

New substituted isoquinoline and isoquinolinone derivatives

The present invention relates to novel isoquinoline and isoquinolinone derivatives as described in the claims, their preparation and their use in the treatment and/or
5 prevention of diseases related to the inhibition of Rho-kinase and/or of Rho-kinase mediated phosphorylation of myosin light chain phosphatase.

Activation of a small GTPase RhoA upon agonist stimulation results in conversion of RhoA from the inactive GDP-bound form to the active GTP-bound form with a
10 subsequent binding to and activation of Rho-kinase. Two isoforms, Rho-kinase 1 and Rho-kinase 2, are known. Rho-kinase 2 is expressed in vascular smooth muscle cells and endothelial cells. Activation of Rho-kinase 2 by the active GTP-bound RhoA leads to calcium sensitization of smooth muscle cells through phosphorylation-mediated inhibition of the myosin light chain phosphatase activity and thereby up-regulation of
15 the activity of myosin regulatory light chain (Uehata et al., Nature 1997, 389, 990-994).

It is known that Rho-kinase is involved in vasoconstriction, including the development of myogenic tone and smooth muscle hypercontractility (Gokina et al. J. Appl. Physiol. 2005, 98, 1940-8), bronchial smooth muscle contraction (Yoshii et al. Am. J. Resp. Cell
20 Mol. Biol. 20, 1190-1200), asthma (Setoguchi et al. Br J Pharmacol. 2001, 132, 111-8; Nakahara, et al. Eur J 2000, 389, 103) and chronic obstructive pulmonary disease (COPD, Maruoka, Nippon Rinsho, 1999, 57, 1982-7), hypertension, pulmonary hypertension (Fukumoto et al. Heart, 91, 391-2, 2005, Mukai et al. Nature 1997, 389, 990-4) and ocular hypertension and regulation of intraocular pressure (Honjo et al.
25 Invest. Ophthalmol. Visual Sci. 2001, 42, 137-144), endothelial dysfunction (Steioff et al. Eur. J. Pharmacol. 2005, 512, 247-249), angina (Masumoto et al. Circ 2002, 105, 1545-47, Shimokawa et al. JCP, 2002, 40, 751-761), nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure and peripheral arterial occlusive disease (PAOD) (Wakino et al. Drug News
30 Perspect. 2005, 18, 639-43), myocardial infarction (Demiryurek et al. Eur J Pharmacol. 2005, 527, 129-40, Hattori et al. Circulation, 2004, 109, 2234-9), cardiac hypertrophy and failure (Yamakawa, et al. Hypertension 2000, 35, 313-318, Liao et al. Am J Physiol

Cell Physiol. 2006, 290, C661-8, Kishi et al. Circ 2005, 111, 2741-2747), coronary heart disease, arteriosclerosis, restenosis (Pacaud et al. Arch. Mal. Coeur 2005, 98, 249-254, Retzer, et al. FEBS Lett 2000, 466, 70, Negoro, et al. Biochem Biophys Res Commun 1999, 262, 211), diabetes, diabetic complications, glucose utilization and metabolic syndrome (Sandu, et al. Diabetes 2000, 49, 2178, Maeda et al. Cell Metab. 2005, 2, 119-29), sexual dysfunction, e.g., penile erectile dysfunction (Chitale et al. Nature Medicine 2001, 7, 119-122), retinopathy, inflammation, immune diseases, AIDS, osteoporosis, endocrine dysfunctions, e.g. hyperaldosteronism, central nervous system disorders such as neuronal degeneration and spinal cord injury (Hara, et al. JNeurosurg 2000, 93, 94), cerebral ischemia (Uehata, et al. Nature 1997, 389, 990; Satoh et al. Life Sci. 2001, 69, 1441-53; Hitomi, et al. Life Sci 2000, 67, 1929; Yamamoto, et al. J Cardiovasc Pharmacol. 2000, 35, 203-11), cerebral vasospasm (Sato, et al. Circ Res 2000, 87, 195; Kim, et al. Neurosurgery 2000, 46, 440), pain, e.g. neuropathic pain (Tatsumi, et al. Neuroscience 2005, 131, 491, Inoue, et al. Nature medicine 2004, 10, 712), infection of digestive tracts with bacteria (WO 98/06433), cancer development and progression, neoplasia where inhibition of Rho kinase has been shown to inhibit tumor cell growth and metastasis (Itoh, et al. Nature Medicine 1999, 5, 221; Somlyo, et al. Res Commun 2000, 269, 652), angiogenesis (Uchida, et al. Biochem Biophys Res 2000, 269, 633-40; Gingras, et al. Biochem J 2000, 348, 273), vascular smooth muscle cell proliferation and motility (Tammy et al. Circ. Res. 1999, 84, 1186-1193; Tangkijvanich et al. Atherosclerosis 2001, 155, 321-327), endothelial cell proliferation, endothelial cell retraction and motility (Oikawa et al. Biochem. Biophys. Res. Commun. 2000, 269, 633-640), stress fiber formation (Kimura et al. Science 1997, 275, 1308-1311; Yamashiro et al. J. Cell Biol. 2000, 150, 797-806), thrombotic disorders (Kikkawa, et al. FEBS Lett. 2000, 466, 70-74; Bauer et al. Blood 1999, 94, 1665-1672, Klages, et al. J Cell Biol 1999, 144, 745; Retzer, et al. Cell Signal 2000, 12, 645) and leukocyte aggregation (Kawaguchi, et al. Eur J Pharmacol. 2000, 403:203-8; Sanchez-Madrid, et al. J Immunol. 2003, 171, 1023-34, Sanchez-Madrid, et al. J Immunol. 2002, 168, 400-10), and bone resorption (Chellaiah, et al. J Biol Chem. 2003, 278, 29086-97). Na/H exchange transport system activation (Kawaguchi, et al. Eur J Pharmacol. 2000, 403:203-8), Alzheimer's disease (Zhou et al. Science 2003, 302, 1215-1217), adducin activation (Fukata et al. J. Biol. Chem.,

1998, 273, 5542-5548), and in SREB (Sterol response binding element) signalling and its effects on lipid metabolism (Lin et al. Circ. Res., 92, 1296-304, 2003).

