₁₈F₁₄N₁₀ (535.25)

52b pyrimidine-5-carboxylic acid-N-1-((5-(2,4-bis(trifluoromethyl)phenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1550] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2,4-bis(trifluoromethyl)phenyl)pyridin-3-amine (from 52a) and 1-[(pyrimidine-5-carboxy)-amino]-cyclopropene carboxylic acid (from 1b).

[1551] C₂₁H₁₈F₅N₅O₂ (524.42)

[1552] Rₜ=3.63 min. method 10

53a 5-(4-bromo-2-(trifluoromethyl)phenylanino)picolinonitride

[1553] Pyrimidine-5-carboxylic acid-N-1-((5-(4-bromo-2-methylphenylamino)pyridin-2-yl)methyl)carbamoyl)cyclopropylamide

[1554] Analogously to method (40a) the title compound was prepared starting from 2-cyano-5-fluoropyridine, 2-amino-5-bromo-benzotriazole and potassium tert-butoxide with DMSO as solvent.

[1555] C₁₂H₁₁BrN₅ (342.11)

[1556] Rₜ=2.50 min. method 2

53b-1 6-(aminomethyl)-N-(4-bromo-2-methylphenyl)pyridin-3-amine

[1557] 1.65 ml (3.3 mmol) 2 molar lithium aluminium hydride solution in THF were added to a solution of 564 mg (1.65 mmol) 5-(4-bromo-2-(trifluoromethyl)phenylanino)picolinic acid nitride in 5 ml THF. The reaction mixture was stirred for 30 minutes at ambient temperature and then mixed with water. The salts were suction filtered and the filtrate was evaporated down in vacuo. The residue was purified by HPLC (with solvent gradient, acetonitrile and water with 0.1% trifluoroacetic acid). 2 products are formed.

[1558] Yield: 65% of theory

[1559] C₁₂H₁₁BrN₅C₂H₅O₂ (406.2)

[1560] Rₜ=1.63 min. method 2

53b-2 6-(aminomethyl)-N-(4-bromo-2-(trifluoromethyl)phenyl)pyridin-3-amine

[1561] Yield: 11% of theory

[1562] C₁₂H₁₁BrN₅C₂H₅O₂ (346.15)

[1563] Rₜ=1.72 min. method 2

53c pyrimidine-5-carboxylic acid-N-1-((5-(4-bromo-2-methylphenylamino)pyridin-2-yl)-methyl)carbamoyl)cyclopropylamide

[1564] Analogously to method (1d) the title compound was prepared starting from 6-(aminomethyl)-N-(4-bromo-2-methylphenyl)pyridin-3-amine, 2,2,2-trifluoroacetate (from 53b-1) and 1-[(pyrimidine-5-carboxy)-amino]-cyclopropene carboxylic acid (from 1b).

[1565] C₂₁H₁₈BrN₅O₂ (481.35)

[1566] Rₜ=1.61 min. method 2
Example 54
Pyrimidine-5-carboxylic acid-N-(1-(5-(4-bromo-2- (trifluoromethyl)phenylamino)pyridin-2-yl)methyl- carbamoyl)cyclopropylamide

[1567]

[1568] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-bromo-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 53b-2) and 1-{[pyrimidine-5-carbonyl]-amino}-cyclopropanecarboxylic acid (from 1b).

[1569] C_{32}H_{18}BrF_{3}N_{3}O_{2} (535.32)
[1570] R_{f}=1.82 min. method 2

Example 55
Pyrimidine-5-carboxylic acid-N-(1-(5-(4-chloro-2- (trifluoromethyl)phenylamino)pyridin-2-yl)methyl- carbamoyl)cyclopropylamide

[1571]

55a) 5-(4-chloro-2-(trifluoromethyl)phenylamino) picolinonitrile

[1572] The reaction took place under protective gas (nitrogen), 21 mg (0.04 mmol) Xanthophos and 10 mg (0.01 mmol) tris(dibenzyldiaminopentane)palladium were added to a solution of 100 mg (0.55 mmol) 5-bromo-2-cyanopyridine, 93 µL (0.66 mmol) 2-amino-5-chlorobenzotrifluoride and 167 mg (0.77 mmol) potassium phosphate in 5 mL toluene. The mixture was stirred overnight at 110 °C, the salts were filtered off and the filtrate was evaporated to dryness in vacuo. The residue was purified by HPLC with eluant gradient, acetonitrile and water with 0.1% trifluoroacetic acid.

[1573] Yield: 68% of theory
[1574] C_{13}H_{12}ClF_{3}N_{3} (297.66)
[1575] R_{f}=2.53 min. method 2

55b) 6-(aminomethyl)-N-(4-chloro-2-(trifluoromethyl) phenyl)pyridin-3-amine

[1576] Analogously to method (53b) the title compound was prepared starting from 5-(4-chloro-2-(trifluoromethyl) phenylamino)picolinic acid nitrile and 2 molar lithium aluminium hydride solution.

[1577] C_{12}H_{11}ClF_{3}N_{3} (301.69)
[1578] R_{f}=1.72 min. method 2

55c) pyrimidine-5-carboxylic acid-N-(1-(5-(4- chloro-2-(trifluoromethyl)phenylamino)pyridin-2-yl) methyl carbamoyl)cyclopropylamide

[1579] Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-chloro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 55b) and 1-{[pyrimidine-5-carbonyl]-amino}-cyclopropanecarboxylic acid (from 1b).

[1580] C_{32}H_{18}ClF_{3}N_{3}O_{2} (490.87)
[1581] R_{f}=1.76 min. method 2

Example 56
5-oxo-N—((S)-3-(4-(2-(trifluoromethyl)phenylamino)benzyl carbamoyl)-tetrahydrofuran-3-yl)pyrrolidine-2-carboxamide

[1582]

56a) (S)-phenethyl-3-(tert-butoxycarbonylamino) tetrahydrofuran-3-carboxylate

[1583] 2 g (9.18 mmol) di-tert-butyl dicarbonate and 11.29 mL (9.18 mmol) TEA were added to a solution of 1.8 g (7.65 mmol) (S)-phenethyl 3-aminotetrahydrofuran-3-carboxylate (from 43a) in 30 mL dichloromethane. The mixture was stirred overnight at ambient temperature and then more di-tert-butyl dicarbonate and 50 mg dimethylaminopyridine were added. The reaction mixture was evaporated to dryness in vacuo and the residue was taken up in 50 mL dioxane and stirred for 6 hours at 60 °C. The solvent was distilled off and the residue was divided between ethyl acetate and 0.5 molar potassium hydrogen sulphate solution. The organic phase was washed with sodium hydrogen sulphate solution, dried on sodium sulphate and evaporated to dryness in vacuo. The residue was purified on silica gel with petroleum ether/ethyl acetate in the ratio 4:1.

[1584] Yield: 63% of theory
[1585] C_{14}H_{16}NO_{3} (335.39)
[1586] R_{f}=2.05 min. method 1
56b) (S)-3-tert-butoxycarbonylamino-tetrahydrofurran-3-carboxylic acid

[1587] 8.94 mL (17.89 mmol) 2 molar sodium hydroxide solution were added to a solution of 1.5 g (4.47 mmol) (S)-phenethyl-3-(tert-butoxycarbonylamino)tetrahydrofurran-3-carboxylate in 20 mL ethanol. The mixture was stirred for 2 hours at ambient temperature and then 8.94 mL (17.89 mmol) 2 molar hydrochloric acid were added thereto. The mixture was evaporated down, the residue was suspended in ethanol and the salts were suction filtered. The filtrate was freed from the solvent and further reacted in crude form.

[1588] Yield: 100% of theory
[1589] C_{13}H_{21}NO_3 (231.25)
[1590] R_f = 1.55 min. method 1

56c) (S)-3-tert-butyl-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)tetrahydrofuran-3-y carbamate

[1591] Analogously to method (1d) the title compound was prepared from N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropaneacetic acid (from 56b).

[1592] C_{23}H_{23}F_{2}N_{3}O_{5} (479.49)

56d) (S)-3-amino-N-(4-(2-(trifluoromethyl)phenyl)amino)benzyl-tetrahydrofurran-3-carboxamide

[1593] 2 g (4.17 mmol) (S)-3-tert-butyl-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)tetrahydrofuran-3-y carbamate were stirred in 15 mL of a 1:1 mixture of dichloromethane and trifluoroacetic acid for 30 minutes at ambient temperature. After evaporation of the reaction mixture the residue was dissolved in dichloromethane, made basic with 4 molar sodium hydroxide solution and added to a phase separation cartridge. The filtrate was freed from the solvent and the crude product was chromatographed on silica gel with cyclohexane/ethyl acetate in the ratio 1:1 and then a second time with dichloromethane/methanol in the ratio 9:1.

[1594] Yield: 77% of theory
[1595] C_{13}H_{23}F_{2}N_{3}O (379.38)
[1596] R_f = 1.97 min. method 6

56e) (S)-5-oxo-N-(3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)tetrahydrofuran-3-yl)pyrrolidine-2-carboxamide

[1597] Analogously to method (1d) the title compound was prepared starting from (S)-3-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamide (from 56d) and 5-oxopyrrolidine-2-carboxylic acid.

[1598] C_{24}H_{23}F_{2}N_{3}O_{5} (490.49)
[1599] R_f = 1.84 min. method 5

Example 57
(S)-6-amino-N-[3-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamido and the corresponding acid.

[1600] Examples 57 to 107 that follow were prepared analogously to the method (1d) from (S)-3-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamide and the corresponding acids.

Example 58
(S)-6-methyl-N-[3-(4-(2-(trifluoromethyl)phenylamino)-benzylcarbamoyl)tetrahydro-furan-3-yl]-nicotinamide

[1602] C_{22}H_{22}F_{2}N_{4}O_{5} (499.5)
[1603] R_f = 1.66 min. method 5

Example 59
3-(2-pyridin-2-yl-acetylamino)-tetrahydro-furan-3-carboxylic acid 4-(2-tri-fluoromethyl-phenylamino)-benzylamide

[1604] C_{24}H_{24}F_{2}N_{4}O_{5} (498.5)
[1605] R_f = 1.69 min. method 5

Example 60
(S)-3-tetrahydro-furan-3-carboxylaminotetrahydro-furan-3-carboxylic acid 4-(2-trifluoromethyl-phenylamino)-benzylamide

[1607] C_{24}H_{22}F_{4}N_{4}O_{5} (506.49)
[1608] R_f = 1.64 min. method 5

Example 61
(S)-6-amino-N-[3-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamido and the corresponding acid.
Example 61
(S)-2-chloro-N-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl]-isonicotinamide

Example 64
(S)-pyridazine-4-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl]-amide

Example 62
(S)-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl]-amide

Example 65
(S)-tetrahydropyran-4-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 63
(S)-2-amino-N-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl]-isonicotinamide

Example 66
(S)-3-(2-cyano-2-hydroxyimino-acetylamino)-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide
Example 67
(S)-6-chloro-pyridine-2-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl]-amide

[1631]

\[
\text{C}_2\text{H}_2\text{Cl}_2\text{N}_2\text{O}_3 (518.9)
\]

[1632] \text{R}_f=2.25 \text{ min. method 5}

Example 68
(S)-5-methoxy-furan-2-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[1634]

\[
\text{C}_2\text{H}_2\text{F}_2\text{N}_2\text{O}_4 (503.5)
\]

[1635] \text{R}_f=2.12 \text{ min. method 5}

Example 69
(S)-3-[3-oxo-cyclohexanecarbonyl]-aminotetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1637]

\[
\text{C}_{25}\text{H}_{28}\text{F}_2\text{N}_2\text{O}_4 (503.5)
\]

[1638] \text{R}_f=2.00 \text{ min. method 5}

Example 70
(S)-6-hydroxy-pyridine-2-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[1640]

\[
\text{C}_2\text{H}_2\text{F}_2\text{N}_2\text{O}_4 (500.5)
\]

[1641] \text{R}_f=1.94 \text{ min. method 5}

Example 71
(S)-1-methyl-5-oxo-pyrrolidine-3-carboxylic acid \{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl\}-amide

[1643]

\[
\text{C}_{22}\text{H}_{23}\text{F}_2\text{N}_2\text{O}_4 (504.5)
\]

[1644] \text{R}_f=1.85 \text{ min. method 5}

Example 72
(S)-6-amino-pyridine-2-carboxylic acid \{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl\}-amide

[1646]

\[
\text{C}_{25}\text{H}_{28}\text{F}_2\text{N}_2\text{O}_4 (499.5)
\]

[1647] \text{R}_f=1.72 \text{ min. method 5}
Example 73
(S)-5-hydroxy-1H-pyrazole-3-carboxylic acid [3-[4-(2-trifluoromethyl-phenyl-amino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

\[ \text{C}_3\text{H}_3\text{F}_3\text{N}_2\text{O}_4 \text{ (489.5)} \]

R_f = 1.89 min. method 5

Example 74
(S)-pyridazine-3-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 75
(S)-3-[[3-methoxy-cyclopentane-carbonyl]-amino]-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamid

\[ \text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_4 \text{ (481.5)} \]

R_f = 2.02 min. method 5

Example 76
(S)-6-oxo-piperidine-3-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

\[ \text{C}_3\text{H}_3\text{F}_3\text{N}_2\text{O}_4 \text{ (504.5)} \]

R_f = 1.81 min. method 5

Example 77
(S)-4-methyl-pyrimidine-5-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

\[ \text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_4 \text{ (499.5)} \]

R_f = 1.96 min. method 5

Example 78
(S)-3-[[3-oxo-cyclopentane-carbonyl]-amino]-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamid

\[ \text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_4 \text{ (489.5)} \]

R_f = 1.97 min. method 5
Example 79

(S)-2-methoxy-N-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-isonicotinamide

Example 82

(S)-2-methylamino-pyrimidine-5-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 80

(S)-2,4-dimethyl-pyrimidine-5-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 83

(S)-2-methyl-pyrimidine-5-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 81

(S)-2-methoxy-pyrimidine-5-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 84

(S)-1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide
Example 85
(S)-oxazole-5-carboxylic acid-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

Example 87
(S)-5-hydroxy-N-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

Example 88
(S)-1-methyl-1H-[1,2,3]triazole-4-carboxylic acid-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 89
(S)-thiazole-5-carboxylic acid-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

Example 90
(S)-2-hydroxy-pyrimidine-5-carboxylic acid-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Example 86
(S)-2-hydroxy-N-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-isonicotinamide

Example 89
(S)-2-hydroxy-pyrimidine-5-carboxylic acid-[[3-[4-(2-trifluoromethyl-phenylamino)]-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide
Example 91
(S)-3-(3,3,3-trifluoro-2-methyl-propionylamino)tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-ethyl-phenylamino)-benzyamide

Example 94
(S)-furan-2-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

Example 92
(S)-5-methoxy-N-[3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

Example 95
(S)—N—[3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydro-furan-3-yl]-isonicotinamide

Example 93
(S)-furan-3-carboxylic acid [3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

Example 96
(S)-pyrazine-2-carboxylic acid- [3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

[1703]

[1704] C_{25}H_{25}F_{6}N_{3}O_{5} (503.4)

[1705] R_f=2.18 min. method 5

[1706]

[1707] C_{25}H_{25}F_{6}N_{3}O_{5} (514.5)

[1708] R_f=1.85 min. method 5

[1709]

[1710] C_{25}H_{25}F_{6}N_{3}O_{5} (473.4)

[1711] R_f=2.09 min. method 5

[1712]

[1713] C_{25}H_{25}F_{6}N_{3}O_{5} (473.4)

[1714] R_f=2.08 min. method 5

[1715]

[1716] C_{25}H_{25}F_{6}N_{3}O_{5} (484.5)

[1717] R_f=1.71 min. method 5

[1718]

[1719] C_{25}H_{25}F_{6}N_{3}O_{5} (485.5)

[1720] R_f=2.06 min. method 5
Example 97
(S)-3-(3-hydroxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1721]

Example 100
(S)-3-(3-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1730]

Example 98
(S)-6-hydroxy-N-[3-[4-(2-trifluoromethyl-phenylamino)-benzyl]carbonyl]-tetrahydrofuran-3-y]-nicotinamide

[1724]

Example 101
(S)-3-(2-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1733]

Example 99
(S)-3-(4-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1725]

Example 102
(S)-3-(3,5-dihydroxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1727]

Example 99
(S)-3-(4-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1728]

Example 102
(S)-3-(3,5-dihydroxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1736]
Example 103
(S)-3-(3,5-dimethoxy-benzyloamino)-tetrahydrofur-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

[1739]

\[ \text{C}_9\text{H}_{15}\text{F}_2\text{N}_2\text{O}_4 \] (543.5)

\[ R_f = 2.20 \text{ min. method 5} \]

Example 106
(S)-1H-pyrazole-3-carboxylic acid \{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl\}-amide

[1748]

\[ \text{C}_{10}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_3 \] (473.5)

\[ R_f = 1.96 \text{ min. method 5} \]

Example 107
(S)-6-fluoro-N-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]nicotinamide

[1751]

\[ \text{C}_{11}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4 \] (502.5)

\[ R_f = 2.10 \text{ min. method 5} \]

Example 108
1-(3-ethylureido)-N-[4-(2-trifluoromethylphenylamino)benzyl]cyclopropanecarboxamide

[1754]

[1755] A solution of 55 mg (0.16 mmol) 1-amine-N-[4-(2-trifluoromethylphenylamino)benzyl]-cyclopropanecarboxamide (from 5a) in 2 mL dichloromethane was combined with 68 µL (0.49 mmol) TEA and 16 µL (0.2 mmol) ethyl isocyanate and stirred overnight at ambient temperature. Then ethylisocyanate was added another three times and the
mixture was stirred at ambient temperature or at 60°C. Then the reaction mixture was evaporated to dryness in vacuo and purified by RP-HPLC-MS with an eluent gradient (water/acetonitrile=1:1 to 1:20+0.1% trifluoroacetic acid).

**Example 109**

Pyrimidine-5-carboxylic acid-N-(1-(4-(methylphenyl)amino)benzylcarbamoyl)cyclopropyl)amide

![Chemical structure](image1)

**Example 110**

Pyrimidine-5-carboxylic acid-N-(1-(4-((2-chlorophenyl)(methyl)amino)benzylcarbamoyl)cyclopropyl)amide

![Chemical structure](image2)

**Example 111**

Pyrimidine-5-carboxylic acid-N-(1-(4-(ethylphenyl)amino)benzylcarbamoyl)cyclopropyl)amide

![Chemical structure](image3)
111a) 4-(aminomethyl)-N-(4-methoxyphenyl)-N-methylamine

[1778] Analogously to method (1c) the title compound was prepared starting from 4-methoxy-N-methylaniline and 4-fluorobenzonitrile using Raney nickel.

[1779] C_{13}H_{18}N_{2}O (242.32)

112b) pyrimidine-5-carboxylic acid-N-(1-4-((4-methoxyphenyl)(methyl)amino)benzyl)cyclopropylamide

[1780] Analogously to method (1d) the title compound was prepared starting from 4-(aminomethyl)N-(4-methoxyphenyl)-N-methylaniline (from 112a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropane-carboxylic acid (from 1b).

[1781] C_{19}H_{20}N_{4}O_{2} (431.49)

[1782] R_{f}=2.13 min. method 11

Example 113
Pyrimidine-5-carboxylic acid-N-(1-4-(methyl(o-tolylamino)benzyl)carbamoyl) cyclopropylamide

[1783]

113a) N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline

[1784] Analogously to method (1c) N-methyl-o-toluidine and 4-fluorobenzonitrile were reacted using Raney nickel to obtain the title compound.

[1785] C_{13}H_{18}N_{2} (226.32)

113b) pyrimidine-5-carboxylic acid-N-(1-4-(methyl(o-tolylamino)benzyl)carbamoyl)-cyclopropylamide

[1786] Analogously to method (1d) the title compound was prepared from N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline (from 113a) and 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropane-carboxylic acid (from 1b).

[1787] C_{23}H_{22}N_{4}O (415.49)

[1788] R_{f}=2.26 min. method 11

Example 114
Pyrimidine-5-carboxylic acid-[1-4-(2-cyano-5-fluoro-phenylamino)-benzyl-carbamoyl]-cyclopropyl-amide

[1789]

114a) tert-butyl [4-(2-cyano-5-fluoro-phenylamino)-benzyl]-carbamate

[1790] Prepared analogously to the method in (55a) from 2-bromo-4-fluoro-benzonitrile and tert-butyl (4-aminobenzyl)-carbamate.

[1791] Yield: 60% of theory

[1792] C_{14}H_{20}FN_{2}O_{2} (341.38)

[1793] R_{f}=2.65 min. method 12

114b) 2-(4-aminomethyl-phenylamino)-4-fluorobenzonitrile di-trifluoroacetate

[1794] 92 mg (0.27 mmol) tert-butyl [4-(2-cyano-5-fluoro-phenylamino)-benzyl]-carbamate were stirred in 1 mL trifluoroacetic acid and 5 mL dichloromethane for 1 hour at ambient temperature. Then the reaction mixture was evaporated to dryness in vacuo.

[1795] Yield: 96% of theory

[1796] C_{14}H_{20}FN_{2}O_{2} (469.31)

[1797] R_{f}=1.81 min. method 12

114c) pyrimidine-5-carboxylic acid [1-4-(2-cyano-5-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl-amide

[1798] 83 mg (0.21 mmol) TBTU, 146 µL (1.0 mmol) triethylamine and 122 mg (0.21 mmol) 2-(4-aminomethyl-phenylamino)-4-fluorobenzonitrile di-trifluoroacetate were added to a solution of 54 mg (0.26 mmol) 1-[pyrimidine-5-carboxyl]-amino]-cyclopropane-carboxylic acid in 5 mL DMF. The mixture was stirred overnight at ambient temperature and then the solvents were distilled off in vacuo. The residue was purified by chromatography (RP with eluent gradient, acetonitrile and water with 0.1% trifluoroacetic acid).

[1799] Yield: 64% of theory

[1800] C_{22}H_{22}FN_{2}O_{2} (430.44)

[1801] R_{f}=1.91 min. method 12

Example 115
Pyrimidine-5-carboxylic acid [1-4-(2-cyano-3-fluoro-phenylamino)-benzyl-carbamoyl]-cyclopropyl-amide

[1802]

115a) tert-butyl [4-(2-cyano-3-fluoro-phenylamino)-benzyl]-carbamate

[1803] The title compound was obtained from 2-bromo-6-fluoro-benzonitrile and tert-butyl (4-aminobenzyl)-carbamate analogously to method (55a).