Therefore, a compound having inhibitory effect on Rho-kinase and/or on Rho-kinase mediated phosphorylation of myosin light chain phosphatase is useful for the treatment
5 and/or prevention of cardiovascular and non-cardiovascular diseases involving Rho-kinase as the primary or secondary disease cause, like hypertension, pulmonary hypertension, ocular hypertension, retinopathy, and glaucoma, peripheral circulatory disorder, peripheral arterial occlusive disease (PAOD), coronary heart disease, angina
10 pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome,
15 thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, e.g. neuropathic pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS,
20 osteopathy such as osteoporosis, infection of digestive tracts with bacteria, sepsis, cancer development and progression, e.g. cancers of the breast, colon, prostate, ovaries, brain and lung and their metastases.

WO 01/64238 describes isoquinoline-5-sulfonamide derivatives optionally substituted
25 by a $-(CH_2)_{1-6}-O-(CH_2)_{0-6}-$, a $-(CH_2)_{0-6}-S-(CH_2)_{0-6}-$ or a $-(CH_2)_{0-6}$ -linked heterocyclic group useful as neuroprotective agents.

WO 2004/106325 (Schering AG) describes prodrugs of the Rho-kinase inhibitor fasudil carrying an ether or ester group in the 1-position of the isoquinoline ring.

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WO 2001/039726 generically describes $-O-(C_0-C_{10})$ alkyl-heteroaryl substituted cyclohexyl derivatives useful for the treatment of microbial infections.

JP 10087629 A describes isoquinoline derivatives useful for the treatment of diseases caused by *Helicobacter pylori* such as for example gastritis cancer or ulcer. The isoquinoline derivatives may be substituted by OH in the 1-position and are preferably 5-substituted by X-[(C₁-C₆)alkylene]₀₋₁-Y wherein X may be oxygen and Y may be an aryl or a heterocyclic group.

Hagihara et al. (Bioorg. Med. Chem. 1999, 7, 2647-2666) disclose 6-benzyloxy-isoquinoline for the treatment of infections caused by *Helicobacter pylori*.

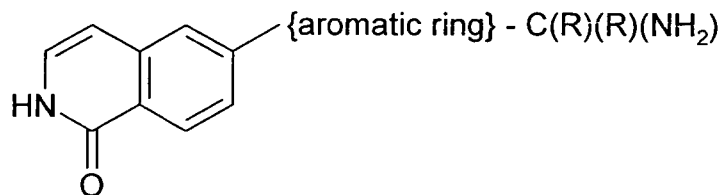
US 5,480,883 generically discloses as EGF and/or PDGF receptor inhibitors useful for inhibiting cell proliferation compounds of the formula "Ar I – X – Ar II" wherein X may be (CHR₁)_m-Z-(CHR₁)_n, e.g. Z-CH₂, wherein Z may be O, R₁ is hydrogen or alkyl, Ar I may be among others an optionally substituted isoquinolone and Ar II may be among others an optionally substituted C₃₋₇ monocyclic saturated heterocyclic system.

WO 2005/030791 (Merck & Co.) generically describes as potassium channel inhibitors for the treatment of cardiac arrhythmias, stroke, congestive heart failure etc. isoquinolone derivatives which are optionally substituted in 6-position by a group (C^{Rf})_pOR⁴³ wherein p may be zero, and R⁴³ is e.g. a (C₃-C₁₀)cycloalkyl residue optionally substituted by NR⁵¹R⁵², wherein R⁵¹ and R⁵² may be hydrogen, (C₁-C₆)alkyl etc.; or R⁴³ is a group R⁸¹ defined as a 4-6 membered unsaturated or saturated monocyclic heterocyclic ring with 1, 2, 3 or 4 heteroatoms; and are substituted by a directly bound optionally substituted aryl or heteroaryl ring in the 4-position.

WO 2005/030130 (Merck & Co.) generically describes as potassium channel inhibitors for the treatment of cardiac arrhythmias, stroke, congestive heart failure etc. isoquinoline derivatives which may be substituted by hydroxyl in the 1-position and are optionally substituted in 6-position by a group (C^{Rf})_pOR⁴³ wherein p may be zero, and R⁴³ is e.g. a (C₃-C₁₀)cycloalkyl residue optionally substituted by NR⁵¹R⁵², wherein R⁵¹ and R⁵² may be hydrogen, (C₁-C₆)alkyl etc.; or R⁴³ is a group R⁸¹

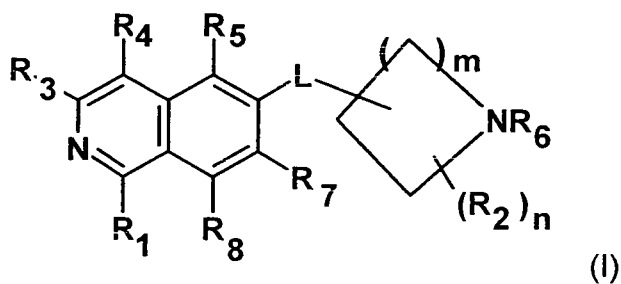
defined as a 4-6 membered unsaturated or saturated monocyclic heterocyclic ring with 1, 2, 3 or 4 heteroatoms; and are substituted by a directly bound optionally substituted aryl or heteroaryl ring in the 4-position.