[1804] C_{14}H_{20}FN_{2}O_{2} (341.38)

[1805] R_{f}=2.65 min. method 12
115b) 2-(4-aminomethyl-phenylamino)-6-fluoro-benzonitrile di-trifluoroacetate

[1806] The title compound was prepared from tert-butyl [4-(2-cyano-3-fluoro-phenylamino)-benzyl]-carbamate analogously to method (114b).
[1807] C_{14}H_{13}F_{2}N_{2}O_{2} (469.31)
[1808] R_{f}=1.46 min. method 12

115c) pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-3-fluoro-phenylamino)-benzyl-carbamoyl}-cyclopropyl]-amide

[1809] The title compound was obtained analogously to method (114c) from 2-(4-aminomethyl-phenylamino)-6-fluoro-benzonitrile di-trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid.
[1810] Yield: 44% of theory
[1811] C_{14}H_{13}F_{2}N_{2}O_{2} (430.44)
[1812] R_{f}=1.94 min. method 12

Example 116
Pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-6-fluoro-phenylamino)-benzyl-carbamoyl}-cyclopropyl]-amide

[1813]

116a) tert-butyl [4-(2-cyano-6-fluoro-phenylamino)-benzyl]-carbimidate

[1814] The title compound was prepared from 2-bromo-3-fluoro-benzonitrile and tert-butyl (4-amino-benzyl)-carbamate according to method (55a).
[1815] C_{14}H_{13}F_{2}N_{2}O_{2} (341.38)
[1816] R_{f}=2.50 min. method 12

116b) 2-(4-aminomethyl-phenylamino)-3-fluoro-benzonitrile di-trifluoroacetate

[1817] Preparation of the title compound from tert-butyl [4-(2-cyano-6-fluoro-phenylamino)-benzyl]-carbamate analogously to method (114b).
[1818] C_{14}H_{13}F_{2}N_{2}O_{2} (469.31)
[1819] R_{f}=1.27 min. method 12

116c) pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-6-fluoro-phenylamino)-benzyl-carbamoyl}-cyclopropyl]-amide

[1820] The title compound was prepared analogously to method (114c) from 2-(4-aminomethyl-phenylamino)-3-fluoro-benzonitrile di-trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid.

[1821] C_{22}H_{23}F_{2}N_{4}O_{2} (430.44)
[1822] R_{f}=1.78 min. method 12

Example 117
Pyrimidine-5-carboxylic acid-[1-{4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl}-cyclopropyl]-amide

[1823]

117a) 444-ethoxy-2-trifluoromethyl-phenylamino)-benzonitrile

[1824] 276 mg (2.28 mmol) 4-fluoro-benzonitrile and 550 mg (2.28 mmol) 4-ethoxy-2-trifluoromethyl-phenylamine-hydrochloride were dissolved in 10 ml DMSO and combined with 630 mg (5.69 mmol) potassium-tert-butoxide while cooling with ice. The reaction mixture was stirred overnight at ambient temperature, diluted with water and extracted with diethyl ether. The organic phase was dried on sodium sulphate and evaporated down. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate=9:1).
[1825] Yield: 20% of theory
[1826] C_{14}H_{13}F_{2}N_{2}O_{2} (306.28)
[1827] mass spectroscopy [M+H]^+=307

117b) (4-aminomethyl-phenyl)-(4-ethoxy-2-trifluoromethyl-phenyl)-amine

[1828] 140 mg (0.46 mmol) 4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzonitrile in 10 ml methanolic ammonia were hydrogenated with Raney nickel as catalyst at 50 psi hydrogen pressure. The catalyst was filtered off and the filtrate was freed from the solvent.
[1829] C_{14}H_{13}F_{2}N_{2}O_{2} (310.31)

117c) pyrimidine-5-carboxylic acid-[1-{4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl}-cyclopropyl]-amide

[1830] 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid and (4-aminomethyl-phenyl)-(4-ethoxy-2-trifluoromethyl-phenyl)-amine were refluxed analogously to method (11d). After the end of the reaction the solvent was distilled off and the residue was combined with ethyl acetate, extracted with sodium hydrogen carbonate solution and dried on sodium sulphate. The solution was evaporated down in vacuo and the residue was purified on a silica gel column (dichloromethane/ethanol=19:1).
[1831] C_{22}H_{23}F_{2}N_{4}O_{2} (499.49)
[1832] mass spectroscopy [M+H]^+=500
Example 118
Pyrimidine-5-carboxylic acid (1-[4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylaminomethyl]-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

118a) 4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylaminomethyl]-benzonitrile

\[ \text{C}_{36} \text{H}_{14} \text{F}_{2} \text{N}_{2} \text{O} \] (342.26)

=[M+H]^+ = 343

118b) 4-(aminomethyl-phenyl)-4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylamine

118c) pyrimidine-5-carboxylic acid (1-[4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylaminomethyl]-benzyl(1-carbamoyle)cyclopropyl]-amido)-hydrochloride

118d) 3-fluoro-5-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylaminomethyl]-pyridine-2-carboxitrole

Example 119
Pyrimidine-5-carboxylic acid (1-[4-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido)

Example 120
Pyrimidine-5-carboxylic acid (1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylaminomethyl)-pyridin-2-ylmethyl]-carbamoyle)cyclopropyl]-amido).

Example 120a) 3-fluoro-5-[2-fluoro-6-trifluoromethyl-phenylaminomethyl]-pyridine-2-carbonitrile

Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido)

Example 121
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 122
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 123
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 124
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 125
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 126
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 127
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 128
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 129
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride

Example 130
Pyrimidine-5-carboxylic acid (1-[4-(isopropoxy-2-trifluoromethyl-phenylaminomethyl)-benzyl(1-carbamoyle)cyclopropyl]-amido) hydrochloride
120c) pyrimidine-5-carboxylic acid (1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}[carbamoyl]-cyclopropyl)-amide

[1861] (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropene-carboxylic acid were reacted analogously to method (1d). For working up solvent was distilled off. Then the residue was mixed with water, made alkaline with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water, dried on sodium sulphate and evaporated down. The crude product was purified by chromatography.

[1862] C_{13}H_{15}F_{2}N_{2}O (492.40)

[1863] mass spectroscopy [M+H]⁺=493

Example 121
Pyrimidine-5-carboxylic acid-(1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl(carbamoyl)}-cyclopropyl)-amide

121a) 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethaneone

[1865] At 25°C, solution of 2.70 g (9.02 mmol) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine in 50 mL diethyl ether was added drop-wise to 12 mL of a 3 molar methanol magnesium bromide solution in 50 mL diethyl ether. The reaction mixture was heated to 5°C and then while being cooled combined with 1 molar aqueous hydrochloric acid. Then the organic phase was separated off, dried on sodium sulphate and evaporated down. The residue was used in the next reaction without any further purification.

[1866] C_{14}H_{15}F_{2}N_{2}O (316.23)

[1867] mass spectroscopy [M+H]⁺=317

121b) 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethaneone-oxide

[1868] 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethaneone was reacted analogously to method (4c). For working up the reaction mixture was evaporated down, mixed with water and extracted with ethyl acetate. The organic phases were washed with water and sodium chloride solution and dried on sodium sulphate. After the solvent has been distilled off the residue was purified by chromatography (silica gel, dichloromethane with 2-6% methanol).

[1869] C_{14}H_{15}F_{2}N_{2}O (331.24)

[1870] mass spectroscopy [M+H]⁺=332

121c) 6-(1-aminooethyl)-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine

[1871] The reaction of 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethane-amino-oxide was carried out analogously to method (4d). The crude product was purified by chromatography (silica gel, ethyl acetate with 0-10% methanol/ammonia=9:1).

[1872] C_{14}H_{15}F_{2}N_{2} (317.26)

[1873] mass spectroscopy [M+H]⁺=318

121d) pyrimidine-5-carboxylic acid-(1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl(carbamoyl)}-cyclopropyl)-amide

[1874] 6-(1-aminooethyl)-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropene-carboxylic acid were reacted analogously to method (1d). For working up the reaction mixture was evaporated down and made alkaline with potassium carbonate solution. The solid was filtered off, washed with water and dried. Then the residue was purified by chromatography on a silica gel column and the fractions containing product were freed from the solvent. The hydrochloride was obtained by dissolving the residue in an amount of ethyl acetate and combining it with ethereal hydrochloric acid.

[1875] C_{15}H_{15}F_{2}N_{2}O·2HCl (579.35)

[1876] mass spectroscopy [M+H]⁺=507

[1877] The (R)- and (S)-anitiomer of Example 121 were obtained by chiral HPLC (SFC) from the racemic compound (column: Deval AD-H, 250×20 mm, eluant: 80% supercritical carbon dioxide and 20% isopropanol with 0.2% diethylamine, flow rate: 70 mL/min).

Example 122
5-amino-N-(1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl(carbamoyl)}-cyclopropyl)-nicotinamide

[1878]

122a) tert-butyl (1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl(carbamoyl)}-cyclopropyl)-carbamate

[1879] 1-tert-butoxycarbonylamino-cyclopropene-carboxylic acid and 6-(1-aminooethyl)-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine were reacted and worked up as described in method (121d). In the final chromatographic purification a silica gel column was used (petroleum ether with 30-50% ethyl acetate).
122b) 1-amino-cyclopropanecarboxylic acid-[1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl]-amide

[1880] 400 mg (0.80 mmol) tert-butyli[1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl-carbamoyl]-cyclopropyl]-carbamate in 10 mL dichloromethane were combined with 3 mL of 4 molar hydrochloric acid in dioxane and stirred for two hours at ambient temperature. Then the solvents were distilled off. The residue was further reacted directly.

122c) 5-amino-N-(1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl)-cyclopropyl]-nicotinamide

[1881] 1-amino-cyclopropanecarboxylic acid [1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl]-amide dihydrochloride and 5-amino-nicotinic acid were reacted and worked up as described in method (121d). During the chromatographic purification through silica gel dichloromethane with 0-15% methanol was used as eluant.

[1882] C_{2}H_{7}F_{4}N_{2}O_{3}*2HCl (593.38)

[1883] mass spectroscopy [M+H]^{+}=521

Example 123

Pyrimidine-5-carboxylic acid-[1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl]-amide

[1884]

123a) 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

[1885] 39.7 mL of a 1.4 molar methylmagnesium bromide solution in toluene/THF (3:1) and 200 mL diethyl ether were taken and cooled to ~30 °C. Then 3.90 g (13.9 mmol) 5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 100 mL diethyl ether were added and the reaction mixture was left overnight with heating to ambient temperature and with stirring. The reaction mixture was mixed with 1 molar aqueous hydrochloric acid and stirred for some time. The organic phase was separated off, dried on sodium sulphate and evaporated down. The crude product was used in the next reaction without any further purification.

[1886] C_{14}H_{13}F_{4}N_{2}O_{2} (298.24)

[1887] mass spectroscopy [M+H]^{+}=299

123b) 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxide

[1888] 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone was reacted and worked up analogously to method (121b). During the subsequent column chromatography on silica gel dichloromethane/ethanol 50:1 was used as eluant.

[1889] C_{14}H_{11}F_{4}N_{2}O (313.25)

123c) 6-[1-(aminomethyl)-pyridin-3-yl]-[2-fluoro-6-trifluoromethyl-phenyl]-amine

[1890] 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxide was hydrogenated analogously to method (40d). The crude product was purified by chromatography (silica gel, dichloromethane with 2 to 5% methanol/ammonia 10:1).

[1891] C_{14}H_{11}F_{4}N_{3} (299.27)

[1892] R_{f}=2.76 min. method 7

123d) pyrimidine-5-carboxylic acid-[1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl]-amide

[1893] 6-[1-(aminomethyl)-pyridin-3-yl]-[2-fluoro-6-trifluoromethyl-phenyl]-amine and 1-[pyrimidine-5-carbonylo]-cyclopropanecarboxylic acid were reacted analogously to method (1d). For working up the reaction mixture was evaporated down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and the solvent was distilled off. The residue was purified by chromatography (silica gel, dichloromethane/ethanol=50:1).

[1894] C_{22}H_{22}F_{6}N_{2}O_{3} (488.44)

[1895] mass spectroscopy [M+H]^{+}=489

Example 124

5-amino-N-(1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl]-nicotinamide

[1896]

124a) tert-butyli[1-[1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl]-carbamate

[1897] tert-butoxycarbonylaminocyclopropanecarboxylic acid and 6-[1-(aminomethyl)-pyridin-3-yl]-[2-fluoro-6-trifluoromethyl-phenyl]-amine were reacted and worked
up as described in method (123d). The crude product was used in the next reaction without being purified by column chromatography.

[1898] C_{22}H_{24}F_{2}N_{2}O_{4} (482.47)
[1899] mass spectroscopy [M+H] + = 483

124b) 1-amino-cyclopropanecarboxylic acid [1-[[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl]-amido hydrochloride

[1900] Reaction of tert-butyl (1-[1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl-carbamoyl]-cyclopropyl)-carbamate analogously to method (122b).

[1901] C_{17}H_{18}F_{5}N_{4}O_{3}HCl (418.82)
[1902] mass spectroscopy [M+H] + = 383

124c) 5-amino-N-(1-[1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl-carbamoyl]-cyclopropyl)-nicotinamide

[1903] 1-amino-cyclopropanecarboxylic acid [1-[[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl][ethyl]-amido hydrochloride and 5-amino-nicotinamide acid were reacted analogously to method (1d). For working up the reaction mixture was stirred down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and the solvent was distilled off. The residue was purified by chromatography (silica gel, dichloromethane:ethanol:9:1).

[1904] C_{17}H_{22}F_{5}N_{2}O_{3} (502.46)
[1905] mass spectroscopy [M+H] + = 503

Example 125
5-amino-N-(1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-nicotinamide

[1906]

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{O} & \quad \text{HN}
\end{align*}
\]

125a) tert-butyl (1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-carbamate

[1907] Reaction of (6-aminoethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-tert-butoxycarbonyl-cyclopropanecarboxylic acid analogously to method (1d). After the end of the reaction the solution was evaporated down and made alkaline with potassium carbonate solution. The precipitate was filtered off, washed with water and dried.

[1908] C_{22}H_{24}F_{2}N_{2}O_{4} (486.44)

125b) 1-amino-cyclopropanecarboxylic acid [1-[[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl]-amido

[1909] tert-butyl (1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-carbamate was reacted analogously to method (122b).

[1910] C_{17}H_{18}F_{5}N_{4}O_{3}HCl (459.24)

125c) 5-amino-N-(1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-nicotinamide

[1911] 5-amino-nicotinic acid and 1-amino-cyclopropanecarboxylic acid [1-[[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl]-amide were reacted as described in method (121d). During the chromatographic purification through silica gel dichloromethane and 0 to 15% methanol were used as eluant.

[1912] C_{17}H_{22}F_{5}N_{2}O_{3} (579.35)
[1913] mass spectroscopy [M+H] + = 507

Example 126
Pyrimidine-5-carboxylic acid (1-[[5-(4-bromo-2-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amid

[1914]

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{N}
\end{align*}
\]

126a) 5-(4-bromo-2-chloro-phenylamino)-pyridine-2-carbonitrile

[1915] 250 mg (2.0 mmol) 5-fluoro-pyridine-2-carbonitrile were added at ambient temperature to a solution of 423 mg (2.0 mmol) 4-bromo-2-chloroaniline and 459 mg (4.0 mmol) potassium-tert-butoxide in 4 mL DMSO. The reaction mixture was stirred overnight, then combined with sodium chloride solution and extracted with tert-butyl-methylether. The organic phases were dried on sodium sulphate and evaporated down.

[1916] C_{17}H_{18}BrClN_{2} (308.56)
[1917] mass spectroscopy [M+H] + = 308

126b) (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-chloro-phenyl-amine

[1918] A solution of 250 mg 5-(4-bromo-2-chloro-phenylamino)-pyridine-2-carbonitrile in 4 mL THF was added dropwise to 0.8 mL of a 2 molar solution of lithium aluminium hyride in THF at ambient temperature. Then the reaction mixture was refluxed for 20 minutes. It was carefully hydrolysed with water and extracted with THF. The organic phases were washed with sodium carbonate solution, dried on sodium sulphate and evaporated down. The residue was purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

[1919] C_{17}H_{19}BrClN_{2} (312.59)
[1920] mass spectroscopy [M+H] + = 311
126c) pyrimidine-5-carboxylic acid-(1-[[5-(4-bromo-2-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[1921] Prepared analogously to method (51b) from (6-amino-phenyl-[pyridin-3-yl]-[4-bromo-2-chloro-phenyl]-amine and 1-(pyrimidine-5-carbamoyl)-amino)cyclopropene-carboxylic acid.

[1922] C_{15}H_{14}BrClN_{2}O_{3} (501.76)

[1923] mass spectroscopy [M+H]^+=501

Example 127
(S)-pyrimidine-5-carboxylic acid-[3-[[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]tetrahydro-furan-3-yl]-amide

[1924]

![Chemical Structure](image)

[1925] (S)-3-(pyrimidine-5-carboxamido)tetrahydrofur-an-3-carboxylic acid and N-(4-amino-methylphenyl)-2-(trifluoromethyl)aniline were reacted analogously to method (51b). The final purification was carried out by chromatography (RP, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[1926] C_{27}H_{22}F_{2}N_{3}O (485.46)


Example 128
Pyridazine-4-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[1928]

![Chemical Structure](image)

128b) 1-amino-cyclopropane-carboxylic acid

[1932] Tert-butyl (1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)carnamate was reacted as described in method (12b).

[1933] C_{17}H_{18}F_{3}N_{2}O_{4} +2HCl (450.24)

[1934] R_{t}=1.50 min. method 12

128c) pyridazine-4-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[1935] 1-amino-cyclopropane-carboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and pyridazine-4-carboxylic acid were reacted analogously to method (1d) and then purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

[1936] Yield: 47% of theory

[1937] C_{28}H_{23}F_{4}N_{3}O (492.40)


[1939] The following Examples 129 to 137 were prepared analogously to method (12c) from 1-amino-cyclopropane-carboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and the corresponding carboxylic acid.

Example 129
2-methoxy-pyrimidine-5-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[1940]

![Chemical Structure](image)

128a) tert-butyl (1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)carnamate

[1929] Reaction of tert-butyl (1-carbamoyl-cyclopentyl)carnamate and (6-amino-phenyl-[5-fluoro-pyridin-3-yl]-[2-fluoro-6-trifluoromethyl-phenyl]-amine analogously to method (1d). For working up the reaction mixture was evaporated down and made alkaline with potassium carbonate solution. The product precipitated was filtered off, washed with water and dried.

[1930] C_{28}H_{25}F_{3}N_{3}O_{3} (486.44)

[1931] R_{t}=2.30 min. method 12

[1941] C_{28}H_{16}F_{3}N_{2}O_{4} \cdot C_{18}H_{4}O_{4} (636.45)


Example 130
N-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-2-hydroxy-isonicotinamide

[1943]

![Chemical Structure](image)

128b) 1-amino-cyclopropane-carboxylic acid

[1932] Tert-butyl (1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)carnamate was reacted as described in method (12b).

[1933] C_{17}H_{18}F_{3}N_{2}O_{4} +2HCl (450.24)

[1934] R_{t}=1.50 min. method 12

128c) pyridazine-4-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[1935] 1-amino-cyclopropane-carboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and pyridazine-4-carboxylic acid were reacted analogously to method (1d) and then purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

[1936] Yield: 47% of theory

[1937] C_{28}H_{23}F_{4}N_{3}O (492.40)


[1939] The following Examples 129 to 137 were prepared analogously to method (12c) from 1-amino-cyclopropane-carboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and the corresponding carboxylic acid.

Example 129
2-methoxy-pyrimidine-5-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[1940]

![Chemical Structure](image)

128a) tert-butyl (1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)carnamate

[1929] Reaction of tert-butyl (1-carbamoyl-cyclopentyl)carnamate and (6-amino-phenyl-[5-fluoro-pyridin-3-yl]-[2-fluoro-6-trifluoromethyl-phenyl]-amine analogously to method (1d). For working up the reaction mixture was evaporated down and made alkaline with potassium carbonate solution. The product precipitated was filtered off, washed with water and dried.

[1930] C_{28}H_{25}F_{3}N_{3}O_{3} (486.44)

[1931] R_{t}=2.30 min. method 12

[1941] C_{28}H_{16}F_{3}N_{2}O_{4} \cdot C_{18}H_{4}O_{4} (636.45)


Example 130
N-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-2-hydroxy-isonicotinamide

[1943]

![Chemical Structure](image)
Example 131
N{(3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl}-5-methyl-nicotinamide

Example 134
2-methyl-pyrimidine-5-carboxylic acid-(1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl)-amide

Example 132
1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-(1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl)-amide

Example 135
Thiazole-5-carboxylic acid-(1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl)-amide

Example 133
2-methylamino-pyrimidine-5-carboxylic acid-(1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl)-amide

Example 136
6-hydroxy-pyridine-2-carboxylic acid-(1-{3-fluoro-5-(2-fluoro-6-trifluoromethyl)phenylamino)-pyridin-2-ylmethyl-[carbamoyl]-cyclopropyl)-amide

[1946] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1948] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1950] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1952] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1955] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1957] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1959] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)

[1961] C_{20}H_{19}F_{15}N_{13}O_{5} (505.44)
Example 137
Isoxazole-5-carboxylic acid-(1-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1964]

C₃H₃F₅N₂O₂ (481.38)

mass spectroscopy (ESI): [M+H]⁺=482

Example 138
2-methoxy-pyrimidine-5-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1965]

Example 139
2-methyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1975] The product was prepared according to method (1d) from 1-amino-cyclopropene-carboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl trifluoracetate and 2-methoxy-pyrimidine-5-carboxylic acid.

[1976] C₃H₃BrF₅N₂O₂ (565.34)

mass spectroscopy (ESI): [M+H]⁺=565

[1978] The following Examples 139 to 141 were prepared from 1-amino-cyclopropene-carboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl trifluoracetate and the corresponding carboxylic acid according to method (1d).

Example 139
2-methyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1979]

C₃H₃BrF₅N₂O₂ (549.34)

mass spectroscopy (ESI): [M+H]⁺=549

Example 140
6-hydroxy-pyridine-2-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1982]

C₃H₃BrF₅N₂O₂ (550.33)

mass spectroscopy (ESI): [M+H]⁺=550

Example 141
N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-5-hydroxy-nicotinamide

[1985]

C₃H₃BrF₅N₂O₂ (550.33)

mass spectroscopy (ESI): [M+H]⁺=550

Example 140
6-hydroxy-pyridine-2-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-amide

[1982]

C₃H₃BrF₅N₂O₂ (550.33)

mass spectroscopy (ESI): [M+H]⁺=550

Example 141
N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-cyclopropyl)-5-hydroxy-nicotinamide

[1985]
Example 142
5-amino-N-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

142a) benzyl 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylate

142b) 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylic acid

142c) 5-amino-N-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

Example 143
3H-imidazo[4,5-b]pyridine-6-carboxylic acid-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

143a) benzyl 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylate

143b) 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylic acid


[1999] C_{14}H_{11}N_{2}O_{3} (336.35)


[2001] Obtained from the reaction of benzyl 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylate according to method (142b).

[2002] C_{15}H_{14}N_{2}O_{3} (246.22)

[2003] Rf = 1.64 min, method 10

Example 144
6-amino-pyrazine-2-carboxylic acid-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2007]
144a) tert-butyl (1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-carbamate [2008]

1-tert-butoxycarbonylaminocyclopropane-carboxylic acid and (6-aminoethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were coupled with TBTU analogously to method (1d). The reaction mixture was evaporated down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. Then the organic phase was dried on sodium sulphate and freed from the solvent. The residue was purfiled on a silica gel column with dichloromethane/ethanol as eluant in the ratio 1:50 to 1:20.

[2009] C_{12}H_{18}F_3N_5O_4 (468.45)

144b) 1-amino-cyclopropane-carboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride [2011] 1.00 g (2.14 mmol) tert-butyl (1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-carbamate was dissolved in 30 mL dioxane and after the addition of 3.2 mL 4 molar hydrochloride solution in dioxane stirred overnight at ambient temperature. The solvent was distilled off in vacuo and the residue was further reacted directly.

[2012] C_{12}H_{18}F_3N_5O_4HCl (404.79)


[2015] C_{12}H_{18}F_3N_5O_4 (489.43)

Example 145
2-methylamino-pyrimidine-5-carboxylic acid(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2017]

145a) tert-butyl (1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-carbamate [2018] 1-(tert-butoxycarbonyl-amino)-cyclopropane-carboxylic acid and (6-aminoethyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine were coupled as described in method (1d). For working up the reaction mixture was mixed with water and extracted with dichloromethane. The organic phases were dried on sodium sulphate and evaporated down.

[2019] C_{22}H_{26}ClF_3N_6O_3 (501.57)
[2020] R_f = 2.23 min. method 12

145b) 1-amino-cyclopropane-carboxylic acid [5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate [2021] 906 mg (1.40 mmol) tert-butyl (1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-carbamate in 5 mL dichloromethane were combined with 2 mL trifluoroacetic acid and stirred for one hour at ambient temperature. Then the solvent was distilled off in vacuo and the residue was worked up without any further purification.

[2022] C_{12}H_{18}ClF_3N_5O_4C_2F_3CO_2 (498.81)
[2023] R_f = 1.54 min. method 12

145c) 2-methylamino-pyrimidine-5-carboxylic acid [1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide [2024] 1-amino-cyclopropane-carboxylic acid [5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate and 2-methylamino-pyrimidine-5-carboxylic acid were reacted analogously to method (1d). Then the reaction mixture was purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

[2025] C_{12}H_{18}ClF_3N_5O_2 (519.51)
[2026] mass spectroscopy (ESI): [M+H]^+ = 520

Example 146
2-methoxy-pyrimidine-5-carboxylic acid (1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2027] Examples 146 to 149 were prepared analogously from 1-amino-cyclopropane-carboxylic acid [5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amidine and the corresponding carboxylic acid.

[2028]

145d) tert-butyl (1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-carbamate [2029] C_{22}H_{26}ClF_3N_6O_3 (520.89)
Example 147
2-methyl-pyrimidine-5-carboxylic acid (1-[(5-[4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl]-amide

$$\text{C}_9\text{H}_9\text{ClIF}_3\text{N}_2\text{O}_2$$ (504.89)

mass spectroscopy (ESI): [M+H]^+ = 505

Example 148
1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (1-[(5-[4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

$$\text{C}_9\text{H}_9\text{ClIF}_3\text{N}_2\text{O}_2$$ (519.90)

mass spectroscopy (ESI): [M+H]^+ = 520

Example 149
Thiazole-5-carboxylic acid (1-[(5-[4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

$$\text{C}_9\text{H}_9\text{ClIF}_3\text{N}_2\text{O}_2\text{S}$$ (495.91)

mass spectroscopy (ESI): [M+H]^+ = 496

Example 150
3-amino-isoxazole-5-carboxylic acid (1-[(5-[4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl]-amide

$$\text{C}_9\text{H}_9\text{IF}_3\text{N}_2\text{O}_2$$ (478.40)

mass spectroscopy (ESI): [M+H]^+ = 479

Example 151
Pyrimidine-5-carboxylic acid (1-[(3-[fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide dihydrochloride

$$\text{C}_9\text{H}_9\text{ClIF}_3\text{N}_2\text{O}_2\text{S}$$ (656.32)

mass spectroscopy (ESI): [M+H]^+ = 493
Example 152

5-amino-N-(1-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide dihydrochloride

[2050]

Obtained analogously to the method of Example 147 from 5-amino-nicotinic acid and 1-amino-cyclopropanecarboxylic acid-[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide. In the chromatographic purification, however, a silica gel column was used (eluant: dichloromethane with 5 to 12% methanol).

[2052] C_{13}H_{14}F_{2}N_{4}O_{3}.2HCl (579.35)

[2053] mass spectroscopy (ESI): [M+H]^+ = 507

Example 153

(S)-pyrimidine-5-carboxylic acid (3-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide dihydrochloride

[2054]

Prepared from (S)-3-(pyrimidin-5-carboxamido)tetrahydrofuran-3-carboxylic acid and (6-aminoethylmethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine analogously to Example 150. The column chromatographic purification used a silica gel column and dichloromethane with 0 to 7% methanol as eluant.

[2056] C_{13}H_{14}F_{2}N_{4}O_{3}.2HCl (595.35)

[2057] mass spectroscopy (ESI): [M+H]^+ = 523

Example 154

(S)-5-amino-N-(3-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2058]

154a) butyl (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylate

[2059] 5-amino-nicotinic acid and butyl (S)-3-amino-tetrahydrofuran-3-carboxylate were coupled with TBTU analogously to method (Id). For working up the reaction mixture was evaporated down, combined with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water and sodium chloride solution, dried on sodium sulphate and freed from the solvent. The residue was chromatographed on a silica gel column (eluant: dichloromethane with 5 to 10% methanol).

[2060] C_{14}H_{15}F_{2}N_{4}O_{3} (307.35)

[2061] mass spectroscopy (ESI): [M+H]^+ = 308

154b) (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid

[2062] 2.45 g (7.97 mmol) butyl (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylate in 50 mL methanol were combined with 16 mL 1 molar sodium hydroxide solution and stirred for one hour at ambient temperature. After the addition of 16 mL of 1 molar hydrochloric acid the solvents were distilled off in vacuo. The residue was dissolved in ethanol and the inorganic salts were filtered off. Then the filtrate was evaporated down.

[2063] Yield: 99% of theory

[2064] C_{14}H_{14}F_{2}N_{4}O_{3} (251.24)

[2065] mass spectroscopy (ESI): [M+H]^+ = 252

154c) (S)-5-amino-N-(3-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide dihydrochloride

[2066] (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminoethylmethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted and purified as described in method (154a). Following the chromatographic purification the product was dissolved in ethyl acetate and precipitated with ethereal hydrochloric solution.

[2067] C_{14}H_{14}F_{2}N_{4}O_{3}.2HCl (609.38)

[2068] mass spectroscopy (ESI): [M+H]^+ = 537

Example 155

(S)-pyrimidine-5-carboxylic acid-[3-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[2069]
A solution of 64 mg (0.27 mmol) (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid, 93 mg (0.28 mmol) O4-(ethoxycarbonyl)-cyano-methyl-eneamine]-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TOTO) and 139 µL (0.81 mmol) DIPEA in 1 mL DMF was stirred for 1 hour at ambient temperature, then combined with 144 mg (0.41 mmol) N-((4-aminomethyl)phenyl)-2-(trifluoromethyl)aniline and left to stand overnight. Then the mixture was purified by chromatography (RP with gradient, eluent: acetonitrile and water with 0.2% trifluoroacetic acid).

Yield: 18% of theory

C_{25}H_{23}F_{6}N_{6}O_{5} (485.46)
mass spectroscopy (ESI): [M+H]^+ = 486
RC = 2.15 min. method 12

Example 156

(S)-5-amino-N-3-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide dihydrochloride

(S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted and purified as described in method (154a). Following the chromatographic purification the product was dissolved in ethyl acetate and precipitated with ether.

C_{25}H_{23}F_{6}N_{6}O_{5}·2HCl (609.38)
mass spectroscopy (ESI): [M+H]^+ = 537

Example 157

(S)-5-amino-N-3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

(S)-3-[(5-aminopyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine according to method (142c).

C_{25}H_{23}F_{6}N_{6}O_{5} (518.46)
mass spectroscopy (ESI): [M+H]^+ = 519

Example 158

(S)-pyrimidine-5-carboxylic acid-3-[[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-tetrahydrofuran-3-yl]-amide dihydrochloride

Prepared analogously to method (154a) from (S)-3-[(pyridine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine.

C_{25}H_{23}F_{6}N_{6}O_{5}·2HCl (595.35)
mass spectroscopy (ESI): [M+H]^+ = 523

Example 159

(S)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid-3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from 3H-imidazo[4,5-b]pyridine-6-carboxylic acid and butyl (S)-3-aminotetrahydrofuran-3-carboxylate as described in method (154a), with no chromatographic purification.

C_{25}H_{23}F_{6}N_{6}O_{5} (332.36)
RC = 1.99 min. method 13

159a) butyl (S)-3-[[3H-imidazo[4,5-b]pyridine-6-carbonyl]-amino]-tetrahydrofuran-3-carboxylate

159b) (S)-3-[[3H-imidazo[4,5-b]pyridine-6-carbonyl]-amino]-tetrahydrofuran-3-carboxylic acid

400 mg (1.20 mmol) butyl (S)-3-[[3H-imidazo[4,5-b]pyridine-6-carbonyl]-amino]-tetrahydrofuran-3-carboxylate were dissolved in 10 mL THF and 5 mL ethanol, combined with 1.2 mL 2 molar lithium hydroxide solution and
stirred overnight at ambient temperature. Then the solvents were distilled off and the residue was combined with 2.4 mL 1 molar aqueous hydrochloric acid. The mixture was evaporated down in vacuo and residual water was eliminated by repeated azeotropic distillation with ethanol.

159c) (S)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

160c) 2-(6-aminomethyl)-5-fluoro-pyridin-3-ylamino)-5-fluoro-benzonitrile-trifluoroacetate

160d) pyrimidine-5-carboxylic acid-(1-[[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 160
Pyrimidine-5-carboxylic acid-(1-[[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 161
Pyrimidine-5-carboxylic acid [1-[4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

160a) tert-butyl (5-bromo-3-fluoro-pyridin-2-ylmethyl)-carbamate

581 mg (2.41 mmol) C5H3NBrF2O2 [305.14]

160b) tert-butyl[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

160c) 2-(6-aminomethyl)-5-fluoro-pyridin-3-ylamino)-5-fluoro-benzonitrile-trifluoroacetate

2106) 51 mg (0.14 mmol) tert-butyl [5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate were stirred with 1.5 mL trifluoroacetic acid and 2.5 mL dichloromethane for 3 hours at ambient temperature. Then the reaction mixture was evaporated down in vacuo and further reacted directly.

Yield: 94% of theory

C6H3F3N2O2 374.27

Rf= 1.17 min. method 12

2110) 28 mg (0.13 mmol) 1-[pyrimidine-5-carbonyl]-cyclopropanecarboxylic acid and 50 mg (0.13 mmol) 2-(6-aminomethyl-5-fluoro-pyridin-3-ylamino)-5-fluorobenzonitrile were reacted with 181 BU using DMF as solvent analogously to method (1d).

Yield: 50% of theory

C7H4F3N2 449.13

Rf= 1.67 min. method 12

2115)

161a) tert-butyl (4-bromo-benzyl)-carbamate

2116) 2.35 g (11 mmol) di-tert-butyl-dicarbonate in 20 mL dichloromethane were added dropwise to a solution of 2.00 g (8.99 mmol) 4-bromobenzylamine hydrochloride and 6.26 g triethylamine in 30 mL dichloromethane while being cooled with the ice bath. Then the mixture was stirred overnight and then evaporated down. The residue was dissolved in ethyl acetate, acidified with citric acid and then washed with water and sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and freed from the solvent.

Yield: 96% of theory

C7H5BrNO2 286.17

Rf= 2.35 min. method 12

2118) mass spectroscopy (ESI): [M+H]+=286
161b) tert-butyl [4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzyl]-carbamate

[2120] Tert-butyl (4-bromo-benzyl)-carbamate and 2-amino-5-trifluoromethoxy-benzonitrile were reacted analogously to method (55a).

[2121] C₂H₂F₃NO₃ (407.39)


[2123] R = 4.63 min. method 13

161c) 2-(4-aminomethyl-phenylamino)-5-trifluoromethoxy-benzonitrile-trifluoroacetate

[2124] To cleave the protective group tert-butyl [4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzyl]-carbamate was treated with trifluoroacetic acid in dichloromethane. Then the solvent was distilled off and the residue was chromatographed (RP with eluent gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2125] C₂H₂F₃NO₃ (421.29)

[2126] mass spectroscopy (ESI): [M+H]^+ = 308

[2127] R = 2.45 min. method 13

161d) pyrimidine-5-carboxylic acid-[1-4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

[2128] 166 mg (0.39 mmol) of 2-(4-aminomethyl-phenylamino)-5-trifluoromethoxy-benzonitrile-trifluoroacetate and 82 mg (0.39 mmol) 1-[pyrimidine-5-carboxylamino]-cyclopropane-carboxylic acid were coupled analogously to method (1d).

[2129] Yield: 33% of theory

[2130] C₂H₂F₃NO₃ (496.44)


[2132] R = 2.24 min. method 13

Example 162

Pyrimidine-5-carboxylic acid [1-4-(4-chloro-2-cyano-phenylamino)-benzyl-carbamoyl]-cyclopropyl]-amide

[2133]

[2134] Prepared by the same reaction sequence (Buchwald reaction, cleaving of protective group, amide linking) as in Example 161 starting from tert-butyl (4-bromobenzyl)-carbamate.

[2135] C₂H₂F₃NO₃ (446.89)


[2137] R = 2.10 min. method 13

Example 163

(S)-pyridine-5-carboxylic acid (3-[1-4-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]ethyl-carbamoyl)-tetrahydrofuran-3-yl)-amide

[2138]

163a) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

[2139] 500 mg (1.68 mmol) 5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 5 ml diethyl ether were added dropwise at –5° C, to a solution of 2.2 ml of 3 molar methylmagnesium bromide in diethyl ether. The reaction mixture was hydrolysed with ammonium chloride solution and combined with 1 molar hydrochloric acid and tert-butylmethyl ether. The organic phase was separated off, dried on sodium sulphate and evaporated down

[2140] Yield: 50% of theory

[2141] C₂H₂F₃NO₃ (314.69)

[2142] mass spectroscopy (ESI): [M+H]^+ = 315

163b) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime

[2143] 266 mg (0.85 mmol) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone, 73 mg (1.04 mmol) hydroxylamine-hydrochloride and 238 μL (1.69 mmol) triethylamine were refluxed overnight in 15 ml acetonitrile with stirring. The reaction mixture was cooled to 20° C, 0.1 molar hydrochloric acid added and the mixture was stirred for 3 hours. The organic phase was dried on sodium sulphate and evaporated down. The residue was used in the next reaction without any further purification.

[2144] Yield: 79% of theory

[2145] C₂H₂F₃NO₃ (329.71)

[2146] R = 2.27 min. method 12

163c) 6-(1-amino-ethyl)-pyridin-3-yl]-4-chloro-2-trifluoromethyl-phenylamine

[2147] 220 mg (0.67 mmol) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime in 1 ml methanol were mixed batchwise with 50 mg zinc powder and 1.1 ml of 4 molar hydrochloric acid in methanol and then refluxed for 3 hours with stirring. Then water was added to the mixture and it was extracted with dichloromethane. The organic phases were dried on sodium sulphate and evaporated down.

[2148] Yield: 62% of theory

[2149] C₂H₂F₃NO₃ (315.72)

[2150] R = 1.76 min. method 12
163d) (S)-pyrimidine-5-carboxylic acid (3-{[1-(5-[4-chloro-2-trifluoromethyl-phenylamino]-pyridin-2-yl)-ethylcarbamoyl]-tetrahydrofuran-3-yl}-amino)trifluoroacetate

[2151] The compound was obtained from (S)-3-[{pyrimidine-5-carbonyl(phenylamino)tetrahydrofuran-3-carboxylic acid and [6-(1-amino-ethyl)-pyridin-3-yl]-[4-chloro-2-trifluoromethyl-phenylamino]-amine analogously to method (51b).}

[2152] C_{38}H_{24}ClF_{16}N_{6}O_{8} (534.93)
[2154] R_f = 1.86 min. method 12

Example 164

Pyrimidine-5-carboxylic acid (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl} -cyclopropyl)-amine trifluoroacetate

[2155]

[2156] Obtained analogously to method (1d) from 6-[1-(amino-ethyl)-pyridin-3-yl]-[4-chloro-2-trifluoromethyl-phenyl]-amine and 1-[{pyrimidine-5-carbonyl(phenylamino)]-cyclopropanecarboxylic acid.

[2157] C_{39}H_{25}ClF_{16}N_{6}O_{7} * C_{4}H_{6}F (618.92)
[2158] mass spectroscopy (ESI): [M+H]^+ = 505
[2159] R_f = 1.84 min. method 12

Example 165
tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

[2160]

165a) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

[2161] Prepared analogously to method (55a) from tert-butyl (5-bromo-3-fluoro-pyridin-2-ylmethyl)-carbamate and 4-chloro-2-trifluoromethyl-phenylamine.

[2162] C_{36}H_{21}ClF_{16}N_{6}O_{3} (419.80)
[2163] mass spectroscopy (ESI): [M+H]^+ = 420

165b) (6-aminomethyl)-5-fluoro-pyridin-3-yl)(4-chloro-2-trifluoromethyl-phenyl)-amine hydrochloride

[2164] 50 mg (0.12 mmol) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate in 3 mL dioxane were combined with 2 mL of semi-concentrated hydrochloric acid and stirred for two hours at 60 °C. After evaporation of the reaction mixture residual water was eliminated by azeotropic distillation with toluene.

[2165] R_f = 1.73 min. method 12

165c) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

[2166] Prepared from (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine hydrochloride and 1-[{pyrimidine-5-carbonyl(phenylamino)]-cyclopropanecarboxylic acid analogously to method (1d).

[2167] C_{35}H_{23}ClF_{16}N_{6}O_{7} (508.86)
[2169] R_f = 2.12 min. method 12

Example 166

Pyrimidine-5-carboxylic acid (1-{[5-(2,4-dichlorophenylamino)-pyridin-2-ylmethyl]-ethylcarbamoyl} -cyclopropyl)-amine trifluoroacetate

[2170]

166a) 5-(2,4-dichlorophenylamino)-pyridine-2-carbonitrile

[2171] 1.33 g (8.2 mmol) 2,4-dichloroaniline in 30 mL DMSO were combined with 1.38 g (12.3 mmol) potassium-tetra-oxide and stirred for one hour at ambient temperature. Then 1.00 g (8.2 mmol) of 2-cyano-5-fluoropyridine in 20 mL DMSO was added and the mixture was stirred for a further six hours. It was diluted with dichloromethane, washed with sodium chloride solution, dried on sodium sulphate and evaporated down. The residue was chromatographed on a silica gel column (eluant: petroleum ether/ethyl acetate = 4:1).

[2172] Yield: 44% of theory

[2173] C_{37}H_{25}Cl_{2}N_{3} (264.11)
[2174] R_f = 2.46 min. method 12

166b) (6-aminomethyl-pyridin-3-yl)-(2,4-dichlorophenyl)-amine

[2175] 3.56 mL of a 2 molar solution of lithium aluminium hydride in THF were added at -10° C. To 0.94 g (3.6 mmol) 5-(2,4-dichlorophenylamino)-pyridine-2-carbonitrile in 60 mL THF. The mixture was stirred for 30 minutes at ambient
temperature, then mixed with water and filtered. The solid was washed with THF and the filtrate was evaporated to dryness.

[2176] C_{3}H_{7}ClI_{2}N_{5} (268.14)

[2177] mass spectroscopy (ESI): [M+H]^+ = 268

166c) pyrimidine-5-carboxylic acid-(1-[[5-(2,4-
dichloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2178] Obtained from (6-aminomethyl-pyridin-3-yl)-(2,4-
dichloro-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid analogously to method (1d).

[2179] C_{2}H_{18}Cl_{2}N_{5}O_{2} (457.31)

[2180] mass spectroscopy (ESI): [M+H]^+ = 457

Example 167

Pyrimidine-5-carboxylic acid (1-[[5-(2-bromo-4-
chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2181]

167a) 5-(2-bromo-4-chloro-phenylamino)-pyridine-
2-carbonitrile

[2182] Prepared from 2-bromo-4-chloroaniline and 2-cy-
ano-5-fluoropyridine analogously to (166a).

[2183] C_{2}H_{14}BrCIN_{3} (308.56)

[2184] mass spectroscopy (ESI): [M+H]^+ = 308

167b) (6-aminomethyl-pyridin-3-yl)-(2-bromo-4-
chloro-phenyl)-amine-trifluoroacetate

[2185] 5-(2-bromo-4-chloro-phenylamino)-pyridine-2-
carbonitrile was reduced analogously to method (166b) with lithium aluminium hydride. The subsequent purification, however, was carried out by chromatography (RP with eluant gradient, eluant: acetonitrile and water with 0.1% trifluoro-
acetic acid).

[2186] C_{2}H_{14}BrClN_{3} (312.59)

[2187] mass spectroscopy (ESI): [M+H]^+ = 312

167c) pyrimidine-5-carboxylic acid-(1-[[5-(2-bromo-
chloro-phenylamino)-pyridin-2-ylmethyl]-
carbamoyl]-cyclopropyl)-amide

[2188] Prepared analogously to method (1d) from (6-ami-
nomethyl-pyridin-3-yl)-(2-bromo-4-chloro-phenyl)-amine-
trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-
cyclopropanecarboxylic acid.

[2189] C_{2}H_{14}BrCIN_{3}O_{2} (351.76)


Example 168

6-methylamino-pyrazine-2-carboxylic acid-(1-[[5-
(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-
ylethyl]-carbamoyl]-cyclopropyl)-amide

[2191]

167a) tert-butyl [5-1-[[5-(4-fluoro-2-trifluoromethyl-
ethoxyphenylamino)-pyridin-2-ylmethyl]-carbamoyl]-
cyclopropyl-carbamoyl]-oxazol-2-yl]-carbamate

[2192] 61 mg (0.40 mmol) 6-methylamino-pyrazine-2-carboxylic acid, 162 mg (0.40 mmol) 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and 167 µL (1.20 mmol) triethylamine were placed in 7 mL THF and 1 mL DMF, combined with 154 mg (0.48 mmol) TBTU and then stirred for 4 days at ambient temperature. The THF was distilled off and the residue was purified by chromatography (RP with eluant gradient, eluant: water and acetonitrile with formic acid). Then the fractions containing product were made alkaline with potassium carbonate solution. The aceto-
nitrile was distilled off and the residue was extracted with ethyl acetate. The organic phases were dried on sodium sul-
phate, freed from the solvent and triturated with diisopropyletha-
ler.

[2193] Yield: 34% of theory

[2194] C_{2}H_{12}F_{2}N_{3}O_{4} (503.45)

[2195] mass spectroscopy (ESI): [M+H]^+ = 504

Example 169

2-amino-oxazole-5-carboxylic acid (1-[[5-(4-fluoro-
2-trifluoromethyl-phenyl-amino)-pyridin-2-ylmethyl]-
carbamoyl]-cyclopropyl)-amide

[2196]

169a) tert-butyl [5-1-[[5-(4-fluoro-2-trifluoromethyl-
ethoxyphenylamino)-pyridin-2-ylmethyl]-carbamoyl]-
cyclopropyl-carbamoyl]-oxazol-2-yl]-carbamate

[2197] Obtained from 2-tert-butoxycarbonylamino-ox-
azole-5-carboxylic acid and 1-amino-cyclopropanecarbox-
yc acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyri-
din-2-ylmethyl]-amide hydrochloride analogously to the
method for Example 168. However, in the working up, no chromatographic purification was carried out.

[2198] C_5H_9F_2N_3O_2 (578.52)
[2199] R_f=3.19 min. method 14

169b 2-amino-oxazole-5-carboxylic acid (1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

[2200] The protective group of the compound tert-butyl [5-1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropylcarbamoyl]-oxazol-2-y]-carbamate was cleaved using the method described for intermediate step (144b).