- 5 WO 03/053330 (Ube) generically describes isoquinolone derivatives of the formula



as Rho-kinase inhibitors.

An embodiment of the present invention is a compound of the formula (I)



wherein

R₁ is H, OH or NH₂;

R₂ is

15 R',

(C₇-C₈)alkyl,

(C₁-C₆)alkylene-R',

(C₂-C₆)alkenyl,

(C₂-C₆)alkynyl,

20 (C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-O-R',

(C₁-C₆)alkylene-CH[R']₂,

(C₁-C₆)alkylene-C(O)-R',

- $(C_1-C_6)alkylene-C(O)NH_2$,
 $(C_1-C_6)alkylene-C(O)NH-R'$,
 $(C_1-C_6)alkylene-C(O)NH-(C_1-C_6)alkyl$,
 $(C_1-C_6)alkylene-C(O)N[(C_1-C_6)alkyl]_2$,
5 $(C_1-C_6)alkylene-C(O)N[R']_2$;
 $(C_1-C_6)alkylene-C(O)O-(C_1-C_6)alkyl$,
 $C(O)O-(C_1-C_6)alkyl$,
 $C(O)OR'$
 $C(O)(C_1-C_6)alkyl$,
10 $C(O)R'$,
 $C(O)NH-(C_1-C_6)alkyl$,
 $C(O)NHR'$,
 $C(O)-NH(C_2-C_6)alkenyl$,
 $C(O)-NH(C_2-C_6)alkynyl$,
15 $C(O)-NH(C_1-C_6)alkylene-R'$,
 $C(O)N[(C_1-C_6)alkyl]R'$
 $C(O)N[(C_1-C_6)alkyl]_2$,
 $C(O)-(C_1-C_6)alkylene-R'$,
 $C(O)O(C_1-C_6)alkylene-R'$;
20
or R_2 is $(C_1-C_6)alkyl$, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;
25
or R_2 is a $(C_1-C_4)alkylene$ bound to the cyclic amine, in which the $(C_1-C_4)alkylene$ forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

R_3 is

H,
halogen,
(C₁-C₆)alkyl,
(C₁-C₆)alkylene-R',
5 OH,
O-R'',
NH₂,
NHR'',
NR''R'' or
10 NH-C(O)-R'',

R₄ is
H,
halogen,
15 hydroxy,
CN,
(C₁-C₆)alkyl,
R',
(C₁-C₆)alkylene-R';

20 R₅ is
H,
halogen,
CN,
25 NO₂,
(C₁-C₆)alkyl,
(C₂-C₆)alkenyl,
R',
(C₁-C₆)alkylene-(C₆-C₁₀)aryl,
30 (C₁-C₆)alkenylene-(C₆-C₁₀)aryl,

- (C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl,
 CH(OH)-(C₁-C₆)alkyl,
 NH₂,
 NH-R',
 5 NH-SO₂H,
 NH-SO₂-(C₁-C₆)alkyl,
 NH-SO₂-R',
 NH-C(O)-(C₁-C₆)alkyl,
 NH-C(O)-R',
 10 C(O)N[(C₁-C₆)alkyl]₂,
 C(O)OH, or
 C(O)O-(C₁-C₆)alkyl;
- R₆ is
- 15 H,
 R',
 (C₁-C₈)alkyl,
 (C₁-C₆)alkylene-R',
 (C₁-C₆)alkylene-O-(C₁-C₆)alkyl,
 20 (C₁-C₆)alkylene-O-R',
 (C₁-C₆)alkylene-CH[R']₂,
 (C₁-C₆)alkylene-C(O)-R',
 (C₁-C₆)alkylene-C(O)NH₂,
 (C₁-C₆)alkylene-C(O)NH-R',
 25 (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,
 (C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,
 (C₁-C₆)alkylene-C(O)N[R']₂;
 (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,
 C(O)O-(C₁-C₆)alkyl,

C(O)OR'

C(O)(C₁-C₆)alkyl,

C(O)R',

C(O)NH-(C₁-C₆)alkyl,

5 C(O)NHR',

C(O)N[(C₁-C₆)alkyl]R'

C(O)N[(C₁-C₆)alkyl]₂,

C(O)-(C₁-C₆)alkylene-R', or

C(O)O(C₁-C₆)alkylene-R';

10

R₇ is

H,

halogen,

CN,

15 NO₂,

(C₁-C₆)alkyl,

O-(C₁-C₆)alkyl,

(C₂-C₆)alkenyl,

R',

20 (C₁-C₆)alkenylene-(C₆-C₁₀)aryl,

(C₁-C₆)alkylene-R',

CH(OH)-(C₁-C₆)alkyl,

NH₂,

NH-R',

25 NH-SO₂H,

NH-SO₂-(C₁-C₆)alkyl,

NH-SO₂-R',

SO₂-NH₂,

SO₂-NHR',

NH-C(O)-(C₁-C₆)alkyl,

NH-C(O)-R',

C(O)N[(C₁-C₆)alkyl]₂,

C(O)OH, or

5 C(O)O-(C₁-C₆)alkyl;

R₈ is H, halogen or (C₁-C₆)alkyl;

n is 1, 2, 3 or 4;

10

m is 1, 2, 3, 4 or 5; and

L is O(CH₂)_p, S(CH₂)_p, S(O)(CH₂)_p, SO₂(CH₂)_p, NH(CH₂)_p, N(C₁-C₆)alkyl-(CH₂)_p,

N(C₃-C₆)cycloalkyl-(CH₂)_p, N[CO(C₁-C₆)alkyl]-(CH₂)_p or N[(C₁-C₃)alkylene-R']-

(CH₂)_p;

15

p is 0, 1, 2, 3, or 4;

wherein

R' is

20

(C₃-C₈)cycloalkyl,

(C₅-C₁₀)heterocyclyl,

(C₆-C₁₀)aryl; and

R'' is

25

(C₃-C₈)cycloalkyl,

(C₅-C₁₀)heterocyclyl,

(C₆-C₁₀)aryl,

(C₁-C₆)alkyl,

(C₁-C₆)alkylene-R',

30

(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-O-R', or

(C₁-C₆)alkylene-NR_xR_y; and

wherein R_x and R_y are independently of each other

(C₁-C₆)alkyl,

5 (C₅-C₁₀)heterocyclyl,

(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,

(C₁-C₄)alkylene-(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-NH(C₁-C₆)alkyl,

10 (C₁-C₄)alkylene-N[(C₁-C₆)alkyl]₂,

(C₁-C₄)alkylene-N[(C₆-C₁₀)aryl]₂, or

(C₁-C₄)alkylene-N[(C₅-C₁₀)heterocyclyl]₂;

wherein in residues R₄, R₅, R₆, R₇ and R₈ alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃,

15 N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂ ;

wherein in residues R₂ to R₈ alkyl or alkylene can optionally be substituted one or more times by halogen;

20 wherein in residues R₂ to R₈ (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl are unsubstituted or substituted one or more times by suitable groups independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₁-C₆)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-OH, (C₁-C₆)alkylene-NH₂, (C₁-C₆)alkylene-NH(C₁-

25 C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl, SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂,

C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl,
 NH-C(O)O-(C₁-C₆)alkyl,
 NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heterocyclyl, N(C₁-
 C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)O-(C₁-C₆)alkyl,

5 N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl],

(C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl,

O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heterocyclyl,

(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, or O-(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl,

wherein the (C₆-C₁₀)aryl or (C₅-C₁₀)heterocyclyl may be substituted one to three
 10 times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl,
 (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)O-(C₁-
 C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl,
 or O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl;

or wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group

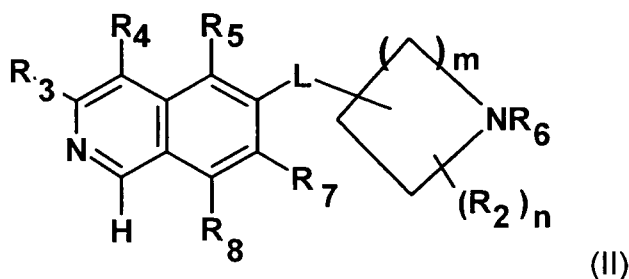
15 whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen
 atoms are attached to;

and wherein aryl or heterocyclyl substituents of (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl
 groups may not be further substituted by an aryl or heterocyclyl containing group;

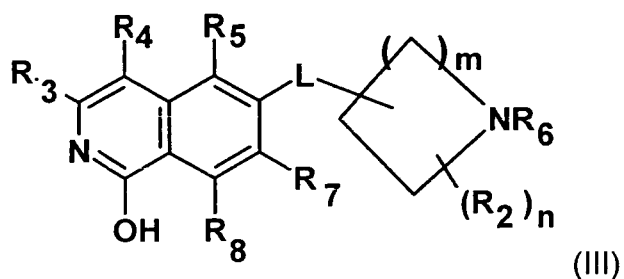
20 or their stereoisomeric forms and/or their tautomeric forms and/or their
 pharmaceutically acceptable salts.

In one embodiment of the present invention R₁ is H, the compound is thus
 characterized by the formula (II)

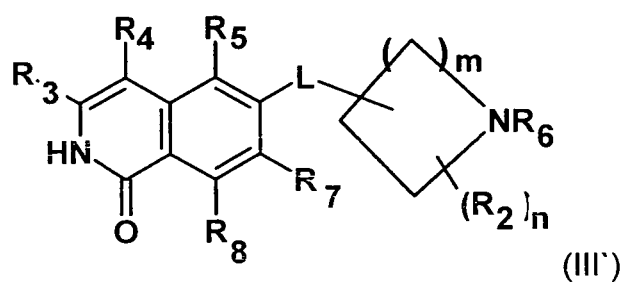
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In another embodiment R_1 is OH, the compound is thus characterized by the formula (III)



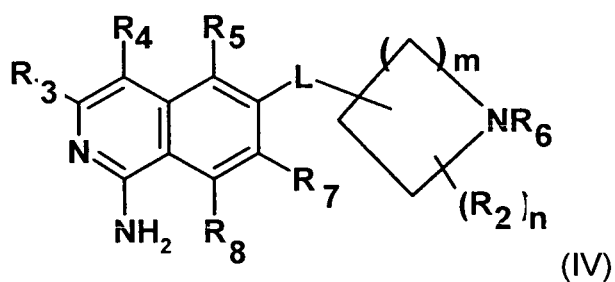
5 The compound of formula (III) has a tautomeric form of the formula (III')



The tautomeric form is also an embodiment of the present invention.