[2201] C_2H_9F_2N_5O_2 (478.40)
[2202] mass spectroscopy (ESI): [M+H]^+=479
[2203] R_f=2.71 min. method 7

Example 170
1-(2-cyano-2-methyl-acetamidino)-cyclopropancarboxylic acid [5-4-(fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[2204]

[2205] Reaction of 40 mg (0.40 mmol) cyanomethyl-acetic acid and 162 mg (0.40 mmol) 1-amino-cyclopropancarboxylic acid [5-4-(fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride analogously to the method for Example 168.

[2206] Yield: 28% of theory
[2207] C_2H_9F_2N_5O_2 (449.40)
[2208] mass spectroscopy (ESI): [M+H]^+=450
[2209] R_f=3.03 min. method 7

Example 171
N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-2-hydroxy-isonicotinamide

[2210]

[2211] 150 mg (0.165 mmol) of 1-amino-cyclopropancarboxylic acid [5-4-(bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide tri-trifluoroacetate were added to a solution of 23 mg (0.165 mmol) 2-hydroxyisonicotinic acid, 56 mg (0.174 mmol) TBTU and 114 µL (0.661 mol) DIPEA in 0.5 mL DMF after 5 minutes stirring at ambient temperature. Then the reaction mixture was left to stand overnight and then chromatographed (RP with gradient, eluant: acetone/nitride and water with 0.2% trifluoroacetic acid).

[2212] Yield: 69% of theory
[2213] C_2H_9BrF_3N_5O_2 (550.33)
[2215] R_f=1.73 min. method 12
[2216] The following Examples 172 to 179 were prepared analogously from 1-amino-cyclopropancarboxylic acid [5-4-(bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide tri-trifluoroacetate and the corresponding acids.

Example 172
Thiazole-5-carboxylic acid-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2217]

[2218] Yield: 94% of theory
[2219] C_2H_9BrF_3N_5O_2S (540.36)
[2221] R_f=1.88 min. method 12

Example 173
6-amino-N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide trifluoroacetate

[2222]

[2223] Yield: 89% of theory
[2224] C_2H_9BrF_3N_5O_2*C_2H_5F_2O_2 (663.37)
[2225] mass spectroscopy (ESI): [M+H]^+=549
Example 174
Pyridazine-4-carboxylic acid-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-amide

[2226]

Yield: 71% of theory
C_{21}H_{15}BrF_{5}N_{3}O_{8} (567.39)
mass spectroscopy (ESI): [M+H]^+ = 567
R_f = 1.80 min. method 12

Example 175
2-dimethylamino-pyrimidine-5-carboxylic acid-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-amide

[2231]

Example 176
2,6-dihydroxy-pyrimidine-4-carboxylic acid-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-amide

[2236]

Example 177
1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-amide

[2241]

Yield: 71% of theory
C_{22}H_{16}BrF_{3}N_{2}O_{3} (564.36)
mass spectroscopy (ESI): [M+H]^+ = 564
R_f = 1.78 min. method 12

Example 178
5-amino-N-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-nicotinamide

[2246]

Example 179
Pyrimidine-5-carboxylic acid-(1-{5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl}-carbamoyl)-cyclopropyl-amide

[2251]
179a) 5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridine-2-carbonitrile

[2252] Obtained from 2-cyano-3,5-difluoropyridine and 4-bromo-2-trifluoromethyl-phenylamine analogously to method (40a).

[2253] C_{17}H_{14}BrF_{9}N_{2} (360.11)


[2255] R_f = 2.68 min. method 12

179b) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine

[2256] 171 mg (0.48 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridine-2-carbonitrile were dissolved in 3 mL pyridine, 1.5 mL glacial acetic acid and 1.5 mL water and combined with 459 mg (5.22 mmol) sodium hypophosphite and Raney nickel. Then the mixture was hydrogenated for three hours at 55°C and 3 bar hydrogen pressure. The catalyst was filtered off, the filtrate was evaporated to dryness and the residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2257] C_{31}H_{29}BrF_{13}N_{2} (364.14)


[2259] R_f = 1.79 min. method 13

179c) pyridimine-5-carboxylic acid (1-[5-(4-bromo-2-trifluoromethylphenylamino)-3-fluoro-pyridin-2-ylmethyl]-cyclopropyl)-amide

[2260] 54 mg (0.26 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid, 36 µL triethylamine and 105 mg (0.31 mmol) TBTU in 4 mL DMF were stirred for 5 minutes at ambient temperature and then combined with another 144 µL triethylamine and 95 mg (0.26 mmol) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine. The reaction mixture was stirred overnight and then evaporated to dryness. The residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2261] C_{31}H_{30}BrF_{13}N_{4}O_{2} (553.31)


[2263] R_f = 2.20 min. method 13

Example 180
Pyrimidine-5-carboxylic acid-1-[5-(4-bromo-2-trifluoromethylphenylamino)-2yl-ethylcarbamoyl]-cyclopropyl)-amide

[2264] 180a) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

[2265] A solution of 3.27 g (9.56 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 100 mL diethyl ether was added dropwise to 5.42 mL 3 molar methylmagnesium bromide in diethyl ether while being cooled with the ice bath. Then the reaction mixture was allowed to come up to ambient temperature and stirred for another hour. The mixture was combined with 2.5 mL 1 molar hydrochloric acid and then evaporated to dryness. The residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2266] C_{17}H_{13}BrF_{9}NO_{2} (359.14)

[2267] R_f = 2.57 min. method 12

180b) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime

[2268] 702 mg (1.96 mmol) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone, 182 mg hydroxylamine-hydrochloride and 549 µL (3.91 mmol) triethylamine in 25 mL acetonitrile were refluxed for 1.5 hours. The solvent was distilled off and the residue was combined with dichloromethane and triethylamine and filtered through silica gel. The filtrate was freed from the solvent and used directly in the next reaction. 870 mg product.

180c) 6-[1-[(amino-ethyl)-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amino trifluoracetate

[2269] A solution of 870 mg (approx. 85%, 2.0 mmol) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime in 20 mL methanol was combined with 6 mL 10 molar hydrochloric acid in methanol and 567 mg zinc and refluxed for 3 hours. Then the mixture was filtered and the filtrate was freed from the solvent. The residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2270] Yield: 78% over two steps

[2271] C_{17}H_{14}BrF_{10}N_{2}O_{2} (360.17)


[2273] R_f = 1.83 min. method 12

180d) pyrimidine-5-carboxylic acid-1-[5-(4-bromo-2-trifluoromethylphenylamino)-2yl-ethylcarbamoyl]-cyclopropyl)-amide

[2274] Analogously to method (179c) from 190 mg (0.92 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and 330 mg (0.69 mmol) 6-[1-(aminoethyl)-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amino trifluoracetate.

[2275] Yield: 55% of theory

[2276] C_{32}H_{28}BrF_{14}N_{4}O_{2} (663.37)


[2278] R_f = 1.92 min. method 12

[2279] The (R)- and (S)-enantiomer of Example 180 were obtained by chiral HPLC (SFC) from the racemic compound (column: Develos ASH, 250 mmx10 mm, flow rate: 10
Example 181

2-methyl-pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl}-cyclopropyl]-amide

[2280]

181a) tert-butyl [1-{4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl}-cyclopropyl]-carbonate

[2281] 877 mg (4.36 mmol) 1-tert-butoxycarbonylaminocyclopropanecarboxylic acid and 2.58 (60%, 4.36 mmol) 2-(4-aminomethyl-phenylamino)-5-fluoro-benzonitrile trifluoroacetate were coupled analogously to method (179c).

[2282] Yield: 30% of theory
[2283] \( C_{19}H_{23}FN_2O_3 \) (424.47)
[2285] R_\text{f} = 2.39 min. method 13

181b) 1-aminocyclopropanecarboxylic acid 4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate

[2286] 560 mg (1.32 mmol) 2-(4-aminomethyl-phenylamino)-5-fluoro-benzonitrile trifluoroacetate in 15 mL dichloromethane were combined with 15 mL trifluoroacetic acid and stirred at ambient temperature. Then the reaction mixture was evaporated to dryness and purified by chromatography (RP with gradient, eluent: acetonitrile and water with 0.2% trifluoroacetic acid).

[2287] \( C_{19}H_{23}FN_2O_3 \) (438.38)
[2289] R_\text{f} = 1.56 min. method 13

181c) 2-methyl-pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl}-cyclopropyl]-amide

[2290] Prepared analogously to method (179c) from 42 mg (0.29 mmol) 2-methyl-pyrimidine-5-carboxylic acid and 167 mg (75%, 0.29 mmol) 1-amino-cyclopropanecarboxylic acid 4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate.

[2291] Yield: 83% of theory
[2292] \( C_{24}H_{22}FN_2O_2 \) (444.46)
[2294] R_\text{f} = 1.92 min. method 13
[2295] Examples 182 and 183 were prepared analogously from 1-amino-cyclopropanecarboxylic acid 4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate and the corresponding carboxylic acids.

Example 182

2-methoxy-pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl}-cyclopropyl]-amide

[2296]

[2297] Yield: 28% of theory
[2298] \( C_{20}H_{24}FN_2O_2 \) (460.46)
[2300] R_\text{f} = 2.03 min. method 13

Example 183

2-methylamino-pyrimidine-5-carboxylic acid-[1-{4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl}-cyclopropyl]-amide

[2301]

[2302] Yield: 58% of theory
[2303] \( C_{24}H_{24}FN_2O_2 \) (459.48)
[2305] R_\text{f} = 1.91 min. method 13

Example 184

2-amino-thiazole-5-carboxylic acid-[1-{5-(4-fluoro-2-trifluoromethyl-phenyl-amino)-pyridin-2-ylmethylcarbamoyl}-cyclopropyl]-amide

[2306]
184a) 2-acetylamino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[2308] Yield: 51% of theory
[2309] C_{2}H_{14}F_{2}N_{2}O_{3}S (536.50)
[2310] \text{R}_{f} = 2.96 \text{ min. method 7}

184b) 2-amino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[2311] 110 mg (0.21 mmol) 2-acetylamino-thiazole-5-carboxylic acid (1-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl-amide were stirred overnight at 80°C in 5 mL 4 molar hydrochloric acid. The reaction mixture was made alkaline with potassium carbonate solution and the precipitated solid was filtered off, washed with water and dried.
[2312] Yield: 43% of theory
[2313] C_{2}H_{14}F_{2}N_{2}O_{3}S (494.47)
[2314] mass spectroscopy (ESI): [M+H]^{+} = 495
[2315] \text{R}_{f} = 2.73 \text{ min. method 7}
[2316] Examples 185 and 186 were prepared analogously from 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and the corresponding acetylamino-carboxylic acid.

Example 185
5-amino-2H-pyrazole-3-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[2317]

187a) 3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile

[2318] C_{3}H_{2}F_{4}N_{3}O_{2} (477.42)
[2319] mass spectroscopy (ESI): [M+H]^{+} = 478
[2320] \text{R}_{f} = 2.69 \text{ min. method 7}

Example 186
2-amino-4-methyl-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[2321]

[2322] C_{2}H_{10}F_{3}N_{2}O_{2}S (508.49)
[2323] mass spectroscopy (ESI): [M+H]^{+} = 509
[2324] \text{R}_{f} = 2.67 \text{ min. method 7}

Example 187
Pyrimidine-5-carboxylic acid (1-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide dihydrochloride

[2325]

187b) (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

[2326] A solution of 5.00 g (28.9 mmol) 3,5-dichloro-pyridine-2-carbonitrile and 5.18 g (28.9 mmol) 4-fluoro-2-trifluoromethylphenylamine in 75 mL DMSO was combined with 5.05 g (45.0 mmol) potassium tert-butoxide while being cooled and then stirred for 30 minutes at ambient temperature. The reaction mixture was stirred into water and then extracted with diethyl ether. The organic phases were washed with water and sodium chloride solution, dried on sodium sulphate and evaporated down. The residue was purified by chromatography through a silica gel column (petroleum ether with 5 to 15% ethyl acetate).
[2327] Yield: 45% of theory

187c) pyrimidine-5-carboxylic acid (1-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide dihydrochloride

[2328] A solution of 100 mg (0.32 mmol) 3-chloro-5-(4-fluoro-2-trifluoromethylphenylamino)-pyridine-2-carbonitrile in 3 mL THF was combined at ambient temperature with 31 µL borane-dimethylsulphide complex and then stirred overnight. Methanol was then added carefully and the mixture was evaporated to dryness. The residue was used in the next reaction without any further purification.

[2329] Prepared from (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine and 1-(pyrimidine-5-carboxylamino)-cyclopropanecarboxylic acid analogously to the method for Example 151.
[2330] C_{2}H_{7}ClF_{3}N_{3}O_{2} \cdot 2\text{HCl} (581.78)
[2331] mass spectroscopy (ESI): [M+H]^{+} = 509
[2332] \text{R}_{f} = 3.68 \text{ min. method 10}
Example 188
Pyrimidine-5-carboxylic acid (3-[[1-[5-(4-bromo-2-
 trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcar-
bamoyl]-tetrahydro-furan-3-yl]-amide

[2333]

A solution of 59 mg (0.25 mmol) (S)-3-[[pyrimi-
dine-5-carboxylic]-amino]-tetrahydrofuran-3-carboxylic acid and 48 mg (0.30 mmol) N,N-carbonyldimidazole in 5 ml 
DMF was stirred for one hour at 50°C and then combined with 
89 mg (0.25 mmol) [3-[1-[5-(1-amino-ethyl)-pyridin-3-yl]-
(4-bromo-2-trifluoromethyl-phenyl)-amino] and 45 µl (0.26 
mmol) DIPEA. It was then stirred for another hour at ambient 
temperature. The reaction mixture was purified by chroma-
tography (RP with eluant gradient, eluant: acetonitrile and 
water with 0.2% trifluoroacetic acid).

[2335] Yield: 41% of theory
[2336] C_{32}H_{35}BrF_{7}N_{4}O_{5} (579.37)
[2337] mass spectroscopy (ESI): [M+H]^+ = 579
[2338] R_f = 1.93 min. method 12

Example 188a
Pyrimidine-5-carboxylic acid (3-[[1-[5-(4-bromo-2-
 trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcar-
bamoyl]-tetrahydrofuran-3-yl]-amide

[2339]

Separation of diastereomers by chiral HPLC (col-
umn: Daicel ASH; 250×4.6 mm; 5 µm; 25°C; eluant CO_{2}/ 
isopropanol 40.2% diethylamine 80:20; flow: 10 mL/min)

[2340] R_f = 8.23-10.51 minutes

Example 189
Pyrimidine-5-carboxylic acid (1-[1-[5-(2-chloro-4-
methyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-
cyclopropyl)-amide

[2344]

Analogously to Example 1d) the product was pre-
pared by amide coupling from 1-(pymidine-5-carboxyl)-
aminocyclopropane carboxylic acid and (6-aminomethyl-
pyridin-3-yl)(2-chloro-4-methyl-phenyl)-amino, using 
TBTU as coupling reagent and disopropylethylamine as base.

[2345]

[2346] C_{32}H_{35}ClF_{7}N_{4}O_{5} (436.90)
[2348] M+H = 435
[2349] R_f = 1.59 min. method 2

Example 190
Pyrimidine-5-carboxylic acid (1-[1-[5-(2-chloro-4-
fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-
cyclopropyl)-amide

[2350]

Analogously to Example 1d) the product was pre-
pared by amide coupling from 1-(pyrimidine-5-carboxyl)-
aminocyclopropane carboxylic acid and (6-aminomethyl-
pyridin-3-yl)(2-chloro-4-fluoro-phenyl)-amino, using 
TBTU as coupling reagent and disopropylethylamine as base.

[2351]

[2352] C_{32}H_{35}ClF_{7}N_{4}O_{5} (440.86)
[2354] R_f = 1.59 min. method 2

Example 191
Pyrimidine-5-carboxylic acid (1-[1-[5-(2-trifluorom-
ethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-
cyclohexyl)-amide

[2355]
191a) 1-amino-cyclohexanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[2356] 61 mg (0.25 mmol) 1-tert-butoxycarbonylaminocyclohexanecarboxylic acid, 80 mg (0.25 mmol) TBTU and 53 µL (0.38 mmol) triethylamine in 2 mL DMF were stirred for 5 minutes at ambient temperature and then mixed with 67 mg (0.25 mmol) (6-aminomethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine. The reaction mixture was then stirred overnight and purified by chromatography (RP with eluting gradient, eluent: acetonitrile and water with 0.1% trifluoroacetic acid). 93 mg of the isolated Boc-protected amine were stirred for 2 hours at ambient temperature in 5 mL of a 1:1 mixture of dichloromethane and trifluoroacetic acid. The reaction mixture was evaporated to dryness and then purified by chromatography (RP with eluting gradient, eluent: acetonitrile and water with 0.1% trifluoroacetic acid).

[2357] Yield: 68% of theory (as trifluoroacetate)

[2358] mass spectroscopy [M+H]^+ = 393

[2359] Rf = 1.70 min method 6

191b) pyrimidine-5-carboxylic acid (1-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclohexyl)-amide


[2361] Yield: 37% of theory

[2362] C_{22}H_{25}FN_2O_2 (498.51)


[2364] [M-H]^− = 497

[2365] Rf = 1.84 min (method 5)

Example 192
Pyrimidine-5-carboxylic acid (3-hydroxy-1-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2366]

192a) 1-amino-3-hydroxy-cyclopentanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[2367] 1-tert-butoxycarbonylaminoc-3-hydroxy-cyclopentanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine were reacted analogously to method 191a).

[2368] Yield: 40% of theory (as trifluoroacetate)

[2369] mass spectroscopy [M+H]^+ = 395

[2370] Rf = 1.62 min method 6

192b) pyrimidine-5-carboxylic acid (3-hydroxy-1-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[2371] The target compound was prepared from 1-amino-3-hydroxy-cyclopentanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide and pyrimidine-5-carboxylic acid analogously to method 191a).

[2372] Yield: 55% of theory

[2373] C_{22}H_{25}FN_2O_2 (500.48)


[2375] Rf = 1.66 min (method 5)

Example 193
Pyrimidine-5-carboxylic acid (3-oxo-1-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide

[2376]

10 mg pyrimidine-5-carboxylic acid (3-hydroxy-1-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopentyl)-amide were mixed with 8 mg Dess-Martin-Periodinane reagent and stirred for 1 hour at ambient temperature. Then the reaction mixture was purified by chromatography (RP with eluting gradient, eluent: acetonitrile and water with 0.1% trifluoroacetic acid).

[2377] Yield: 90% of theory

[2378] C_{22}H_{25}FN_2O_2 (498.46)


[2380] [M-H]^− = 497

[2381] Rf = 1.73 min (method 5)

Example 194
Pyrimidine-5-carboxylic acid (1-oxo-3-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydro-1lambdastar*4*-thiophen-3-yl)-amide
194a) 3-amino-1-oxo-tetrahydrothiophene-3-carboxylic acid [5-(2-trifluoromethyl-phenyl-aminoo)-pyridin-2-yl methyl]-amide
[2384] The product was obtained from 3-tert-butoxycarboxaldehyde-1-oxo-tetrahydrothiophene-3-carboxylic acid and
(6-aminoethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amidine analogously to method 191a.
[2385] Yield: 96% of theory (as trifluoroacetate)
[2387] Rf=1.62 min method 6

194b) pyrimidine-5-carboxylic acid (1-oxo-3-[[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-
carbamoyl]-tetrahydrothiophen-3-yl)-amide
[2389] Yield: 58% of theory
[2390] C₃₉H₂₆F₃N₅O₆S (518.52)
[2392] [M+H]⁺=519
[2393] Rf=1.66 min (method 5)

Example 195
4-[[6-[[1-{pyrimidine-5-carbonyl}-amino]-cyclopropene carbonyl]-amino]-methyl]-pyridin-3-
ylaminoo]-3-trifluoromethyl-benzoic acid

[2394]

[2395] 469 (0.91 mmol) methyl 4-[[6-[[1-{pyrimidine-5-
carbonyl}-amino]-cyclopropene carbonyl]-amino]-methyl]-
pyridin-3-ylamine]-3-trifluoromethyl benzooate were stirred overnight in 5 mL of 1N aqueous sodium hydroxide solution and 20 mL of ethanol at ambient temperature. Then the reaction mixture was neutralised with 1N aqueous hydrochloric acid and evaporated to dryness. The residue was dissolved in methanol and DMF, filtered and then chromatographed (RP with eluting gradient, eluent: acetonitrile and water with 0.2% trifluoroacetic acid).

[2396] Yield: 69% of theory
[2397] C₃₉H₂₄F₃N₅O₆S (500.44)
[2399] [M–H]⁻=499

Example 196
Methyl 4-[[6-[[1-{pyrimidine-5-carbonyl}-amino]-
cyclopropene carbonyl]-amino]-methyl]-pyridin-3-
ylaminoo]-3-trifluoromethyl-benzoate

[2400]

196a) methyl 4-(6-cyano-pyridin-3-ylamino)-3-trifluoromethyl-benzoate
[2401] 1190 mg (3.48 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile, 221 µL (1.6
mmol) triethylamine and 97 mg (0.13 mmol) Pd(dppf)Cl₂ in 10 mL of methanole and 2 mL DMF were heated to 50°C in an autoclave under a carbon monoxide pressure of 5 bar for 60 hours. After removal of the solvents by distillation the residue was dissolved in acetonitrile and methanol and filtered. The filtrate was then evaporated down and purified by chromatography (1st column: RP with eluting gradient, eluent: acetonitrile and water with 0.1% trifluoroacetic acid; 2nd column: silica gel, eluant: dichloromethane).
[2402] Yield: 78% of theory

196b) methyl 4-(6-aminomethyl-pyridin-3-ylamino)-
3-trifluoromethyl-benzoate
[2404] 860 mg (2.7 mmol) methyl 4-(6-cyano-pyridin-3-
ylaminoo)-3-trifluoromethyl-benzoate in 30 mL methanolic ammonia were hydrogenated at ambient temperature under a hydrogen pressure of 50 psi in the presence of 100 mg Raney nickel. The catalyst was filtered off and the filtrate was freed from solvent.
[2405] Yield: 76% of theory

196c) methyl 4-[[6-[[1-{pyrimidine-5-carbonyl}-
amino]-cyclopropene carbonyl]-amino]-methyl]-
pyridin-3-ylaminoo]-3-trifluoromethyl-benzoate
[2407] 191 mg (0.92 mmol) 1-[pyrimidine-5-carbonyl-
amino]-cyclopropene carbonylic acid, 305 mg (0.95 mmol) TBTU and 203 µL (1.85 mmol) N-methylmorpholine in 3 mL DMF were stirred for 5 minutes at ambient temperature. The solution was combined with 300 mg (0.92 mmol) methyl 4-(6-aminomethyl-pyridin-3-ylamino)-3-trifluoromethyl-benzoate and left to stand over the weekend. Then the reaction mixture was purified by chromatography (RP with eluting gradient, eluent: acetonitrile and water with 0.2% trifluoroacetic acid).
[2408] Yield: 62% of theory
[2409] C₃₉H₂₄F₃N₅O₆S (514.46)
[2411] Rf=1.73 min (method 12)

Example 197
Pyrimidine-5-carboxylic acid (1-[[5-(4-cyano-2-
trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-
carbamoyl]-cyclopropyl)-amidine

[2412]

[2413] 55 mg (0.18 mmol) pyrimidine-5-carboxylic acid
[1-[5-amino-pyridin-2-ylmethyl]-carbamoyl]-cyclopro-
pyl]-amidine, 33 mg (0.18 mmol) 4-fluoro-3-(trifluoromethyl)
benzonitrile and 42 mg (0.35 mmol) potassium-tert-butoxide in
5 mL DMSO were stirred for 1 h at 50°C. The reaction mixture was filtered and the filtrate was purified by chroma-
toography (RP with eluting gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

Yield: 23% of theory

C\textsubscript{24}H\textsubscript{18}F\textsubscript{6}N\textsubscript{2}O\textsubscript{2} (481.44)

Mass spectrum (ESI): [M+H]\textsuperscript{+} = 482

[M-H]\textsuperscript{-} = 480

R\textsubscript{f} = 1.69 min (method 12)

Example 198
Pyrimidine-5-carboxylic acid (1-[(5-(4-carbamoyl)-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-amide

A solution of 50 mg (0.10 mmol) 4-[(1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxyl]-amino)-methyl]-pyridin-3-ylamino]-3-trifluoromethyl-benzoic acid, 53 mg (0.10 mmol) TBTU and 12 μL (0.11 mmol) N-methylmorpholine in 0.5 mL DMF was stirred for 3 minutes at ambient temperature, then combined with 17 μL (0.11 mmol) 2,4-dimethoxybenzylamine, stirred for a further 10 minutes and left to stand overnight. In order to cleave the benzyl group the mixture was combined with 10 mL dichloromethane and 10 mL trifluoroacetic acid, left to stand overnight and evaporated to dryness. The residue was filtered and then purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

Yield: 6% of theory

C\textsubscript{24}H\textsubscript{19}F\textsubscript{5}N\textsubscript{2}O\textsubscript{2} (499.45)

Mass spectrum (ESI): [M+H]\textsuperscript{+} = 500

[M-H]\textsuperscript{-} = 498

Example 199
Pyrimidine-5-carboxylic acid [1-[(4-methoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

Obtained from 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxylic acid and (4-aminomethyl-phenyl)-(4-methoxy-phenyl)-amine analogously to method 191a).