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In a further embodiment R_1 is NH_2 and the compound has the formula (IV)



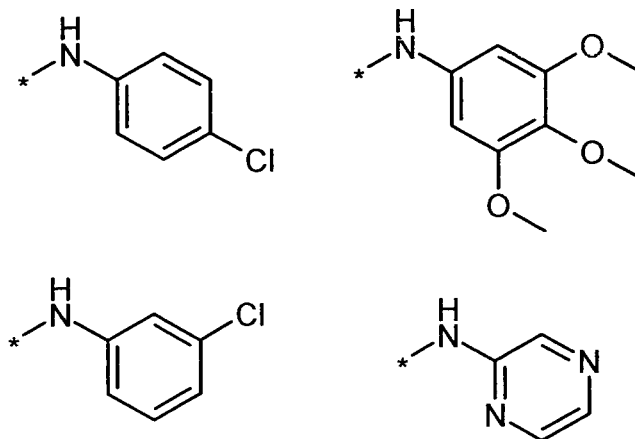
R_1 is preferably H or OH.

15

R_3 is preferably H, halogen, (C_1-C_4) alkylene- R' , O- R'' or NHR'' . More preferred, R_3 is H or NHR'' . Most preferred, R_3 is H, $NH-(C_5-C_6)$ heterocyclyl or NH -phenyl, especially

preferred are H, NH-(C₅-C₆)heteroaryl containing one or more N atoms or NH-phenyl.
Most especially preferred, R₃ is H.

Examples of R₃ substituents are



- 5 Preferably, R₄ is H, halogen or (C₁-C₆)alkyl. More preferred, R₄ is H, halogen or (C₁-C₄)alkyl. Most preferred, R₄ is H.

Preferably, R₅ is H, halogen, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, R', NH-(C₆-C₁₀)aryl or (C₁-C₆)alkylene-R'. More preferably, R₅ is H, halogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, R', NH-(C₆-C₁₀)aryl or (C₁-C₆)alkylene-R'. Most preferably, R₅ is H,

- 10 halogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl, NH-(C₆-C₁₀)aryl, (C₁-C₂)alkyl-(C₆-C₁₀)aryl or (C₅-C₁₀)heteroaryl. Especially preferred, R₅ is H, halogen, phenyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl or (C₅-C₆)heteroaryl. Most especially preferred R₅ is H, halogen, methyl, ethyl, vinyl, phenyl, thienyl or pyridyl.

- 15 Examples of R₅ are hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, vinyl, phenyl, thienyl or pyridyl, nitrile, nitro, (p-methoxy)-phenyl, N-aniline, benzyl, 2-propenyl, s-butenyl, cyclopropyl, tetrazol, amino, 4-methoxy-aniline or N-acetyl, preferably hydrogen, fluoro, chloro, bromo, iodo, methyl, ethyl, vinyl, phenyl, thienyl or pyridyl. More preferred, R₅ is H, halogen, methyl, or ethyl, most preferred R₅ is H.

20

Preferably, R₆ is H, (C₁-C₆)alkyl, R', (C₁-C₄)alkylene-(C₅-C₁₀)aryl, (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl, (C₁-

C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₄)alkylene-C(O)-(C₅-C₁₀)heterocyclyl,
 (C₁-C₄)alkylene-C(O)-(C₆-C₁₀)aryl, (C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂, (C₁-
 C₆)alkylene-C(O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,
 C(O)O-(C₁-C₆)alkyl, C(O)(C₁-C₆)alkyl, C(O)R', C(O)NH-(C₁-C₆)alkyl, C(O)N[(C₁-
 5 C₆)alkyl]₂, or C(O)(C₁-C₆)alkylene-R'.

In a further preferred embodiment R₆ is H, (C₁-C₆)alkyl, (C₅-C₁₀)heterocyclyl,
 (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl, (C₁-C₄)alkylene-(C₆-C₁₀)aryl, (C₁-
 10 C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂, (C₁-C₆)alkylene-
 C(O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl, C(O)O-(C₁-C₆)alkyl,
 C(O)(C₁-C₆)alkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)(C₃-C₈)cycloalkyl, C(O)NH-(C₁-
 C₆)alkyl, C(O)N[(C₁-C₆)alkyl]₂, C(O)(C₁-C₆)alkylene-(C₃-C₈)cycloalkyl, C(O)
 (C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, or C(O)(C₁-C₆)alkylene--(C₆-C₁₀)aryl.

15

In a further more preferred embodiment R₆ is H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl,
 (C₅-C₁₀)heterocyclyl, (C₅-C₁₀)aryl, (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl, (C₁-C₄)alkylene-(C₆-C₁₀)aryl, (C₁-
 C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkylene-
 20 C(O)N[(C₁-C₆)alkyl]₂, C(O)O-(C₁-C₆)alkyl, C(O)(C₁-C₆)alkyl, C(O)(C₃-C₈)cycloalkyl,
 C(O)-(C₅-C₁₀)heterocyclyl, C(O)NH-(C₁-C₆)alkyl, C(O)N[(C₁-C₆)alkyl]₂,
 C(O)(C₁-C₆)alkylene-(C₃-C₈)cycloalkyl, C(O)(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl,
 or C(O)(C₁-C₆)alkylene--(C₆-C₁₀)aryl.

25 In an more preferred embodiment R₆ is H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, (C₆-
 C₁₀)aryl, (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl, (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,
 (C₁-C₄)alkylene-(C₆-C₁₀)aryl, (C₁-C₄)alkylene-O-(C₁-C₄)alkyl, C(O)(C₁-C₆)alkyl,
 C(O)(C₃-C₈)cycloalkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)(C₁-C₄)alkylene-
 (C₅-C₁₀)heterocyclyl, or C(O)(C₁-C₄)alkylene-(C₆-C₁₀)aryl.

In an even more preferred embodiment R_6 is

H,

(C_1 - C_6)alkyl,

(C_3 - C_8)cycloalkyl;

5 (C_1 - C_4)alkylene-(C_3 - C_8)cycloalkyl;

(C_1 - C_4)alkylene-(C_5 - C_{10})heterocyclyl wherein heterocyclyl is unsubstituted or substituted one or more times, preferably one or two times, by (C_1 - C_4)alkyl;

(C_1 - C_4)alkylene-(C_6 - C_{10})aryl wherein aryl is unsubstituted or substituted one or more times, preferably one to three times, by halogen, (C_1 - C_4)alkyl especially CH_3 or CF_3 ,

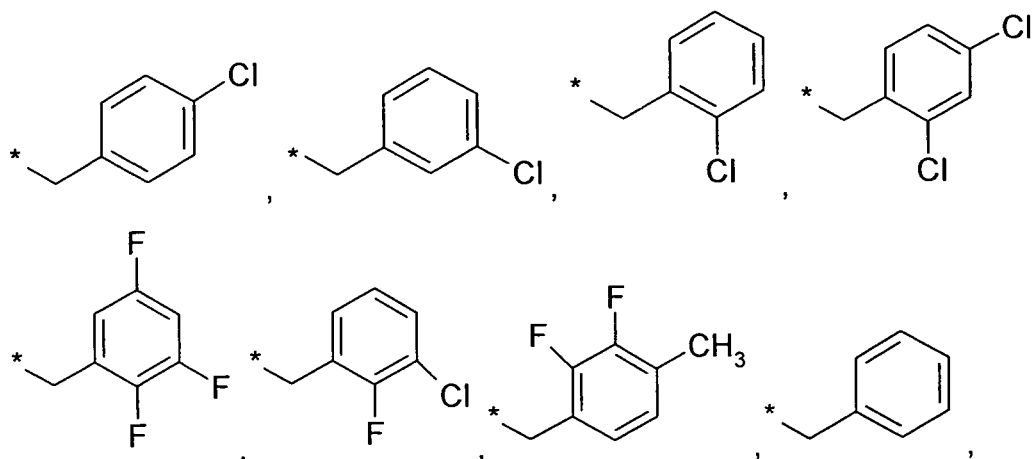
10 O-(C_1 - C_4)alkyl especially OCH_3 , SO_2 -(C_1 - C_4)alkyl especially $S(O)_2CH_3$ or SO_2CF_3 , or $SO_2-N=CH-N[(C_1-C_6)alkyl]_2$ especially $SO_2-N=CH-N(CH_3)_2$.

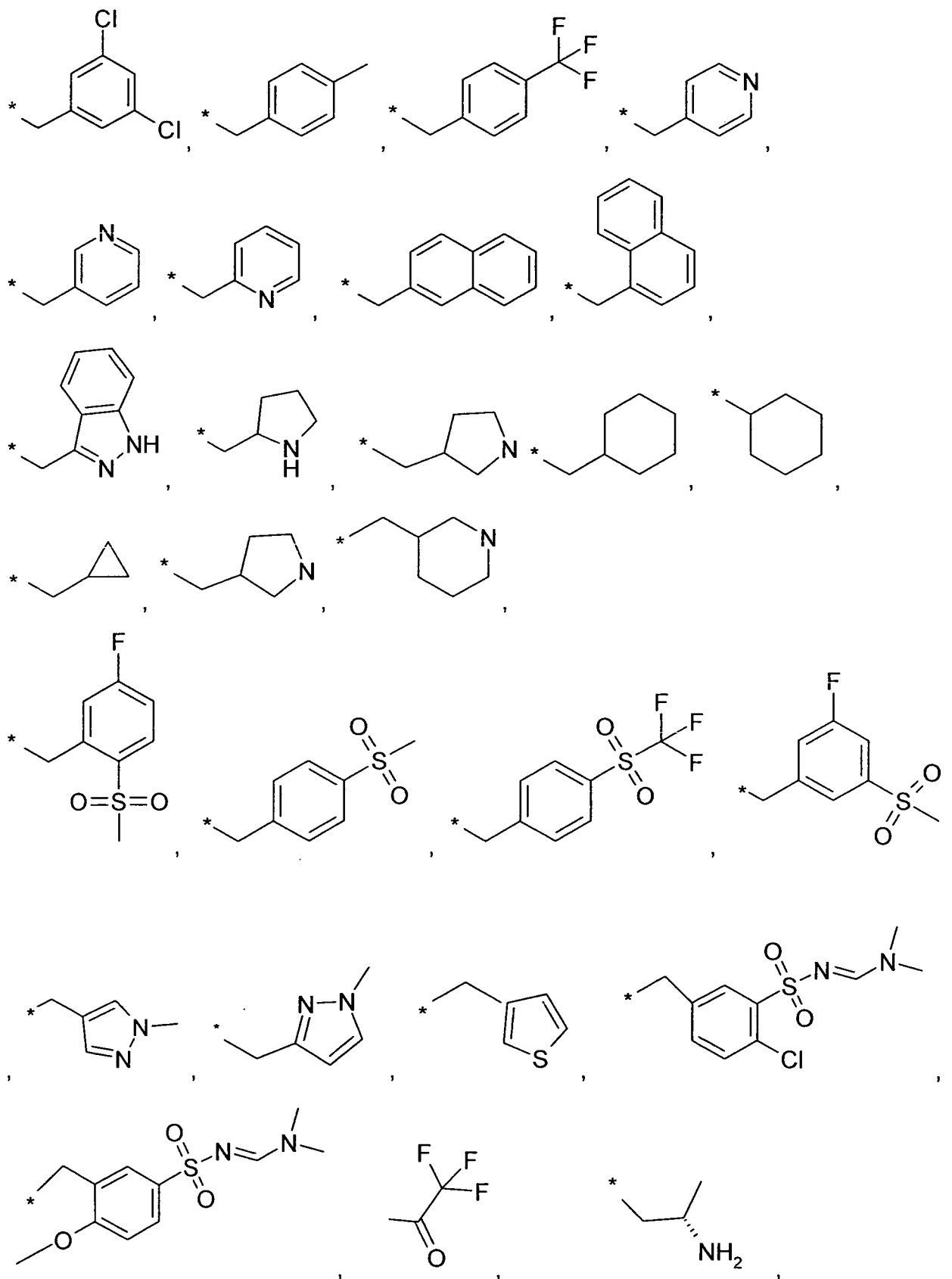
Especially preferred R_6 is H, (C_1 - C_6)alkyl or (C_3 - C_8)cycloalkyl. In an even more especially preferred embodiment R_6 is H, preferably unsubstituted (C_1 - C_6)alkyl or