Yield: 37% of theory

C\textsubscript{24}H\textsubscript{21}N\textsubscript{2}O\textsubscript{3} (417.47)

Example 200
Pyrimidine-5-carboxylic acid (1-[(5-(2-chloro-6-fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Coupling of 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)(2-chloro-6-fluoro-phenyl)-amine trifluoroacetate with TBTU analogously to method 191a).

C\textsubscript{24}H\textsubscript{18}ClF\textsubscript{6}N\textsubscript{2}O\textsubscript{2} (440.86)

Mass spectrum (ESI): [M+H]\textsuperscript{+} = 441

[M-H]\textsuperscript{-} = 439

R\textsubscript{f} = 1.38 min (method 2)

Example 201
Pyrimidine-5-carboxylic acid [1-[(4-(4-methoxy-2-methyl-phenylamino)-benzylcarbamoyl]-cyclopropyl]-amide

Prepared from 1-[(pyrimidine-5-carboxyl)-amino]-cyclopropanecarboxylic acid and (4-aminomethyl-phenyl)-(4-methoxy-2-methyl-phenyl)-amine according to method 191a).

C\textsubscript{24}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2} (431.49)

Mass spectrum (ESI): [M+H]\textsuperscript{+} = 432

[M+H]\textsuperscript{+} = 430

R\textsubscript{f} = 1.97 min (method 12)
[2445] 73 mg (0.35 mmol) of 1-[(pyrimidine-5-carbonyl)amino]-cyclopropanecarbonylic acid and 57 mg (0.35 mmol) CDI were stirred for 30 minutes at 50°C in 5 mL DMF. 90 mg (0.35 mmol) (4-aminoethyl-phenyl)-(4-methoxy-2-methyl-phenyl)methyl amine and 101 µL diisopropylethylamine were added at ambient temperature and the mixture was left overnight with stirring. The solvent was distilled off and the residue was dissolved in methanol and purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

[2446] Yield: 19% of theory

[2447] C₂₆H₂₆N₂O₃ (445.52)


[2449] Rₚ = 2.16 min (method 12)

Example 203

Pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl)-amide

Example 203b

(S)-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl)-amide

[2458]

Example 204

Pyrimidine-5-carboxylic acid-(1-[[5-(4-isopropyl-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 203a

(R)-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl]-cyclopropyl)-amide

[2455]

Example 205

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-hydroxy-nicotinamide

[2465]
[2466] Prepared from intermediate C1 and 5-hydroxynicotinic acid according to AAV1

[2467] \( C_{21}H_{12}ClF_3N_2O_5 \) (505.88)

[2468] \( R_f = 1.74 \) minutes (method 13)

Example 206
6-amino-N-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl-nicotinamide

[2469]

[2470] Prepared from intermediate C1 and 6-aminonicotinic acid according to AAV1

[2471] \( C_{21}H_{12}ClF_3N_2O_5 \) (505.90)

[2472] \( R_f = 1.60 \) minutes (method 13)

Example 207
N-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-2-hydroxy-isonicotinamide

[2473]

[2474] Prepared from intermediate C1 and 2-hydroxyisonicotinic acid according to AAV1

[2475] \( C_{21}H_{12}ClF_3N_2O_5 \) (505.88)

[2476] \( R_f = 1.69 \) minutes (method 13)

Example 208
2,6-dihydroxy-pyrimidine-4-carboxylic acid(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2477]

[2478] Prepared from intermediate C1 and 2,6-dihydroxy-pyrimidine-4-carboxylic acid according to AAV1

[2479] \( C_{21}H_{12}ClF_3N_2O_5 \) (522.87)

[2480] \( R_f = 1.70 \) minutes (method 13)

Example 209
Pyridazine-4-carboxylic acid(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2481]

[2482] Prepared from intermediate C1 and pyridazine-4-carboxylic acid according to AAV1

[2483] \( C_{21}H_{12}ClF_3N_2O_5 \) (522.87)

[2484] \( R_f = 1.76 \) minutes (method 13)

Example 210
2-dimethylamino-pyrimidine-5-carboxylic acid(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2485]

[2486] Prepared from intermediate C1 and 2-dimethylamino-pyrimidine-5-carboxylic acid according to AAV1

[2487] \( C_{21}H_{12}ClF_3N_2O_5 \) (533.94)

[2488] \( R_f = 1.94 \) minutes (method 13)

Example 211
6-hydroxy-pyridine-2-carboxylic acid(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2489]
[2490] Prepared from intermediate C1 and 6-hydroxy-pyridine-2-carboxylic acid according to AAV1

[2491] C$_2$H$_6$CF$_2$N$_2$O$_2$ (505.88)

[2492] R$_f$=1.75 minutes method 13

Example 212
Pyrimidine-5-carboxylic acid-(1-[1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2493]

[2494] Prepared from intermediates A4 and B1 according to AAV1

[2495] C$_3$H$_8$F$_3$N$_2$O$_2$ (463.45)

[2496] R$_f$=1.81 minutes method 2

[2497] The racemate was separated into the enantiomers by chiral HPLC (column: Daicel AD-H 250×20 mm; 5 µm; 25° C.; eluent CO$_2$/isopropanol (40.2% diethylamine) 80:20; flow: 10 mL/min):

Example 212a
(R)-pyrimidine-5-carboxylic acid-(1-[1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2498]

[2499] R$_f$=2.75 minutes

Example 212b
(S)-pyrimidine-5-carboxylic acid-(1-[1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2500]

[2501] R$_f$=5.12 minutes

Example 213
Pyrimidine-5-carboxylic acid-(1-[1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2502]

[2503] Prepared from intermediates A5 and B1 according to AAV1

[2504] C$_3$H$_8$BrF$_3$N$_2$O$_2$ (567.34)

[2505] R$_f$=2.34 minutes (method 2)

[2506] The racemate was separated into the enantiomers by chiral HPLC:

Example 213a
(R)-pyrimidine-5-carboxylic acid-(1-[1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2507]

[2508] Analytical chiral HPLC (column: Daicel AD-H; 250×4.6 mm; 5 µm; 25° C.; eluent CO$_2$/isopropanol 80:20; flow: 4 mL/min)

[2509] R$_f$=1.78 minutes

Example 213b
(S)-pyrimidine-5-carboxylic acid-(1-[1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]ethylcarbamoyl]-cyclopropyl)-amide

[2510]
[2511] Analytical chiral HPLC (column: Daicel AD-H; 250x4.6 mm; 5 μm; 25°C; eluant CO2/isopropanol 80:20; flow: 4 mL/min)

[2512] Rf=2.55 minutes

Example 214
(S)-5-amino-N-(3-[[5-(4-fluoro-2-trifluoromethyl)phenylamino]-pyridin-2-yl-methyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2513]

[2514] Prepared from intermediates A6 and B2 according to AAV1

[2515] C_{25}H_{23}F_{3}N_{6}O_{3} (517.48)

[2516] Rf=3.33 minutes (method 7)

Example 215
6-oxo-5,6-dihydro-pyrazidine-4-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl)phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2517]

[2518] Prepared from intermediate C2 and 6-oxo-5,6-dihydro-pyrazidine-4-carboxylic acid according to AAV1

[2519] C_{25}H_{23}F_{3}N_{6}O_{3} (490.42)

[2520] Rf=2.80 minutes (method 7)

Example 216
(S)-pyridine-5-carboxylic acid-(3-[[3-chloro-5-(4-fluoro-2-trifluoromethyl)phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2521]

[2522] Prepared from intermediates A8 and B3 according to AAV1

[2523] C_{27}H_{19}F_{3}ClN_{4}O_{3} (538.89)

[2524] Rf=3.86 minutes (method 7)

Example 217
5-amino-N-(1-[[5-(4-chloro-2-trifluoromethyl)phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[2525]

[2526] Prepared from intermediate C1 and 5-aminonicotinic acid according to AAV1

[2527] C_{27}H_{19}F_{3}ClN_{4}O_{3} (504.90)

[2528] Rf=2.01 minutes (method 2)

Example 218
5-amino-N-(1-[[5-chloro-5-(4-fluoro-2-trifluoromethyl)phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[2529]

[2530] Prepared from intermediates A8 and B4 according to AAV1

[2531] C_{27}H_{19}F_{3}ClN_{4}O_{3} (522.89)

[2532] Rf=3.21 minutes (method 7)

Example 219
(S)-5-amino-N(3-[[3-chloro-5-(4-fluoro-2-trifluoromethyl)phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2533]
[2534] Prepared from intermediates A8 and B2 according to AAV1
[2535] C_{12}H_{13}ClF_{3}N_{4}O_{3} (552.91)
[2536] R_f=3.22 minutes (method 7)

Example 220
(S)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid-(3-[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)amide

[2537]

[2538] Prepared from intermediates A8 and B5 according to AAV1
[2539] C_{12}H_{13}ClF_{3}N_{4}O_{3} (577.92)
[2540] R_f=3.62 minutes (method 7)

Example 221
1-methyl-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-(1-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)amide

[2541]

[2542] Prepared from intermediate C2 and 1-methyl-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1
[2543] C_{12}H_{13}F_{3}N_{4}O_{3} (504.44)
[2544] R_f=2.95 minutes (method 7)

Example 222
(S)-5-amino-N-[3-(5-[4-bromo-2-trifluoromethyl-phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2545]

[2546] Prepared from intermediates A9 and B2 according to AAV1
[2547] C_{12}H_{13}BrF_{3}N_{4}O_{3} (579.37)
[2548] R_f=1.88 minutes (method 2)

Example 223
(S)-pyrimidine-5-carboxylic acid-(3-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)amide

[2549]

[2550] Prepared from intermediates A9 and B3 according to AAV1
[2551] C_{12}H_{13}BrF_{3}N_{4}O_{3} (565.35)
[2552] R_f=1.74 minutes (method 2)

Example 224
(S)-2-methylamino-pyrimidine-5-carboxylic acid-(3-[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)amide

[2553]

[2554] Prepared from intermediate C3 and 2-methylamino-pyrimidine-5-carboxylic acid according to AAV1
[2555] C_{12}H_{13}ClF_{3}N_{4}O_{3} (567.93)
[2556] R_f=3.89 minutes (method 7)

Example 225
(S)-3-(3,3,3-trifluoro-propionylamino)-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[2557]
[2558] Prepared from intermediate C3 and 3,3,3-trifluoropropionic acid according to AAV1
[2559] C₃H₂ClF₃N₂O₃ (542.84)
[2560] Rₚ=4.18 minutes (method 7)

Example 226
(S)-5-amino-N-(3-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2561]

[2562] Prepared from intermediates A3 and B2 according to AAV1
[2563] C₃H₂ClF₃N₂O₃ (534.92)
[2564] Rₚ=1.57 minutes (method 2)

Example 227
6-methylamino-pyridazine-4-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2565]

[2566] Prepared from intermediate C2 and 6-methylamino-pyridazine-4-carboxylic acid according to AAV1
[2567] C₃H₂ClF₃N₂O₃ (503.46)
[2568] Rₚ=1.55 minutes (method 5)

Example 228
(S)-pyrimidine-5-carboxylic acid-(3-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2569]

[2570] Prepared from intermediates A3 and B3 according to AAV1
[2571] C₃H₂ClF₃N₂O₃ (520.90)
[2572] Rₚ=1.74 minutes (method 2)

Example 229
(S)-5-amino-N-(3-[[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2573]

[2574] Prepared from intermediates A10 and B2 according to AAV1
[2575] C₃H₂ClF₃N₂O₃ (534.92)
[2576] Rₚ=3.19 minutes (method 7)

Example 230
(S)-2-methoxy-pyrimidine-5-carboxylic acid-(3-[[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2577]

[2578] Prepared from intermediate C3 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1
[2579] C₃H₂ClF₃N₂O₃ (568.91)
[2580] Rₚ=4.01 minutes (method 7)

Example 231
(S)-5-amino-N-[3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

[2581]
[2582] Prepared from intermediates A11 and B2 according to AAV1
[2583] \( C_{25}H_{23}F_3N_4O_5 \) (535.47)
[2584] \( R_\gamma = 1.23 \) minutes (method 2)

Example 232
2-methyl-pyrimidine-5-carboxylic acid-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2585]

[2586] Prepared from intermediate C2 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1
[2587] \( C_{25}H_{23}F_3N_4O_5 \) (488.44)
[2588] \( R_\gamma = 1.94 \) minutes (method 2)

Example 233
2-methoxy-pyrimidine-5-carboxylic acid-(1-[(5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2589]

[2590] Prepared from intermediate C2 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1
[2591] \( C_{25}H_{23}F_3N_4O_5 \) (504.44)
[2592] \( R_\gamma = 2.00 \) minutes (method 2)

Example 234
N-(1-[(5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-hydroxy-nicotinamide

[2593]

[2594] Prepared from intermediate C4 and 6-hydroxy-nicotinic acid according to AAV1
[2595] \( C_{25}H_{23}BrF_3N_4O_5 \) (550.33)
[2596] \( R_\gamma = 1.79 \) minutes (method 2)

Example 235
N-(1-[(5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-methoxy-nicotinamide

[2597]

[2598] Prepared from intermediate C4 and 6-methoxy-nicotinic acid according to AAV1
[2599] \( C_{25}H_{23}BrF_3N_4O_5 \) (564.36)
[2600] \( R_\gamma = 1.84 \) minutes (method 2)

Example 236
(S)-5-amino-N-3-(3-fluoro-4-(2-trifluoromethyl-phenylamino)-benzyl]-carbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

[2601]

[2602] Prepared from intermediates A12 and B2 according to AAV1
[2603] \( C_{25}H_{23}F_3N_4O_5 \) (517.48)
[2604] \( R_\gamma = 3.07 \) minutes (method 3)

Example 237
(S)-5-amino-N-(3-[(3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]carbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

[2605]
[2606] Prepared from intermediate C5 and 5-aminonicotinic acid according to AAV1

[2607] C₆H₄Cl₂N₂O₂ (552.91)

[2608] Rᵣ=3.28 minutes (method 3)

Example 238

(S)-2-methoxy-pyrimidine-5-carboxylic acid-(3-[(3-fluoro-5-((4-fluoro-2-trifluoromethyl)-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2609]

[2610] Prepared from intermediate C6 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

[2611] C₆H₄Cl₂N₂O₂ (552.96)

[2612] Rᵣ=3.62 minutes (method 3)

Example 239

N-([15-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-6-hydroxy-nicotinamide

[2613]

[2614] Prepared from intermediate Cl and 6-hydroxy-nicotinic acid according to AAV1

[2615] C₆H₄Cl₂N₂O₂ (505.88)

[2616] Rᵣ=1.71 minutes (method 2)

Example 240

N-([15-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-6-methoxy-nicotinamide

[2617]

[2618] Prepared from intermediate Cl and 6-methoxy-nicotinic acid according to AAV1

[2619] C₆H₄Cl₂N₂O₂ (519.91)

[2620] Rᵣ=1.75 minutes (method 2)

Example 241

(S)-2-methylamino-pyrimidine-5-carboxylic acid-(3-[[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2621]

[2622] Prepared from intermediate C5 and 2-methylamino-pyrimidine-5-carboxylic acid according to AAV1

[2623] C₆H₄Cl₂N₂O₂ (567.93)

[2624] Rᵣ=4.64 minutes (method 3)

Example 242

(S)-pyrimidine-5-carboxylic acid-(3-[[15-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2625]

[2626] Prepared from intermediates A15 and B3 according to AAV1

[2627] C₆H₄Cl₂N₂O₂ (538.89)

[2628] Rᵣ=2.15 minutes (method 2)

Example 243

N-([15-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl)-cyclopropyl)-5-hydroxy-nicotinamide

[2629]
Example 244

6-amino-N-(1-[[3-(4-fluoro-2-trifluoromethyl-phenoxy)pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

Example 245

2-isopropyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 246

2-trifluoromethyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 247

2-ethylamino-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 248

2-piperidin-1-yl-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 249

5-acetylaminoo-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide
[2657] Prepared from intermediate C2 and 5-acetylaminonicotinic acid according to AAV1

[2658] C₈H₄F₄N₂O₂ (530.48) mass spectroscopy (ESI): [M+H]+=531

Example 250
2-pyridolin-1-yl-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2659] 

[2660] Prepared from intermediate C2 and 2-pyridolin-1-yl-pyrimidine-5-carboxylic acid according to AAV1

[2661] C₂₈H₂₅F₄N₂O₂ (543.52)

[2662] mass spectroscopy (ESI): [M+H]+=544

Example 251
6-acetylaminopicolin-1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[2663] 

[2664] Prepared from intermediate C2 and 6-acetylaminonicotinic acid according to AAV1

[2665] C₈H₄F₄N₂O₂ (530.48)

[2666] mass spectroscopy (ESI): [M+H]+=531

Example 252
6-dimethylaminopicolin-4-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2667] 

[2668] Prepared from intermediate C2 and 6-dimethylaminopicolin-4-carboxylic acid according to AAV1

[2669] C₂₈H₂₅F₄N₂O₂ (517.48)

[2670] mass spectroscopy (ESI): [M+H]+=518

Example 253
6-chloro-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[2671] 

[2672] Prepared from intermediate C2 and 6-chloronicotinic acid according to AAV1

[2673] C₂₈H₂₅ClF₄N₂O₂ (507.87)

[2674] mass spectroscopy (ESI): [M+H]+=508

Example 254
N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-trifluorometyl-nicotinamide

[2675] 

[2676] Prepared from intermediate C2 and 6-trifluoroethyl-nicotinic acid according to AAV1

[2677] C₂₈H₂₅F₄N₂O₂ (541.43)

[2678] mass spectroscopy (ESI): [M+H]+=542

Example 255
1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2679] 

[2680] Prepared from intermediate C2 and 1H-pyrolo[3,2-b]pyridine-6-carboxylic acid according to AAV1
[2681] C_{22}H_{19}F_{2}N_{5}O_{2} (512.47)
[2682] mass spectroscopy (ESI): [M+H]⁺ = 513
Example 256
6-cyano-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenoxyimino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[2683]

[2684] Prepared from intermediate C2 and 6-cyano-nicotinic acid according to AAV1
[2685] C_{21}H_{18}F_{2}N_{4}O_{2} (498.44)
[2686] mass spectroscopy (ESI): [M+H]⁺ = 499
Example 257
2-acetylamino-thiazole-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[2687]

[2688] Prepared from intermediate C2 and 2-acetylamino-thiazole-5-carboxylic acid according to AAV1
[2689] C_{21}H_{18}F_{2}N_{4}O_{2}S (536.51)
[2690] mass spectroscopy (ESI): [M+H]⁺ = 537
Example 258
(S)-2-methoxy-pyrimidine-5-carboxylic acid-(3-[[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2691]

[2692] Prepared from intermediate C3 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1
[2693] C_{22}H_{21}ClF_{2}N_{5}O_{2} (568.91)
[2694] R_f = 3.59 minutes (method 3)
Example 259
(S)-N-(3-[[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-5-methylnicotinamide

[2695]

[2696] Prepared from intermediate C3 and 5-methylnicotinic acid according to AAV1
[2697] C_{22}H_{21}ClF_{2}N_{5}O_{2} (568.94)
[2698] R_f = 3.59 minutes (method 3)
Example 260
(S)-N-(3-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-5-methylnicotinamide

[2699]

[2700] Prepared from intermediate C6 and 5-methylnicotinic acid according to AAV1
[2701] C_{22}H_{21}ClF_{2}N_{5}O_{2} (550.49)
[2702] R_f = 3.81 minutes (method 3)
Example 261
(S)-3-(3,3,3-trifluoropropionylamino)-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

[2703]

[2704] Prepared from intermediate C5 and 3,3,3-trifluoropropionic acid according to AAV1
[2705] C_{22}H_{21}ClF_{2}N_{5}O_{2} (542.84)
[2706] R_f = 4.11 minutes (method 3)
Example 262
6-amino-pyridazine-4-carboxylic acid-(1-\{5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-cyclopropyl-amide

[2707]

[2708] Prepared from intermediate C2 and 6-amino-pyridazine-4-carboxylic acid according to AAV1

[2709] C_{23}H_{13}F_{13}N_{5}O_{2} (589.43)

[2710] R_f=1.81 minutes (method 6)

Example 263
N-(1-\{5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-cyclopropyl-6-dimethylenamino-nicotinamide

[2711]

[2712] Prepared from intermediate C1 and 6-dimethylamino-nicotinic acid according to AAV1

[2713] C_{23}H_{13}ClF_{13}N_{5}O_{2} (532.95)

[2714] R_f=1.90 minutes (method 2)

Example 264
1-methyl-1H-benzimidazole-5-carboxylic acid-(1-\{5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-cyclopropyl-amide

[2715]

[2716] Prepared from intermediate C1 and 1-methyl-1H-benzimidazole-5-carboxylic acid according to AAV1

[2717] C_{23}H_{13}ClF_{13}N_{5}O_{2} (542.95)

[2718] R_f=1.72 minutes (method 2)

Example 265
2-amino-1H-benzimidazole-5-carboxylic acid-(1-\{5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-cyclopropyl-amide

[2719]

[2720] Prepared from intermediate C1 and 2-amino-1H-benzimidazole-5-carboxylic acid according to AAV1

[2721] C_{23}H_{13}ClF_{13}N_{5}O_{2} (543.93)


Example 266
1H-benzimidazole-5-carboxylic acid-(1-\{5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-cyclopropyl-amide

[2723]

[2724] Prepared from intermediate C1 and 1H-benzimidazole-5-carboxylic acid according to AAV1

[2725] C_{23}H_{13}ClF_{13}N_{5}O_{2} (528.92)

[2726] R_f=1.79 minutes (method 2)