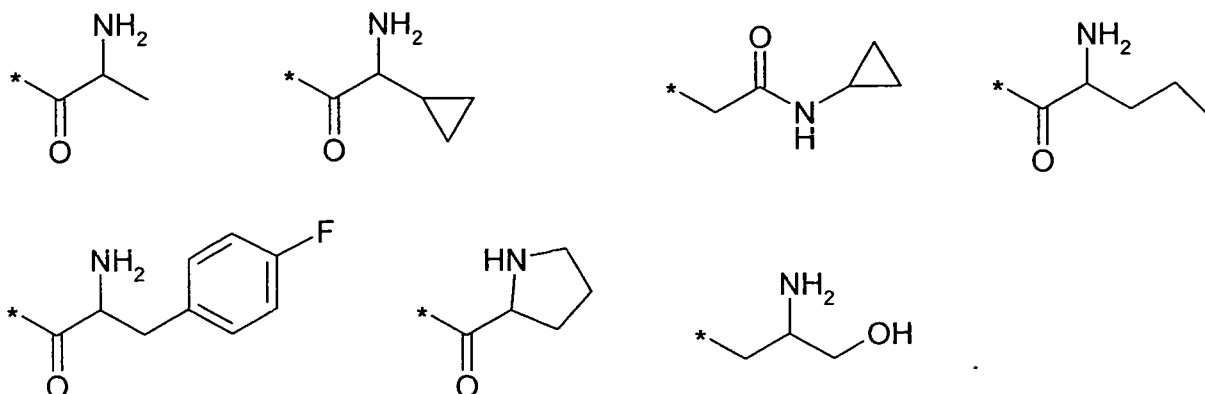
15 preferably unsubstituted (C_3 - C_8)cycloalkyl. Most preferred R_6 is H.

As examples for these embodiments, R_6 is hydrogen, methyl, ethyl, propyl, isopropyl, 3-methyl-butyl, 2-methyl-propyl, 1-ethyl-propyl, butyl, pentyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl or a substituent selected from the group consisting of

20







The asterisk (*) denotes where the bond is connected to the N-atom of the ring.

- 5 Preferably, R₇ is H, halogen, CN, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, (C₂-C₆)alkenyl, R' or (C₁-C₆)alkylene-(C₃-C₈)cycloalkyl. More preferred, R₇ is H, halogen, CN, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, (C₁-C₄)alkenyl, phenyl, cyclopropyl or (C₅-C₆)heteroaryl. Most preferably, R₇ is H, fluoro, chloro, bromo, methyl, ethyl, methoxy, propyl, phenyl, nitrile, cyclopropyl, thienyl or vinyl, most especially preferred
- 10 R₇ is H, fluoro, chloro, bromo, methyl, propyl or methoxy. Most preferred R₇ is H. R₈ is preferably H, halogen or (C₁-C₄)alkyl. More preferred, R₈ is H, Cl, F, methyl or ethyl. Most preferred R₈ is H.