Example 267
(S)-2-methyl-pyrimidine-5-carboxylic acid-(3-\{3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl)-tetrahydrofuran-3-yl-amide

[2727]
[2730] \( R_t = 3.91 \) minutes (method 3)

Example 268

N-(1-\{5-(4-bromo-2-trifluoromethyl)-phenylamino\}-pyridin-2-y1methyl\}-carbamoyl\}-cyclopropyl\}-6-dimethylamino-nicotinamide

[2731]

[2732] Prepared from intermediate C4 and 6-dimethylamino-nicotinic acid according to AAV1

[2733] \( C_{22}H_{17}BrF_{2}N_{3}O_5 \) (577.40)

[2734] \( R_t = 2.09 \) minutes (method 2)

Example 269

(S)-N-\{3-Chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl\}-carbamoyl\}-4-ethyl-3-methyl-4,5-dihydro-1H-imidazol-2-one

[2735]

[2736] Prepared from intermediate C3 and 5-methylamino-nicotinic acid according to AAV1

[2737] \( C_{22}H_{17}ClF_{2}N_{3}O_5 \) (566.94)

[2738] \( R_t = 3.66 \) minutes (method 3)

Example 270

N-(1-\{5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}-carbamoyl\}-cyclopropyl\}-5-methylamino-nicotinamide

[2739]

[2740] Prepared from intermediate C2 and 5-methylamino-nicotinic acid according to AAV1

[2741] \( C_{22}H_{17}F_{2}N_{3}O_5 \) (502.47)

[2742] \( R_t = 1.97 \) minutes (method 2)

Example 271

(S)-5-amino-N-(3-[3-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-tetrahydrofurran-3-yl)-nicotinamide

[2743]

[2744] Prepared from intermediates A15 and B2 according to AAV1

[2745] \( C_{22}H_{17}ClF_{2}N_{3}O_5 \) (552.91)

[2746] \( R_t = 2.48 \) minutes (method 2)

Example 272

N-(1-\{3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl\}[carbamoyl]-cyclopropyl\}-5-methylamino-nicotinamide

[2747]

[2748] Prepared from intermediate C7 and 5-methylamino-nicotinic acid according to AAV1

[2749] \( C_{22}H_{17}F_{2}N_{3}O_5 \) (520.46)

[2750] \( R_t = 1.87 \) minutes (method 2)

Example 273

5-amino-N-\{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-oxetan-3-yl\}-nicotinamide

[2751]
Prepared from intermediate C8 and 5-aminonicotinic acid according to AAV1

$\text{C}_9\text{H}_8\text{F}_5\text{N}_2\text{O}_3$ (485.46)

$R_t=2.17$ minutes (method 6)

Example 274

(S)-2-methyl-pyridine-5-carboxylic acid-[3-(4-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates A15 and B6 according to AAV1

$\text{C}_9\text{H}_8\text{ClF}_4\text{N}_2\text{O}_3$ (567.93)

$R_t=2.16$ minutes (method 2)

Example 277

(S)-2-methyl-pyridine-5-carboxylic acid-3-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediate C9 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$\text{C}_9\text{H}_8\text{F}_5\text{N}_2\text{O}_3$ (535.47)

$R_t=3.61$ minutes (method 3)

Example 275

5-acetamino-N-1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl-nicotinamide

Prepared from intermediates A15 and B7 according to AAV1

$\text{C}_9\text{H}_8\text{ClF}_4\text{N}_2\text{O}_3$ (552.91)

$R_t=2.30$ minutes (method 2)

Example 278

(S)-pyridine-5-carboxylic acid-3-[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediate Cl and 5-acetamino-nicotinic acid according to AAV1

$\text{C}_9\text{H}_8\text{ClF}_4\text{N}_2\text{O}_3$ (546.93)

$R_t=1.78$ minutes (method 2)

Example 276

(S)-2-methylamino-pyrimidine-5-carboxylic acid-3-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediates A18 and B3 according to AAV1

$\text{C}_9\text{H}_8\text{ClF}_4\text{N}_2\text{O}_3$ (555.34)

$R_t=2.36$ minutes (method 2)

Example 279

(S)-2-methyl-pyrimidine-5-carboxylic acid-3-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediates A15 and B6 according to AAV1

$\text{C}_9\text{H}_8\text{ClF}_4\text{N}_2\text{O}_3$ (567.93)

$R_t=2.16$ minutes (method 2)

Example 277

(S)-2-methyl-pyridine-5-carboxylic acid-3-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-tetrahydrofuran-3-yl)-amide
Example 280

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl] carbamoyl]-cyclopropyl)-5-methylamino-nicotinamide

Example 281

(S)-2-methylamino-pyrimidine-5-carboxylic acid-3-[[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl-amide

Example 282

(S)-2-methyl-pyrimidine-5-carboxylic acid-3-[[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl-amide

Example 284

6-oxo-1,6-dihydropyridazine-4-carboxylic acid-1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

Example 285

(S)-5-amino-N-3-[[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl-nicotinamide
Example 286
(S)-N-(3-[(3-chloro-5-(4-chloro-2-trifluoromethyl)phenylamino)pyridin-2-yl-methyl]-carbamoyl)-tetrahydrofuran-3-yl)-5-hydroxy-nicotinamide

Prepared from intermediates A6 and B7 according to AAV1

C_22H_{20}F_3N_5O_4 (570.35)

R_f = 2.52 minutes (method 2)

mass spectroscopy (ESI): [M+H]^+ = 570; [M−H]^− = 568

Example 287
(S)-pyrimidine-5-carboxylic acid-3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates A18 and B8 according to AAV1

C_{23}H_{24}F_3N_5O_3 (532.50)

R_f = 2.44 minutes (method 2)

Example 288
(S)-2-methyl-pyrimidine-5-carboxylic acid-3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates A6 and B3 according to AAV1

C_{23}H_{20}F_3N_5O_3 (503.45)

R_f = 2.43 minutes (method 2)

Example 289
(S)-2-methylamino-pyrimidine-5-carboxylic acid-3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates A6 and B6 according to AAV1

C_{22}H_{20}F_3N_5O_4 (517.48)

R_f = 2.64 minutes (method 2)

Example 290
(S)-5-amino-N-[3-[2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

Prepared from intermediate C11 and 5-aminonicotinic acid according to AAV1

C_{23}H_{20}F_3N_5O_3 (535.47)

R_f = 1.63 minutes (method 7)

Example 291
(S)-2-methyl-pyrimidine-5-carboxylic acid-3-[2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediate C11 and 5-aminonicotinic acid according to AAV1
[2825] Prepared from intermediate C11 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1
[2826] C₂₃H₂₂F₆N₂O₅ (535.47)
[2827] Rᵣ=1.83 minutes (method 7)

Example 292
(S)-2-methyl-pyrimidine-5-carboxylic acid-(3-[[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2828]

[2829] Prepared from intermediates A10 and B7 according to AAV1
[2830] C₂₃H₂₃ClF₆N₂O₅ (534.92)
[2831] Rᵣ=1.78 minutes (method 7)

Example 293
(S)-6-amino-N-(3-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2832]

[2833] Prepared from intermediates A15 and B9 according to AAV1
[2834] C₂₃H₂₂F₆ClN₂O₅ (552.91)
[2835] Rᵣ=2.14 minutes (method 2)

Example 294
2-methyl-pyrimidine-5-carboxylic acid-[[1-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzyl]-carbamoyl]-cyclopropyl]-amide

[2836]

[2837] Prepared from intermediate C12 and 2-methylpyrimidine-5-carboxylic acid according to AAV1
[2838] C₂₃H₂₂F₆N₂O₅ (487.45)
[2839] Rᵣ=1.91 minutes (method 7)

Example 295
Pyrimidine-5-carboxylic acid-[[1-[[5-(2-cyano-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

[2840]

[2841] Prepared from intermediates A20 and B1 according to AAV1
[2842] C₂₃H₂₄FN₂O₂ (431.43)
[2843] Rᵣ=1.62 minutes (method 2)

Example 296
Pyrimidine-5-carboxylic acid-[[1-[4-(2-cyano-phenylamino)-2-fluoro-benzyl]-carbamoyl]-cyclopropyl]-amide

[2844]

[2845] Prepared from intermediates A30 and B1 according to AAV1
[2846] C₂₃H₂₄FN₂O₂ (430.44)
[2847] Rᵣ=1.88 minutes (method 2)

Example 297
(S)-6-amino-N-(3-[[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[2848]
Prepared from intermediates A18 and B9 according to AAV1

C\textsubscript{3}H\textsubscript{4}ClF\textsubscript{3}N\textsubscript{2}O\textsubscript{3} (569.37)

R\textsubscript{f}=2.46 minutes (method 2)

Example 298
2-methyl-pyrimidine-5-carboxylic acid-(1-[[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino) pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Prepared from intermediate C14 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

C\textsubscript{2}H\textsubscript{3}F\textsubscript{2}N\textsubscript{2}O\textsubscript{4} (533.48)

R\textsubscript{f}=2.61 minutes (method 2)

Example 301
2-methyl-pyrimidine-5-carboxylic acid-(1-[[3-chloro-5-(2-trifluoromethyl-phenylamino) pyridin-2- ylmethyl]-carbamoyl]-cyclopropyl)-amide

Prepared from intermediate C13 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

C\textsubscript{3}H\textsubscript{5}F\textsubscript{6}N\textsubscript{2}O\textsubscript{3} (506.43)

R\textsubscript{f}=1.74 minutes (method 7)

Example 299
(S)-thiazole-5-carboxylic acid-[3-[[4-(4-fluoro-2 trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediate C15 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

C\textsubscript{7}H\textsubscript{3}F\textsubscript{5}N\textsubscript{2}O\textsubscript{4} (504.90)

R\textsubscript{f}=1.79 minutes (method 7)

Example 302
N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)- pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5methyl-nicotinamide

Prepared from intermediate C14 and thiazole-5-carboxylic acid according to AAV1

C\textsubscript{3}H\textsubscript{4}F\textsubscript{3}N\textsubscript{2}O\textsubscript{2} (508.49)

R\textsubscript{f}=2.43 minutes (method 2)

Example 300
(S)-2-methoxy-pyrimidine-5-carboxylic acid-[3-[[4-(4fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediate C2 and 5-methyl-nicotinic acid according to AAV1

C\textsubscript{3}H\textsubscript{4}F\textsubscript{3}N\textsubscript{2}O\textsubscript{2} (487.45)

R\textsubscript{f}=1.96 minutes (method 2)

Example 303
2-methyl-thiazole-5-carboxylic acid-(1-[[5-(4-fluoro-2 trifluoromethyl-phenylamino)-pyridin-2- ylmethyl]-carbamoyl]-cyclopropyl)-amide
Prepared from intermediate C2 and 2-methyl-thiazole-5-carboxylic acid according to AAV1

C₂H₁₇F₆N₂O₂S (493.48)

Rₜ=2.07 minutes (method 2)

Example 304

(S)-2-methylamino-pyrimidine-5-carboxylic acid-(3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediates A21 and B1 according to AAV1

C₂H₂₅F₆N₄O₂ (488.44)

Rₜ=1.81 minutes (method 2)

Example 307

(S)-2-methyl-pyrimidine-5-carboxylic acid-(3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

Prepared from intermediates A7 and B6 according to AAV1

C₂H₁₇F₆N₂O₃ (533.48)

Rₜ=1.88 minutes (method 2)

Example 305

(S)—N—[3-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-5-methylamino-nicotinamide

Prepared from intermediates A7 and B7 according to AAV1

C₂H₂₅F₆N₄O₃ (518.47)

Rₜ=2.32 minutes (method 2)

Example 308

(S)—N—[3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-5-methyl-nicotinamide

Prepared from intermediate C14 and 5-methylaminonicotinic acid according to AAV1

C₂H₂₃F₆N₂O₃ (531.51)

Rₜ=1.83 minutes (method 7)

Example 306

Pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Prepared from intermediates C14 and 5-methylnicotinic acid according to AAV1

C₂H₂₃F₆N₂O₃ (516.49)

Rₜ=2.45 minutes (method 2)

Example 309

(S)—6-amino-N—[3-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-nicotinamide
Prepared from intermediates C14 and 6-aminonicotinic acid according to AAV1
C$_2$H$_5$F$_3$N$_2$O$_5$ (517.48)
R$_f$ = 2.09 minutes (method 2)

Example 310
(S)-2-isopropyl-pyridine-5-carboxylic acid-[3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates C14 and 2-isopropyl-pyridine-5-carboxylic acid according to AAV1
C$_2$H$_5$F$_3$N$_2$O$_5$ (545.53)
R$_f$ = 2.60 minutes (method 2)

Example 311
(S)—N—C3-[5-[[4-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl]-5-methylamino-nicotinamide

Prepared from intermediates C16 and 5-methylamino-nicotinic acid according to AAV1
C$_2$H$_5$F$_3$N$_2$O$_5$ (532.50)
R$_f$ = 2.22 minutes (method 2)

Example 312
N—C5-[[5-[[4-chloro-2-trifluoromethyl-phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-6-methyl-nicotinamide

Prepared from intermediates C17 and 2-methoxy-pyridine-5-carboxylic acid according to AAV1
C$_2$H$_5$F$_3$N$_2$O$_5$ (568.81)
R$_f$ = 2.53 minutes (method 2)

Example 315
N—C5-[[5-[[4-bromo-2-trifluoromethyl-phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-6-methyl-nicotinamide
Prepared from intermediates C4 and 6-methyl-nicotinic acid according to AAV1

C₂₃H₂₉BrF₃N₂O₅ (548.36)

Rₚ=2.24 minutes (method 2)

Example 316

N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-methoxy-nicotinamide

Prepared from intermediates A22 and B9 according to AAV1

C₂₂H₂₁ClF₃N₂O₅ (533.94)

Rₚ=2.25 minutes (method 2)

Example 319

(S)-N-(3-[[5-(4-chloro-2-trifluoromethyl-phenylamino)3-fluoro-pyridin-2-yl-methyl]-carbamoyl]-tetrahydrofuran-3-yl)-5-methy lamino-nicotinamide

Prepared from intermediates C4 and 5-methoxy-nicotinic acid according to AAV1

C₂₃H₂₇BrF₃N₂O₅ (564.36)

Rₚ=2.34 minutes (method 2)

Example 317

(S)-2-methyl-pyrimidine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

Prepared from intermediates C17 and 5-methy lamino-nicotinic acid according to AAV1

C₂₂H₂₁ClF₃N₂O₅ (566.94)

Rₚ=2.21 minutes (method 2)

Example 320

(S)-5-amino-N-(3-[[3-fluoro-5-(2-trifluoromethyl phenylamino)pyridin-2-yl-methyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

Prepared from intermediates A22 and B7 according to AAV1

C₂₃H₂₉BrF₃N₂O₅ (533.94)

Rₚ=2.60 minutes (method 2)

Example 318

(S)-6-amino-N-{3-[4-(4-chloro-2-trifluoromethyl phenylamino)benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

Prepared from intermediates A23 and B2 according to AAV1

C₂₃H₂₉F₂N₂O₅ (518.47)

Rₚ=1.52 minutes (method 7)

Example 321

(S)-5-amino-N-{3-[4-(4-chloro-2-trifluoromethyl phenylamino)benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide
Prepared from intermediates A22 and B2 according to AAV1.

\[ \text{C}_2\text{H}_2\text{Cl}_2\text{N}_2\text{O}_3 (533.94) \]

R\(_f\)=2.36 minutes (method 2)

Example 322

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-
\[ \{4-(4-fluoro-2-trifluoromethyl-phenylamino)-
\text{benzy carbamoyl}\}-
\text{tetrahydrofuran-3-yl}\}-\text{amide} \]

Prepared from intermediates C14 and 6-oxo-1,6-
dihydro-pyridazine-4-carboxylic acid according to AAV1.

\[ \text{C}_2\text{H}_2\text{F}_2\text{N}_2\text{O}_3 (519.45) \]

R\(_f\)=2.39 minutes (method 2)

Example 323

(S)-2-methylamino-pyrimidine-5-carboxylic acid-
\[ \{3-
\text{[4-(4-chloro-2-trifluoromethyl-phenylamino)-
\text{benzy carbamoyl}]-}
\text{tetrahydrofuran-3-yl}\}-\text{amide} \]

Prepared from intermediates A22 and B6 according to AAV1.

\[ \text{C}_2\text{H}_2\text{Cl}_2\text{N}_2\text{O}_3 (548.95) \]

R\(_f\)=2.57 minutes (method 2)

Example 324

(S)-pyrimidine-5-carboxylic acid-\[\{3-(4-fluoro-2-
\text{trifluoromethyl-phenylamino)-3-methyl-
\text{pyridin-2-ylmethyl}-
\text{carbamoyl}\}-
\text{tetrahydrofuran-3-yl}\}-\text{amide} \]

Prepared from intermediates A21 and B3 according to AAV1.

\[ \text{C}_2\text{H}_2\text{F}_2\text{N}_2\text{O}_3 (518.47) \]

R\(_f\)=1.80 minutes (method 2)

Example 325

Pyrimidine-5-carboxylic acid-(1-\{5-(4-bromo-2-
\text{chloro-6-fluoro-phenylamino)-pyridin-2-ylmethyl}-
\text{carbamoyl}\}-
\text{cyclopropyl}\}-\text{amide} \]

Prepared from intermediates A24 and B1 according to AAV1.

\[ \text{C}_2\text{H}_2\text{BrClF}_2\text{N}_2\text{O}_2 (519.76) \]

R\(_f\)=2.01 minutes (method 2)

Example 326

Pyrimidine-5-carboxylic acid-(1-\{5-(2-bromo-6-
\text{fluoro-phenylamino)-pyridin-2-ylmethyl}-
\text{carbamoyl}\}-
\text{cyclopropyl}\}-\text{amide} \]

Prepared from intermediates A25 and B1 according to AAV1.

\[ \text{C}_2\text{H}_2\text{BrF}_2\text{N}_2\text{O}_2 (485.32) \]

R\(_f\)=1.64 minutes (method 2)
Example 327

(S)-2-methoxy-pyrimidine-5-carboxylic acid-(3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2970]

Example 329

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-ethylnamino-nicotinamide

[2978]

[2979] Prepared from intermediates C1 and 6-ethylnamino-nicotinic acid according to AAV1.

[2980] C_{25}H_{23}ClF_{3}N_{5}O_{4} (532.95)  
R_f=2.32 minutes (method 2)

Example 330

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-propylamino-nicotinamide

[2981]

Example 328

(S)-2-ethylamino-pyrimidine-5-carboxylic acid-(3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl)-amide

[2974]

Example 322

Prepared from intermediates C1 and 6-propylamino-nicotinic acid according to AAV1.

[2982] C_{25}H_{23}ClF_{3}N_{5}O_{4} (546.98)  
R_f=2.04 minutes (method 2)

Example 331

(S)-N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-5-hydroxy-nicotinamide

[2985]

[2975] Prepared from intermediates C14 and 2-ethylamino-pyrimidine-5-carboxylic acid according to AAV1.

[2976] C_{25}H_{23}F_{3}N_{5}O_{4} (546.52)  
R_f=2.62 minutes (method 2)

[2986] Prepared from intermediates A15 and B8 according to AAV1.

[2987] C_{25}H_{23}ClF_{3}N_{5}O_{4} (555.90)  
R_f=2.48 minutes (method 2)
Example 332
(S)-pyrimidine-5-carboxylic acid-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyle]-tetrahydrofuran-3-yl]-amide

Example 334
N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-ethylamino-nicotinamide

Prepared from intermediates C4 and 6-ethylamino-nicotinic acid according to AAV1.

C$_2$H$_2$Cl$_2$F$_2$N$_2$O$_4$ (577.40)

R$_f$ 2.01 minutes (method 2)

Example 335
N-(1-[[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-propylamino-nicotinamide

Example 333
(S)-2-methoxy-pyrimidine-5-carboxylic acid-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyle]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates C4 and 6-propylamino-nicotinic acid according to AAV1.

C$_2$H$_2$Cl$_2$F$_2$N$_2$O$_4$ (591.45)

R$_f$ 2.12 minutes (method 2)

Example 336
(S)-thiazole-5-carboxylic acid-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyle]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates C18 and thiazole-5-carboxylic acid according to AAV1.

C$_2$H$_2$Cl$_2$F$_2$N$_2$O$_4$S (524.95)

R$_f$ 2.58 minutes (method 2)
Example 337

(S)-N-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofurran-3-yl]-5-methoxy-nicotinamide

[3009]

Example 340

N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-trifluoromethyl-nicotinamide

[3021]

Example 341

N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-methyl-nicotinamide

[3025]

Example 338

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofurran-3-yl]-amide

[3013]

Example 339

5-chloro-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[3017]

Example 342

(S)-5-amino-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofurran-3-yl)-nicotinamide

[3029]

Example 337

C_{26}H_{14}ClF_{2}N_{3}O_{4} (548.95)

[3011]

R_{f}=2.62 minutes (method 2)

[3012]

Prepared from intermediates C18 and 5-methoxy-nicotinic acid according to AAV1.

Example 338

C_{26}H_{14}ClF_{3}N_{4}O_{5} (535.91)

[3015]

R_{f}=2.28 minutes (method 2)

[3016]

Prepared from intermediates A22 and B10 according to AAV1.

Example 339

C_{26}H_{14}ClF_{2}N_{3}O_{4} (507.87)

[3019]

R_{f}=2.18 minutes (method 2)

[3020]

Prepared from intermediates C2 and 5-chloro-nicotinic acid according to AAV1.

Example 340

C_{26}H_{14}ClF_{2}N_{4}O_{5} (487.45)

[3027]

R_{f}=1.85 minutes (method 2)

[3028]

Prepared from intermediates C2 and 6-methyl-nicotinic acid according to AAV1.

Example 341

C_{26}H_{14}F_{2}N_{4}O_{5} (487.45)

[3030]

R_{f}=1.85 minutes (method 2)

[3032]

Prepared from intermediates A21 and B2 according to AAV1.
Example 343

N-(1-[[5-(4-bromo-2-trifluoromethyl)-phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-methylamino-nicotinamide

Example 344

2-methyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

Example 345

(S)-2-methyl-pyrimidine-5-carboxylic acid-(3-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

Example 346

Prepared from intermediates A26 and B2 according to AAV1.

Example 347

Prepared from intermediates A26 and B2 according to AAV1.

Example 348

Prepared from intermediates C1 and 6-methylamino-nicotinamide according to AAV1.
[3054] Prepared from intermediates A14 and B9 according to AAV1.

[3055] C$_2$H$_2$F$_3$N$_2$O$_3$ (536.46)

[3056] R = 1.96 minutes (method 2)


[3058] [M–H] = 535

Example 349

(S)-6-amino-N-3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-nicotinamide

[3059]

[3060] Prepared from intermediates A7 and B9 according to AAV1.

[3061] C$_2$H$_2$F$_3$N$_2$O$_3$ (518.47)


[3063] [M–H] = 517

Example 350

2-hydroxy-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[3064]

[3065] Prepared from intermediates C1 and 2-hydroxy-pyrimidine-5-carboxylic acid according to AAV1.

[3066] C$_2$H$_2$F$_3$N$_2$O$_3$ (506.87)

[3067] R = 2.42 minutes (method 2)

Example 351

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-fluoro-nicotinamide

[3068]

[3069] Prepared from intermediates C1 and 5-fluoro-nicotinic acid according to AAV1.

[3070] C$_2$H$_2$ClF$_3$N$_2$O$_3$ (507.87)

[3071] R = 1.96 minutes (method 2)

Example 352

5-chloro-N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[3072]

[3073] Prepared from intermediates C1 and 5-chloro-nicotinic acid according to AAV1.

[3074] C$_2$H$_2$ClF$_3$N$_2$O$_3$ (524.33)

[3075] R = 2.10 minutes (method 2)

Example 353

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-methyl-nicotinamide

[3076]

[3077] Prepared from intermediates C1 and 5-methyl-nicotinic acid according to AAV1.

[3078] C$_2$H$_2$ClF$_3$N$_2$O$_3$ (503.91)

[3079] R = 1.86 minutes (method 2)

Example 354

N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-trifluoromethyl-nicotinamide

[3080]
[3081] Prepared from intermediates C1 and 5-trifluoromethyl-isonicotinic acid according to AAV1.
[3082] C₂H₁₅ClF₃N₂O₂ (557.88)
[3083] R_f=2.22 minutes (method 2)

Example 355
N-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-2-fluoro-isonicotinamide

[3084] 

[3085] Prepared from intermediates C1 and 2-fluoro-isonicotinic acid according to AAV1.
[3086] C₂H₁₅ClF₂N₂O₂ (507.87)
[3087] R_f=2.02 minutes (method 2)

Example 356
3-methoxy-isoxazole-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-amide

[3088] 

[3089] Prepared from intermediates C1 and 3-methoxy-isoxazole-5-carboxylic acid according to AAV1.
[3090] C₂H₁₅ClF₂N₂O₂ (509.87)
[3091] R_f=1.96 minutes (method 2)

Example 357
Isothiazole-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-amide

[3092] 

[3093] Prepared from intermediates C1 and isothiazole-5-carboxylic acid according to AAV1.
[3094] C₂H₁₅ClF₃N₂O₅ (495.91)
[3095] R_f=1.88 minutes (method 2)

Example 358
Isothiazol-4-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-amide

[3096] 

[3097] Prepared from intermediates C1 and isothiazole-4-carboxylic acid according to AAV1.
[3098] C₂H₁₅ClF₃N₂O₅ (495.91)
[3099] R_f=1.84 minutes (method 2)

Example 359
(S)-5-amino-N-[[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl][carbamoyl]-tetrahydrofuran-3-yl]-nicotinamide

[3100] 

[3090] Prepared from intermediates A27 and B2 according to AAV1.
[3102] C₂H₁₅ClF₃N₂O₅ (514.51)
[3103] R_f=1.51 minutes (method 2)

Example 360
2-methyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl][carbamoyl]-cyclopropyl]-amide

[3104]
Prepared from intermediates A26 and B11 according to AAV1.

$\text{C}_2\text{H}_2\text{ClF}_2\text{N}_3\text{O}_2$ (518.92)

$R_f = 2.11$ minutes (method 2)

Example 361
5-amino-N-[[5-[4-chloro-2-trifluoromethyl-phenylamino]-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

Prepared from intermediates A26 and B4 according to AAV1.

$\text{C}_2\text{H}_2\text{ClF}_2\text{N}_3\text{O}_2$ (518.92)

$R_f = 1.83$ minutes (method 2)

Example 362
1-(2,2,2-trifluoro-acetylamo)-cyclopropanecarboxylic acid-[5-[4-chloro-2-trifluoromethyl-phenylamino]-pyridin-2-ylmethyl]-amide

Prepared from intermediates C1 and 2-cyano-acetic acid according to AAV1.

$\text{C}_2\text{H}_2\text{ClF}_2\text{N}_3\text{O}_2$ (451.83)

$R_f = 1.85$ minutes (method 2)

Example 365
(S)-1H-pyrrrol[3,2-b]pyridine-6-carboxylic acid-[3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)]-benzyl-carbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates C14 and 1H-pyrrrol[3,2-b]pyridine-6-carboxylic acid according to AAV1.

$\text{C}_2\text{H}_2\text{F}_2\text{N}_3\text{O}_2$ (541.50)

$R_f = 2.14$ minutes (method 2)

Example 366
(S)-2-methyl-pyrimidine-5-carboxylic acid-[3-[3-methyl-5-[2-trifluoromethyl-phenylamino]-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl]-amide

Prepared from intermediates A27 and B7 according to AAV1.

$\text{C}_2\text{H}_2\text{F}_2\text{N}_3\text{O}_2$ (514.51)

$R_f = 1.84$ minutes (method 2)
Example 367
1-cyano-1-(cyclopropanecarbonyl-aminocyclopropanecarbonylacid-5-[4-chloro-2-trifluoromethylphenylamino)-pyridin-2-ylmethyl]-amide

Example 370
2-amino-pyridimine-5-carboxylic acid-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl-amide

Example 368
1-(2-cyano-2-methyl-acetylaminocyclopropanecarbonylacid-5-[4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

Example 371
2-ethyl-pyridimine-5-carboxylic acid-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

Example 369
Isoxazole-5-carboxylic acid-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

Example 372
1H-pyrazole-4-carboxylic acid-(1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-amide

Example 373
Prepared from intermediates C1 and 1-cyano-1-cyclopropanecarbonylic acid according to AAV1.

Example 374
C_{2}H_{6}Cl_{2}N_{2}O_{3} (478.84)
R_{t}=1.89 minutes (method 2)

Example 375
Prepared from intermediates C1 and 2-amino-pyridimine-5-carboxylic acid according to AAV1.

Example 376
C_{2}H_{6}Cl_{2}N_{2}O_{3} (505.89)
R_{t}=2.11 minutes (method 2)

Example 377
Prepared from intermediates C1 and 2-ethyl-pyridimine-5-carboxylic acid according to AAV1.

Example 378
C_{2}H_{6}Cl_{2}N_{2}O_{3} (518.92)
R_{t}=2.38 minutes (method 2)

Example 379
Prepared from intermediates C1 and 1H-pyrazole-4-carboxylic acid according to AAV1.

Example 380
C_{2}H_{6}Cl_{2}N_{2}O_{3} (478.86)
R_{t}=1.69 minutes (method 2)
Example 373
1-methyl-1H-pyrazole-4-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[3155]

[3156] Prepared from intermediates C1 and 1-methyl-1H-pyrazole-4-carboxylic acid according to AAV1.

[3157] C_{22}H_{31}ClF_{2}N_{5}O_{2} (492.89)
[3158] R_{f}=1.74 minutes (method 2)

Example 374
2-methyl-pyrimidine-5-carboxylic acid-(1-[[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[3159]

[3160] Prepared from intermediates C20 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1.

[3161] C_{22}H_{31}F_{2}N_{5}O_{2} (484.48)
[3162] R_{f}=1.81 minutes (method 2)

Example 375
5-amino-N-(1-[[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl]-cyclopropyl)-nicotinamide

[3163]

[3164] Prepared from intermediates C20 and 5-amino-nicotinic acid according to AAV1.

[3165] C_{22}H_{31}F_{2}N_{5}O_{2} (484.48)
[3166] R_{f}=1.29 minutes (method 2)

Example 376
N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-methoxy-nicotinamide

[3167]

[3168] Prepared from intermediates C2 and 5-methoxy-nicotinic acid according to AAV1.

[3169] C_{22}H_{31}F_{2}N_{5}O_{2} (503.45)
[3170] R_{f}=2.02 minutes (method 2)

Example 377
N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-6-methylamino-nicotinamide

[3171]

[3172] Prepared from intermediates C2 and 6-methylamino-nicotinic acid according to AAV1.

[3173] C_{22}H_{31}F_{2}N_{5}O_{2} (502.47)
[3174] R_{f}=2.01 minutes (method 2)

Example 378
6-amino-5-bromo-N-(1-[[5-(4-chloro-2-trifluoromethyl-ethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-nicotinamide

[3175]
[3176] Prepared from intermediates C1 and 6-amino-5-bromo-nicotinic acid according to AAV1.
[3177] C₇H₆BrClF₃N₂O₂ (583.79)
[3178] Rₚ=1.91 minutes (method 2)

Example 379
2-cyclopropylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[3179]

[3180] Prepared from intermediates C1 and 2-cyclopropylamino-pyrimidine-5-carboxylic acid according to AAV1.
[3181] C₇H₆ClF₃N₂O₂ (545.95)
[3182] Rₚ=2.29 minutes (method 2)

Example 380
2-propylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[3183]

[3184] Prepared from intermediates C1 and 2-propylamino-pyrimidine-5-carboxylic acid according to AAV1.
[3185] C₇H₆ClF₃N₂O₂ (547.97)
[3186] Rₚ=2.42 minutes (method 2)

Example 381
(S)-N-[3-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylecarbamoyl]-tetrahydrofuran-3-yl]-5-methoxy-nicotinamide

[3187]

[3188] Prepared from intermediates C14 and 5-methoxy-nicotinic acid according to AAV1.
[3189] C₇H₆F₃N₂O₄ (532.49)
[3190] Rₚ=2.50 minutes (method 2)

Example 382
2-isopropylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

[3191]

[3192] Prepared from intermediates C1 and 2-isopropylamino-pyrimidine-5-carboxylic acid according to AAV1.
[3193] C₇H₆ClF₃N₂O₂ (547.97)
[3194] Rₚ=2.41 minutes (method 2)

Example 383
(S)-1H-pyrrol(2,3-b)pyridine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylecarbamoyl]-tetrahydrofuran-3-yl]-amide

[3195]
[3196] Prepared from intermediates C14 and 1H-pyrrolo[2, 3-b]pyridine-5-carboxylic acid according to AAV1.

[3197] C_{12}H_{12}F_{2}N_{2}O_{2} (541.50)

[3198] R_f=2.48 minutes (method 2)

Example 384

1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)amide

[3199]

[3200] Prepared from intermediates C2 and 1H-pyrrolo[2, 3-b]pyridine-5-carboxylic acid according to AAV1.

[3201] C_{12}H_{12}F_{2}N_{2}O_{2} (512.47)

[3202] R_f=2.27 minutes (method 2)

Example 385

2-cyano-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)amide

[3203]

[3204] Prepared from intermediates C18 and 1H-pyrrolo[2, 3-b]pyridine-5-carboxylic acid according to AAV1.

[3205] C_{12}H_{12}ClF_{2}N_{2}O_{2} (515.88)

[3206] R_f=2.39 minutes (method 2)

Example 386

2-methyl-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-difluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)amide

[3207]

[3208] Prepared from intermediates C21 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1.

[3209] C_{12}H_{12}ClF_{2}N_{2}O_{2} (486.91)

[3210] R_f=1.68 minutes (method 2)

Example 387

(S)-2-methyl-pyrimidine-5-carboxylic acid-(3-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl]-tetrahydrofuran-3-yl)-amide

[3211]

[3212] Prepared from intermediates A21 and B7 according to AAV1.

[3213] C_{12}H_{12}ClF_{2}N_{2}O_{2} (532.50)

[3214] R_f=1.86 minutes (method 2)

Example 388

(S)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid-[[3-[(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[3215]

[3216] Prepared from intermediates C18 and 1H-pyrrolo[2, 3-b]pyridine-5-carboxylic acid according to AAV1.

[3217] C_{12}H_{12}ClF_{2}N_{2}O_{2} (557.96)


[3219] [M-H]=556

Example 389

N-[[1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl]-6-cyclopropylamino-nicotinamide

[3220]
[3221] Prepared from intermediates C1 and 6-cyclopropylamino-nicotinoic acid according to AAV1.

[3222] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (544.96) \)

[3223] \( R_f=1.67 \) minutes (method 2)

Example 390

2-ethoxy-pyrimidine-5-carboxylic acid-(1-[[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-amide

[3224]

[3225] Prepared from intermediates C1 and 2-ethoxy-pyrimidine-5-carboxylic acid according to AAV1.

[3226] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (534.92) \)

[3227] \( R_f=1.99 \) minutes (method 2)

Example 391

6-amino-N-(1-[[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl]-cyclopropyl)-5-methyl-nicotinamide

[3228]

[3229] Prepared from intermediates C2 and 6-amino-5-methyl-nicotinamide acid according to AAV1.

[3230] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (502.47) \)

[3231] \( R_f=1.38 \) minutes (method 2)

Example 392

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-[3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[3232]

[3233] Prepared from intermediates A17 and B10 according to AAV1.

[3234] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (501.46) \)

[3235] \( R_f=2.09 \) minutes (method 2)

Example 393

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-[3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[3236]

[3237] Prepared from intermediates A11 and B10 according to AAV1.

[3238] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (537.44) \)

[3239] \( R_f=2.15 \) minutes (method 2)

Example 394

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-[3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-2-fluoro-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[3240]

[3241] Prepared from intermediates A29 and B10 according to AAV1.

[3242] \( \text{C}_2\text{H}_5\text{ClF}_3\text{N}_2\text{O}_2 (553.90) \)

[3243] \( R_f=2.31 \) minutes (method 2)

Example 395

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-[3-[4-(4-bromo-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl]-amide

[3244]
Prepared from intermediates A31 and B10 according to AAV1.

C₄H₆BrF₃N₂O₄ (580.35)

R₉=2.32 minutes (method 2)

Example 396

(S)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid

{3-[2-fluoro-4-(2-trifluoromethyl)-phenylamino]-
benzylcarbamoyl}-tetrahydro-furan-3-y1-amide

Prepared from intermediates A12 and B10 according to AAV1.

C₃H₂F₂N₂O₄ (519.45)

R₉=1.35 minutes (method 7)

mass spectroscopy (ESI): [M+H]⁺=520

The following Examples describe pharmaceutical formulations which contain as active substance any desired compound of general formula I, without restricting the scope of the present invention thereto:

Example I

Dry Ampoule with 75 mg of Active Compound Per 10 ml

Composition:

<table>
<thead>
<tr>
<th>Active compound</th>
<th>75.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>500.0 mg</td>
</tr>
<tr>
<td>Water for injection</td>
<td>ad 16.0 ml</td>
</tr>
</tbody>
</table>

Production:

Active compound and mannitol are dissolved in water. The charged ampoules are freeze dried. Water for injection is used to dissolve to give the solution ready for use.

Example II

Tablet with 50 mg of Active Compound

Composition:

<table>
<thead>
<tr>
<th>Active compound</th>
<th>50.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>98.0 mg</td>
</tr>
</tbody>
</table>

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, bilinear with a bevel on both sides and dividing groove on one side.

Example III

Tablet with 350 mg of Active Compound

Composition:

<table>
<thead>
<tr>
<th>Active compound</th>
<th>350.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>125.0 mg</td>
</tr>
<tr>
<td>Maize starch</td>
<td>80.0 mg</td>
</tr>
<tr>
<td>Polymethylpyridone</td>
<td>30.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4.0 mg</td>
</tr>
</tbody>
</table>

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, bilinear with a bevel on both sides and dividing groove on one side.

Example IV

Capsule with 50 mg of Active Compound

Composition:

<table>
<thead>
<tr>
<th>Active compound</th>
<th>50.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>58.0 mg</td>
</tr>
<tr>
<td>Powdered Lactose</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.0 mg</td>
</tr>
</tbody>
</table>

Production:

(1) is triturated with (3). This triturant is added to the mixture of (2) and (4) with vigorous mixing.
This powder mixture is packed into hard gelatine two-piece capsules of size 3 in a capsule-filling machine.

**Example V**

Capsules with 350 mg of Active Compound

**Composition:**

<table>
<thead>
<tr>
<th>(1) Active compound</th>
<th>350.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) Maize starch dried</td>
<td>46.0 mg</td>
</tr>
<tr>
<td>(3) Lactose powdered</td>
<td>30.0 mg</td>
</tr>
<tr>
<td>(4) Magnesium stearate</td>
<td>4.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>430.0 mg</td>
</tr>
</tbody>
</table>

**Production:**

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous stirring.

This powder mixture is packed into hard gelatine two-piece capsules of size 0 in a capsule-filling machine.

**Example VI**

Suppositories with 100 mg of Active Compound

**1 suppository comprises:**

<table>
<thead>
<tr>
<th>Active compound</th>
<th>100.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol (M.W. 1500)</td>
<td>600.0 mg</td>
</tr>
<tr>
<td>Polyethylene glycol (M.W. 6000)</td>
<td>460.0 mg</td>
</tr>
<tr>
<td>Polyethylene sorbitan monoestearate</td>
<td>840.0 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2000.0 mg</td>
</tr>
</tbody>
</table>

1. A compound of the formula I

![Chemical Structure](image)

wherein:

- n denotes one of the numbers 0, 1 or 2,
- \( R^0 \) denotes:
  - (a) a \( C_{1-3}- alkyl \) group optionally substituted by a group \( R^1 \),
  - (b) a \( C_{3-5}- alkyl \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
  - (c) a substituted \( C_9-^{cycloalkyl} \) group optionally substituted by a group \( R^1 \) wherein \( \text{—CH}_2- \) unit may be replaced by a \( —C(O)- \) group,
  - (d) an \( \text{aryl-C}_9-^{cycloalkyl} \) group optionally substituted by 1, 2 or 3 groups \( R^1 \),
  - (e) a \( \text{five-membered heteroaryl-C}_9-^{cycloalkyl} \) group optionally substituted by 1, 2 or 3 groups \( R^1 \), which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,
  - (f) a \( \text{six-membered heteroaryl-C}_9-^{cycloalkyl} \) group optionally substituted by 1 or 2 groups \( R^1 \), which contains one, two or three N-atoms and which may additionally be benzo-condensed,
  - (g) a \( \text{nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R}^1 \) substituted, which contains one, two or three N-atoms,
  - (h) a \( \text{5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R}^1 \), in which a \( \text{—CH}_2— \) unit may be replaced by a \( —C(O)- \) group,
  - (i) \( \text{—O—R}^1 \),
  - (j) \( \text{—NR}^1 \) or
  - (k) \( \text{—CN} \)

\( R^1 \) denotes halogen, \( —\text{NO}_2 \), \( —\text{CN} \), \( C_3-^{cycloalkyl} \),

- \( \text{—OR}^1 \), \( —\text{SR}^1 \), \( —\text{CO}_2H \), \( —\text{CO}_2R \), \( —\text{SO}_2 \), \( —\text{SO}_2R \), \( —\text{SO}_3 \), \( —\text{SO}_2\text{—} \), \( —\text{O—C(O)—} \),

\( R^1 \) denotes independently one another halogen or \( C_3-^{cycloalkyl} \).

- \( C_1-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_3-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
- \( C_1-^{cycloalkyl} \) or
- \( C_3-^{cycloalkyl} \) group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_1_4-cycloalkyl, or
R^1.1.3 and R^1.1.4 together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O, and S, or
R^1.1.3 and R^1.1.4 together with the N atom to which they are attached, form a cyclic imide,
R^1.4 independently of one another halogen denote
—NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2 or
—SO_2, R^1.1.1
R^1.2 denotes halogen, —NO_2, —CN, OH, —O—CH_3 or phenyl,
R^1.3 denotes
(a) halogen, —NO_2, —CN, —OR^1.1.1, —SR^1.1.1, —CO_2R^1.1.1, C_1_4-alkyl, or
(b) a C_1_4-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R^1.4 independently of one another denote
(a) halogen, —NO_2, —CN, —OR^1.1.1, —SR^1.1.1, —SO_2, R^1.1.1, —SO_2R^1.1.1, —NHR_1.1.3, NR_1.1.3, —N(R_1.1.3)_2, —C(O)—C(O)—C_1_4-alkyl, C_1_4-alkyl
(b) a C_1_4-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or
(c) an oxo group,
R^1.5 denotes H or C_1_4-alkyl,
R^1.6 denotes —OH or —O—C_1_4-alkyl,
R^1 denotes
(a) H,
(b) C_1_4-alkyl,
(c) a C_1_4-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R^2 independently of one another denote
(a) H, halogen, —CN, —OH, C_1_4-cycloalkyl, —O—C_1_4-alkyl, —O—CF_3, —O—C_1_4-cycloalkyl, —N(C_1_4-alkyl)_2, —C(O)—NH_2, —SO_2—C_1_4-alkyl, or
(b) a C_1_4-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R^3 denotes
(a) H, halogen, —CN, —OH,
(b) C_1_4-alkyl,
(c) C_1_4-alkyl or —O—C_1_4-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_1_4-cycloalkyl,
(e) —O—C_1_4-alkyl,
(f) —O—C_1_4-cycloalkyl,
(g) —NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2,
(h) —C(O)—R^1.1.1,
(i) —S—C_1_4-alkyl, —SO_2—R^1.1.2
(j) a five-membered heteroaryl group optionally substituted by one or two C_1_4-alkyl groups which is selected from among pyrrole, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or
(k) a six-membered heteroaryl group optionally substituted by one or two C_1_4-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,
R^1.7 denotes —NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2, N-acetylindin, N-pyridolindin, N-piperidinyl, N-morpholinyl, —OH, —O—C_1_4-alkyl or —O—C_1_4-cycloalkyl,
R^1.8 denotes —NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2, N-acetylindin, N-pyridolindin, N-piperidinyl or N-morpholinyl and
R^1.9 denotes H, halogen, C_1_4-alkyl,
R^1.10 denotes
(a) H, halogen, —CN, —OH,
(b) C_1_4-alkyl,
(c) C_1_4-alkyl or —O—C_1_4-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_1_4-cycloalkyl,
(e) —O—C_1_4-alkyl,
(f) —O—C_1_4-cycloalkyl,
(g) —NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2,
(h) —C(O)—R^1.1.1,
(i) —S—C_1_4-alkyl, —SO_2—C_1_4-alkyl, —SO_2—C_1_4-cycloalkyl,
R^1.11 denotes —NH_2, —NH(C_1_4-alkyl), —N(C_1_4-alkyl)_2, N-acetylindin, N-pyridolindin, N-piperidinyl, N-morpholinyl, —OH, —O—C_1_4-alkyl or —O—C_1_4-cycloalkyl,
R^1.12 denotes H, halogen, C_1_4-alkyl,
R^1.13 denotes
(a) H, halogen, —CN, —OH,
(b) C_1_4-alkyl,
(c) C_1_4-alkyl or —O—C_1_4-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R<sup>1.1</sup> denotes —NH<sub>2</sub>, —NH(C<sub>1-5</sub>-alkyl), —N(C<sub>1-5</sub>-alkyl),
N-acetadiniyl, N-pyrrolidinyl, N-piperidinyl, N-morpholinyl, —OH, —O—C<sub>1-5</sub>-alkyl or —O—C<sub>1-5</sub>-cycloalkyl,
X independently of one another denote C—R<sup>5</sup> or N, or a salt thereof.

2. A compound of the formula I according to claim 1, wherein:
R<sup>1</sup> denotes
(a) a C<sub>1-5</sub>-alkyl group optionally substituted by a group R<sup>1.1</sup>—
(b) a C<sub>1-5</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(c) a C<sub>3-8</sub>-cycloalkyl group optionally substituted by a group R<sup>1.1</sup>— wherein a —CH<sub>2</sub>—unit may be replaced by a —CO— group,
(d) a phenyl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—
(e) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,
(f) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, which contains one, two or three N-atoms,
(g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, which contains one, two or three N-atoms,
(h) a five- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, in which a —CH<sub>2</sub>— unit may be replaced by a —C(O)— group,
(i) —O—R<sup>1.1.1</sup>—
(j) —NR<sup>1.1</sup>—R<sup>1.1.1</sup>—
R<sup>1.1</sup>—denotes CN, C<sub>3-8</sub>-cycloalkyl, —OR<sup>1.1</sup>—, —NR<sup>1.1</sup>-
R<sup>1.1.</sup>1.1.1 denotes
(a) H, (b) C<sub>1-4</sub>-alkyl,
(c) a C<sub>1-3</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R<sup>1.1.3</sup>—denotes halogen, —NO<sub>2</sub>, —CN, —OH, —O—CH<sub>3</sub> or phenyl.
R<sup>1.1.3</sup>—independently of one another denote
(a) halogen, —NO<sub>2</sub>, —CN, —OR<sup>1.1</sup>—, C<sub>1-4</sub>-alkyl or
(b) a C<sub>1-5</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(a) halogen, —NO<sub>2</sub>, —CN, —OR<sup>1.1.1</sup>—, C<sub>1-4</sub>-alkyl or
(b) a C<sub>1-5</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(b) a C<sub>1-5</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and
R<sup>1.1.4</sup>—denotes halogen or C<sub>1-4</sub>-alkyl, or a salt thereof.

3. A compound of the formula I according to claim 1, wherein:
R<sup>1</sup> denotes
(a) a C<sub>1-5</sub>-alkyl group optionally substituted by a group R<sup>1.1</sup>—
(b) a phenyl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, which contains one, two or three N-atoms,
(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, which contains one, two or three N-atoms,
(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R<sup>1.1</sup>—, in which a —CH<sub>2</sub>— unit may be replaced by a —C(O)— group,
R<sup>1.1</sup>—denotes CN, C<sub>3-8</sub>-cycloalkyl, —OH, —O—CH<sub>3</sub>, —NH<sub>2</sub>, —NHCH<sub>3</sub>, —N(CH<sub>3</sub>)<sub>2</sub>.
R<sup>1.1</sup>—independently of one another denote
(a) F, Cl, Br, —OH, —O—CH<sub>3</sub>, C<sub>1-4</sub>-alkyl or
(b) a C<sub>1-3</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R<sup>1.1.1</sup>—independently of one another denote
(a) F, Cl, Br, —OH, —O—CH<sub>3</sub>, —NH<sub>2</sub>, —NHCH<sub>3</sub>, —N(CH<sub>3</sub>)<sub>2</sub>, —NH—C(O)—C<sub>1-4</sub>-
alkyl, C<sub>1-4</sub>-alkyl, or
(b) a C<sub>1-5</sub>-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or a salt thereof.

4. A compound of the formula I according to claim 1, wherein:
R<sup>1</sup> denotes
(a) a C<sub>1-5</sub>-alkyl group optionally substituted by a group R<sup>1.1</sup>—
(b) a phenyl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R<sup>1.1</sup>—, which is
5. A compound of the formula 1 according to claim 1, wherein:
R⁶ is

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R¹⁴, which is

(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups R¹⁴, which is

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R¹⁴, which is

R¹⁴ denotes —CN, cyclopropyl, —OH, —OCH₃, —NH₂, —NHCH₃, —N(CH₃)₂,
R³ independently of one another denotes
(a) F, Cl, Br, —OH, —OCH₃, —OCH₂CH₃, —C₆H₄-alkyl or
(b) a C₃₋₆-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and
R¹⁻⁴ independently of one another denotes
(a) F, Cl, Br, —OH, —OCH₃, —OCH₂CH₃, —NH₂, —NH—C₆H₄-alkyl, —N(C₃₋₆-alkyl)₂, —NH—C(O)—C₆H₄-alkyl, C₃₋₆-alkyl, or
(b) a C₃₋₆-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or a salt thereof.
or a salt thereof.

6. A compound of the formula I according to claim 1, wherein:
   
   R¹ is
or a salt thereof.

7. A compound of the formula I according to claim 1, wherein:

n denotes one of the numbers 0, 1 or 2,

R³ denotes
(a) H,
(b) C₁₋₄-alkyl,

R³ and R⁴ together with the carbon atom to which they are bound denote a C₃₋₅-cycloalkylene group optionally
substituted by a group R\(^1\), wherein a —CH\(_2\)— unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO\(_2\),

R\(^1\) denotes H, —OH,
R\(^2\) denotes (a) H,
(b) C\(_3\)-alkyl,
(c) a C\(_3\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R\(^3\) independently of one another denotes (a) H, halogen, —CN, —OH, C\(_3\)-cycloalkyl,
—O—CF\(_3\), —O—C\(_3\)-cycloalkyl, —N(C\(_1\)-alkyl),
—S(=O)NH\(_2\), —SO\(_2\)NH\(_2\), —SO\(_2\)C\(_1\)-alkyl,
denotes (a) a C\(_3\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
R\(^4\) denotes (a) H, halogen, —CN, —OH,
(b) C\(_3\)-alkyl,
(c) C\(_3\)-alkyl or —O—C\(_3\)-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C\(_3\)-cycloalkyl,
(e) —O—C\(_3\)-alkyl,
(f) —O—C\(_3\)-alkyl,
(g) —NH\(_2\), —NH(C\(_3\)-alkyl), —N(C\(_1\)-alkyl)\(_2\),
(h) —C(O)—R\(^1\),
(i) —S—C\(_3\)-alkyl,
R\(^2\) denotes —NH\(_2\), —OH, —O—C\(_3\)-alkyl,
R\(^6\) denotes H, halogen, C\(_3\)-alkyl,
R\(^7\) denotes (a) H, halogen, —CN, —OH,
(b) C\(_3\)-alkyl,
(c) C\(_3\)-alkyl or —O—C\(_3\)-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C\(_3\)-cycloalkyl,
(e) —O—C\(_3\)-alkyl,
(f) —O—C\(_3\)-alkyl,

(g) —NH\(_2\), —NH(O\(_1\)-alkyl), —N(C\(_1\)-alkyl)\(_2\),
(h) —C(O)—R\(^1\),
(i) —S—C\(_3\)-alkyl,
R\(^1\) denotes —NH\(_2\), —OH, —O—C\(_3\)-alkyl, and
X independently of one another represent C—R\(^8\) or N,
or a salt thereof.

8. A compound of the formula I according to claim 1,

wherein: R\(^2\) denotes H or CH\(_3\),
or a salt thereof.

9. A compound of the formula I according to claim 1,

wherein: R\(^2\) denotes H, or a salt thereof.

10. A compound of the formula I according to claim 1,

wherein: R\(^2\) and R\(^3\) together with the carbon atom to which they are bonded denote a C\(_3\)-cycloalkyl group wherein a —CH\(_2\)— unit may be replaced by an oxygen atom, or a salt thereof.

11. A compound of the formula I according to claim 1,

wherein: R\(^2\) and R\(^3\) together with the carbon atom to which they are bonded denote

![Chemical structure](image)
or a salt thereof.

12. A compound of the formula I according to claim 1,

wherein: R\(^2\) denotes H or CH\(_3\),
or a salt thereof.

13. A compound of the formula I according to claim 1,

wherein: R\(^2\) denotes H, F, Cl or methyl,
or a salt thereof.

14. A compound of the formula I according to claim 1,

wherein: R\(^7\) denotes H, F, Cl, Br, —CN, C\(_1\)-alkyl, CF\(_3\) or CHF\(_2\),
R\(^8\) denotes H,
R\(^9\) denotes F, Cl, Br, C\(_1\)-alkyl,
R\(^1\) denotes H and
R\(^1\) denotes F, Cl, Br, —CN, C\(_1\)-alkyl, CF\(_3\) or CHF\(_2\),
or a salt thereof.

15. A compound of the formula Ia,

![Chemical structure](image)
wherein

R\(^3\) denotes

(a) a C\(_{1-4}\)-alkyl group optionally substituted by a group R\(^{1,4}\),

(b) a phenyl group optionally substituted by 1, 2 or 3 groups R\(^{1,3}\),

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R\(^{1,4}\), which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R\(^{1,4}\), which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R\(^{1,4}\), which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R\(^{1,4}\), in which a —CH\(_2\) unit may be replaced by a —C(O) group,

R\(^{1,4}\) denotes —CN, C\(_{3,6}\)-cycloalkyl, —OH, —OCH\(_3\), —NH\(_2\), —NHCH\(_3\), —N(CH\(_3\))\(_2\),

R\(^3\) independently of one another denotes

(a) F, Cl, Br, —OH, —OCH\(_3\), C\(_{1-4}\)-alkyl or

(b) a C\(_\alpha\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

and

R\(^{1,4}\) independently of one another denotes

(a) F, Cl, Br, —OH, —OCH\(_3\), —NH\(_2\), —NHCH\(_3\), —N(CH\(_3\))\(_2\), —NH-C(O)-C\(_\alpha\)-alkyl, C\(_\alpha\)-alkyl, or

(a) a C\(_\alpha\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R\(^2\) denotes H or CH\(_3\),

R\(^2\) and R\(^4\) together with the carbon atom to which they are bonded denote a C\(_{3,6}\)-cycloalkylene group wherein a —CH\(_2\) unit may be replaced by an oxygen atom,

R\(^2\) denotes H or C\(_\alpha\)-alkyl,

R\(^2\) denotes H, F, Cl, Br or C\(_\alpha\)-alkyl,

R\(^2\) denotes H, F, Cl, Br, —CN, C\(_{1-4}\)-alkyl, CF\(_3\), CHF\(_2\),

R\(^2\) denotes F, Cl, Br, C\(_\alpha\)-alkyl, —S—C\(_\alpha\)-alkyl,

R\(^3\) denotes F, Cl, Br, —CN, C\(_{1-4}\)-alkyl, CF\(_3\), CHF\(_2\), and X denotes CH or N,

or a salt thereof.

16. A compound of the formula Ia according to claim 14, wherein

R\(^3\) denotes

(a) a C\(_1\)-alkyl group optionally substituted by a group R\(^{1,4}\),

(b) a phenyl group optionally substituted by 1, 2 or 3 groups R\(^{1,4}\),

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R\(^{1,4}\), which is

R\(^{1,4}\) denotes —CN, cyclopropyl, —OH, —OCH\(_3\), —NH\(_2\), —NHCH\(_3\), —N(CH\(_3\))\(_2\), or —N(CH\(_3\))\(_2\),

R\(^3\) denotes independently of one another

(a) F, Cl, Br, —OH, —OCH\(_3\), —OCF\(_3\), or C\(_1\)-alkyl or

(b) a C\(_1\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

and

R\(^{1,4}\) denotes independently of one another

(a) F, Cl, Br, —OH, —OCH\(_3\), —OCF\(_3\), or C\(_1\)-alkyl or

(b) a C\(_1\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R\(^2\) denotes H or CH\(_3\),

R\(^2\) and R\(^4\) together with the carbon atom to which they are bonded denote a C\(_{3,6}\)-cycloalkylene group wherein a —CH\(_2\) unit may be replaced by an oxygen atom,
R³ denotes H or CH₃,
R₄ denotes H, F, Cl, or methyl,
R⁵ denotes H, F, Cl, Br, –CN, C₃₋₄-alkyl, CF₃, CHF₂,
R⁶ denotes F, Cl, Br, C₃₋₄-alkyl, –O–C₃₋₄-alkyl,
R⁷ denotes F, Cl, Br, –CN, C₃₋₄-alkyl, CF₃, CHF₂, and
X denotes CH or N,
or a salt thereof.

17. A compound of the formula Ia according to claim 14,
wherein
R³ denotes

[Chemical structures and molecular diagrams]
18. A compound of the formula la according to claim 15, wherein

R¹ denotes
R\(^2\) denotes H or CH\(_3\).
R\(^3\) and R\(^4\) together with the carbon atom to which they are attached denote a C\(_{5-6}\)-cyclealkylenegroup wherein a \(-\text{CH}_2-\) unit may be replaced by an oxygen atom.
R\(^5\) denotes H or CH\(_3\).
R\(^6\) denotes H, F, Cl or methyl.
R\(^7\) denotes H, F, Cl, Br, \(-\text{CN}, \text{C}_1-\text{alkyl}, \text{CF}_3, \text{CHF}_2\),
R\(^8\) denotes F, Cl, Br, \text{C}_1-\text{alkyl}, \text{O-C}_1-\text{alkyl}, \text{S-C}_1-\text{alkyl},
R\(^9\) denotes F, Cl, Br, \(-\text{CN}, \text{C}_1-\text{alkyl}, \text{CF}_3, \text{CHF}_2\), and X denotes CH or N,
or a salt thereof.
19. A compound of the formula 1b

![Chemical Structure](image)

wherein:
R\(^1\) denotes
(a) a C\(_{1-6}\)-alkyl group optionally substituted by a group R\(^{1,1}\),
(b) a phenyl group optionally substituted by 1, 2 or 3 groups R\(^{1,5}\),
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R\(^{1,4}\), which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R\(^{1,4}\), which contains one, two or three N-atoms,
(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups R\(^{1,4}\), which contains one, two or three N-atoms,
(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R\(^{1,4}\), in which a \(-\text{CH}_2-\) unit may be replaced by a \(-\text{C}(\text{O})-\) group.
R\(^{1,1}\) denotes \(-\text{CN}, \text{C}_3-\text{cycloalkyl}, \text{-OH}, \text{-OCH}_3, \text{-NH}_2, \text{-NHCH}_3, \text{-N(CH}_3)_2\),
R\(^{1,5}\) denotes independently of one another
(a) F, Cl, Br, \(-\text{OH}, \text{-OCH}_3, \text{C}_1-\text{alkyl}\), or
(b) a C\(_{1-6}\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
and
R\(^{1,4}\) denotes independently of one another
(a) F, Cl, Br, \(-\text{OH}, \text{-OCH}_3, \text{-NH}_2, \text{-NHCH}_3, \text{-N(CH}_3)_2, \text{-NH-C(O)-C}_1-\text{alkyl}, \text{C}_1-\text{alkyl},\), or
(a) a C\(_{1-5}\)-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorne atoms and each methyl group may be substituted by 1, 2 or 3 fluorne atoms,
R\(^2\) denotes H or CH\(_3\),
R\(^3\) denotes H or CH\(_3\),
R\(^4\) denotes H, F, Cl or methyl.
R\(^5\) denotes H, F, Cl, Br or C\(_{1-5}\)-alkyl,
R\(^6\) denotes H, F, Cl, Br, \(-\text{CN}, \text{C}_1-\text{alkyl}, \text{CF}_3, \text{CHF}_2\),
R⁰ denotes F, Cl, Br, C₃₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl.
R¹ denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and X denotes CH or N, or a salt thereof.

20. A compound of the formula Ib according to claim 17, wherein
R¹ denotes
(a) a C₁₋₄-alkyl group optionally substituted by a group R¹⁻¹,
(b) a phenyl group optionally substituted by 1, 2 or 3 groups R¹⁻³,
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups R¹⁻⁴, which is

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R¹⁻⁴, which is

(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups R¹⁻⁴, which is

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups R¹⁻⁴, which is

R¹⁻³ denotes independently of one another
(a) F, Cl, Br, —OH, —OCH₃, —OCF₃, C₁₋₄-alkyl or
(b) a C₁₋₄-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and
R¹⁻⁴ denotes independently of one another
(a) F, Cl, Br, —NH₂, —OCH₃, —OCF₃, —NH—C₁₋₄-alkyl, —N(C₁₋₄-alkyl)₂, —NH—C(O)—C₁₋₄-alkyl, C₁₋₄-alkyl, or
(a) a C₁₋₃-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R² denotes H or CH₃,
R³ denotes H or CH₃,
R⁴ denotes H, F, Cl or methyl.
R⁷ denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂.
R⁸ denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl.
R¹¹ denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and X denotes CH or N, or a salt thereof.

21. A compound of the formula Ib according to claim 17, wherein
R¹ denotes
R² denotes H or CH₃,
R³ denotes H, F, Cl or methyl,
R⁴ denotes H, F, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
R⁵ denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl,
—S—C₁₋₄-alkyl,
R¹¹ denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and X denotes CH or N,
or a salt thereof.

22. A compound of the formula Ib according to claim 19,
wherein
R¹ denotes
R² denotes \( \text{H} \),
R³ denotes \( \text{H} \) or \( \text{CH₃} \),
R⁴ denotes \( \text{H} \), F, Cl, or methyl,
R⁵ denotes \( \text{H} \), F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
R⁶ denotes \( \text{CN} \), C₁₋₄-alkyl, —O—C₁₋₄-alkyl, —S—C₁₋₄-alkyl,
R⁷ denotes \( \text{F} \), Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and
X denotes CH or N,
or a salt thereof.

23. A compound of the formula 1c,

\[ \text{\( \text{R} \)} \]

wherein
R³ denotes
(a) a C₁₋₄-alkyl group optionally substituted by a group R¹₁,
(b) a phenyl group optionally substituted by 1, 2 or 3
groups R¹₁,
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3
groups R¹₁, which contains at least
one N, O or S atom and which optionally additionally
contains one, two or three further N-atoms,
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups R¹₁, which contains one, two or
three N-atoms,
(e) a nine- or ten-membered heteroaryl group optionally
substituted by 1 or 2 groups R¹₁, which contains one,
two or three N-atoms,
(f) a 5- or 6-membered heterocyclic group optionally
substituted by 1 or 2 groups R¹₁, in which a —CH₂—
unit may be replaced by a —C(O)— group,
R¹₁ denotes —CN, C₁₋₄-alkyl, —OH, —OCH₃,
—NH₂, —NHCH₃, —N(CH₃)₂,
R¹₃ denotes independently of one another
(a) \( \text{F}, \text{Cl}, \text{Br}, —\text{OH}, —\text{OCH₃} \),
C₁₋₄-alkyl or
(b) a C₁₋₄-alkyl group wherein each methylene group
may be substituted by 1 or 2 fluorne atoms and each
methyl group may be substituted by 1, 2 or 3 fluorne
atoms, and
R¹₉ denotes independently of one another
(a) \( \text{F}, \text{Cl}, \text{Br}, —\text{OH}, —\text{OCH₃}, —\text{NH₂}, —\text{NHCH₃}, —\text{N(CH₃)₂}, —\text{OH} —\text{N—C(O)—C₁₋₄-alkyl},
(b) a C₁₋₄-alkyl group wherein each methylene group
may be substituted by 1 or 2 fluorne atoms and each
methyl group may be substituted by 1, 2 or 3 fluorne
atoms,
R² denotes \( \text{H} \) or \( \text{CH₃} \),
R³ denotes \( \text{H} \) or C₁₋₄-alkyl,
R⁴ denotes \( \text{H} \), F, Cl, Br or C₁₋₄-alkyl,
R⁵ denotes \( \text{H} \), F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
R⁶ denotes \( \text{F} \), Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl,
—S—C₁₋₄-alkyl,
R¹₁ denotes \( \text{F} \), Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and
X denotes CH or N,
or a salt thereof.
24. A compound of the formula 1c according to claim 20,
wherein
R¹ denotes
(a) a C₁₋₄-alkyl group optionally substituted by a group
R¹₁,
(b) a phenyl group optionally substituted by 1, 2 or 3
groups R¹₁,
(c) a five-membered heterocyclic group optionally substituted by 1, 2 or 3 groups R¹₁,
(d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₁,
which is

\[ \text{\( \text{R} \)} \]

(d) a six-membered heterocyclic group optionally substituted by 1 or 2 groups R¹₁, which is

\[ \text{\( \text{R} \)} \]
(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1,4}$, which is

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1,4}$, which is

\[ R^{1,4} \text{ denotes } -CN, \text{ cyclopropyl}, \text{ -OH, -OCH}_3, \text{ -NH}_2, \text{ -NHCH}_2, \text{ -N(CH}_3)_2, \]
\[ R^{1,4} \text{ denotes independently of one another } \]
\[ (a) \text{ F, Cl, Br, -OH, -OCH}_3, \text{ -OCF}_3, \text{ C}_1\text{-alkyl} \text{ or} \]
\[ (b) \text{ a C}_1\text{-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and} \]
\[ R^{1,4} \text{ denotes independently of one another } \]
\[ (a) \text{ F, Cl, Br, -OH, -OCH}_3, \text{ -OCF}_3, \text{ -NH}_2, \text{ -NH- C}_1\text{-alkyl}, \text{ -N(C}_1\text{-alkyl)}_2, \text{ -NH-C(O)-C}_1\text{-alkyl, C}_1\text{-alkyl, or} \]
\[ (a) \text{ a C}_1\text{-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,} \]

\[ R^2 \text{ denotes H or CH}_3, \]
\[ R^3 \text{ denotes H or CH}_3, \]
\[ R^4 \text{ denotes H, F or methyl,} \]
\[ R^5 \text{ denotes H, F, Cl or methylyl,} \]
\[ R^6 \text{ denotes H, F, Cl, Br, - CN, C}_1\text{-alkyl, CF}_3, \text{ CHF}_2, \]
\[ R^7 \text{ denotes F, Cl, Br, C}_1\text{-alkyl, -O- C}_1\text{-alkyl,} \]
\[ R^8 \text{ denotes F, Cl, Br, - CN, C}_1\text{-alkyl, CF}_3, \text{ CHF}_2, \text{ and X denotes CH or N, or a salt thereof.} \]

25. A compound of the formula Ic according to claim 20, wherein

\[ R^1 \text{ denotes} \]
R² denotes H or CH₃,
R³ denotes H or CH₃,
R⁴ denotes H, F, Cl or methyl,
R⁵ denotes H, F, Cl, Br, –CN, C₃₋₅-alkyl, CF₃, CHF₂,
R⁶ denotes F, Cl, Br, C₁₋₃-alkyl, –O–C₁₋₃-alkyl,
–S–C₁₋₅-alkyl,
R¹¹ denotes F, Cl, Br, –CN, C₃₋₅-alkyl, CF₃, CHF₂, and
X denotes CH or N,
or a salt thereof.
26. A compound of the formula Ic according to claim 23,
wherein
R¹ denotes
R² denotes H or CH₃,
R³ denotes H or CH₃,
R⁴ denotes H, F, Cl or methyl,
R⁵ denotes H, F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂,
R⁶ denotes F, Cl, Br, C₁₋₄-alkyl, —O—C₁₋₄-alkyl,
—S—C₁₋₄-alkyl,
R⁷ denotes F, Cl, Br, —CN, C₁₋₄-alkyl, CF₃, CHF₂, and
X denotes CH or N,
or a salt thereof.
27. A compound of the formula \( \text{I} \),

\[
\text{II}
\]

wherein:

- \( R^3 \) denotes

\[
\text{III}
\]

\( R^3 \) and \( R^8 \) together with the carbon atom to which they are attached denote a \( C_3 \) or cycloalkylene group wherein a \( \text{-CH}_2 \text{CH}_2 \text{-} \) unit may be replaced by an oxygen atom,

- \( R^6 \) denotes \( H \) or \( \text{CH}_3 \),

- \( R^7 \) denotes \( \text{C}_1 \) or \( \text{CH}_3 \),

- \( R^7 \) denotes \( H \) or \( F \), and

- \( X \) denotes \( \text{CH} \) or \( \text{N} \),

or a salt thereof.

28. A compound according to claim 1 selected from the group consisting of:

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29. A physiologically acceptable salt of a compound according to any one of claims 1 to 28.

30. A pharmaceutical composition comprising a compound according to any one of claims 1 to 28 or a physiologically acceptable salt thereof, together with an inert carrier and/or diluent.

31. A method for treatment of acute pain, visceral pain, neuropathic pain, inflammatory/pain receptor-mediated pain, tumour pain and headache which comprises administration to a host in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 28 or a physiologically acceptable salt thereof.

32. A method for treatment of osteoarthritis which comprises administration to a host in need of such treatment a therapeutically effective amount of a compound according to any one of claims 1 to 28 or a physiologically acceptable salt thereof.