Preferably, R₂ is

- 15 R',
(C₇-C₈)alkyl,
(C₁-C₆)alkylene-R',
(C₂-C₆)alkenyl,
(C₁-C₆)alkylene-C(O)NH₂,
- 20 (C₁-C₆)alkylene-C(O)NH-R',
(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,
(C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,
(C₁-C₆)alkylene-C(O)N[R']₂;

- (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,
 C(O)NH-(C₁-C₆)alkyl,
 C(O)NHR',
 C(O)-NH(C₁-C₆)alkenyl,
 5 C(O)-NH(C₁-C₆)alkynyl,
 C(O)-NH(C₁-C₆)alkylene-R',
 C(O)N[(C₁-C₆)alkyl]R',
 C(O)N[(C₁-C₆)alkyl]₂,
 C(O)-(C₁-C₆)alkylene-R',
 10 C(O)O(C₁-C₆)alkylene-R';

or R₂ is (C₁-C₆)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

15

or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;
 More preferably, R₂ is

- 20 R',
 (C₁-C₆)alkylene-R',
 (C₂-C₆)alkenyl,
 (C₁-C₆)alkylene-C(O)NH₂,
 (C₁-C₆)alkylene-C(O)NH-R',
 25 (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,
 C(O)NH-(C₁-C₆)alkyl,
 C(O)NHR',
 C(O)-NH(C₂-C₆)alkynyl,
 C(O)-NH(C₁-C₆)alkylene-R',

or R₂ is (C₁-C₃)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

- 5 or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring.

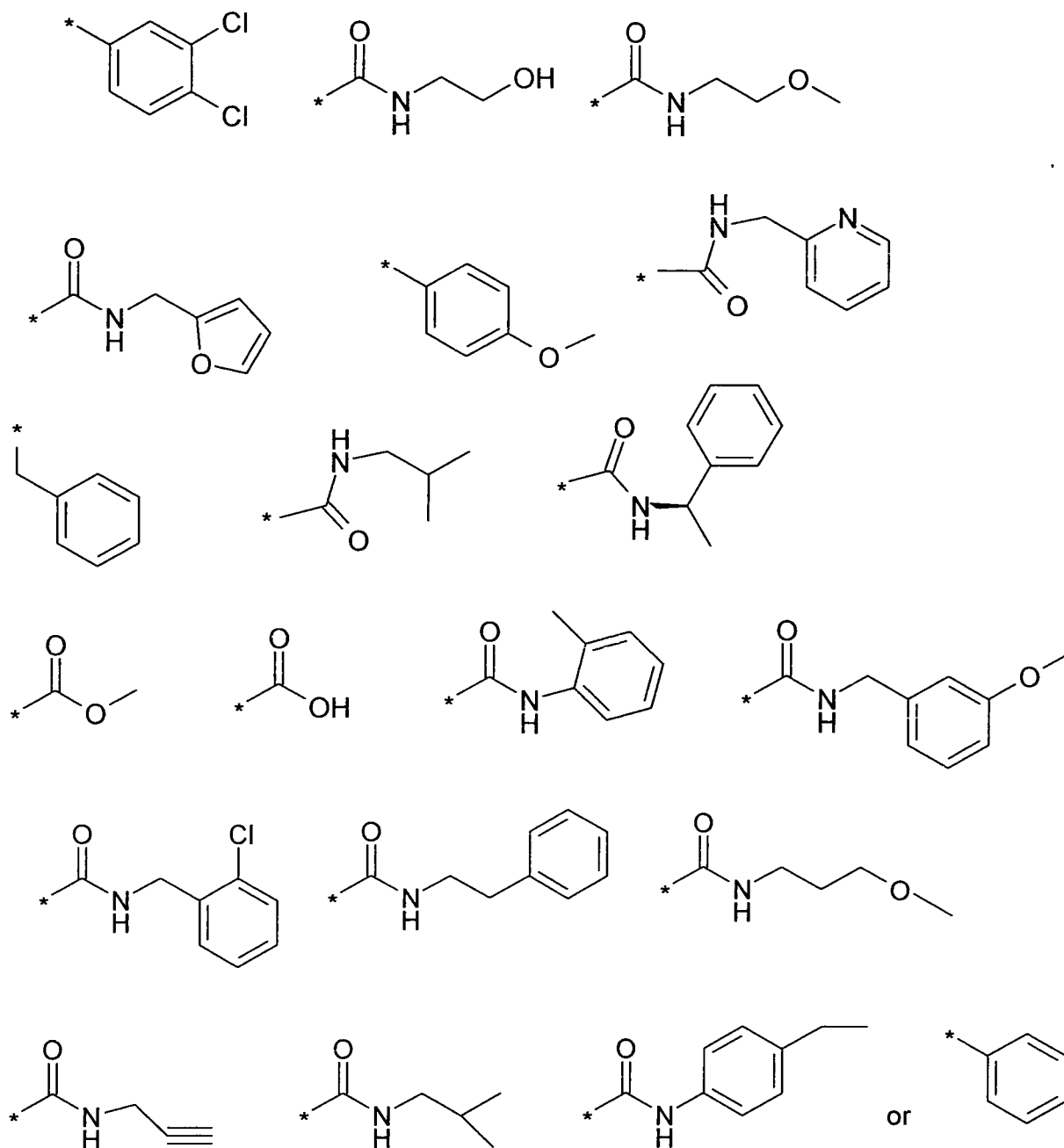
Most preferably, R₂ is

- 10 R',
 (C₁-C₆)alkylene-R',
 (C₂-C₆)alkenyl,
 (C₁-C₆)alkylene-C(O)NH-R',
 (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,
 15 C(O)NH-(C₁-C₆)alkyl,
 C(O)NHR',
 C(O)-NH(C₂-C₆)alkynyl,
 C(O)-NH(C₁-C₆)alkylene-R',

- 20 or R₂ is a (C₁-C₂)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

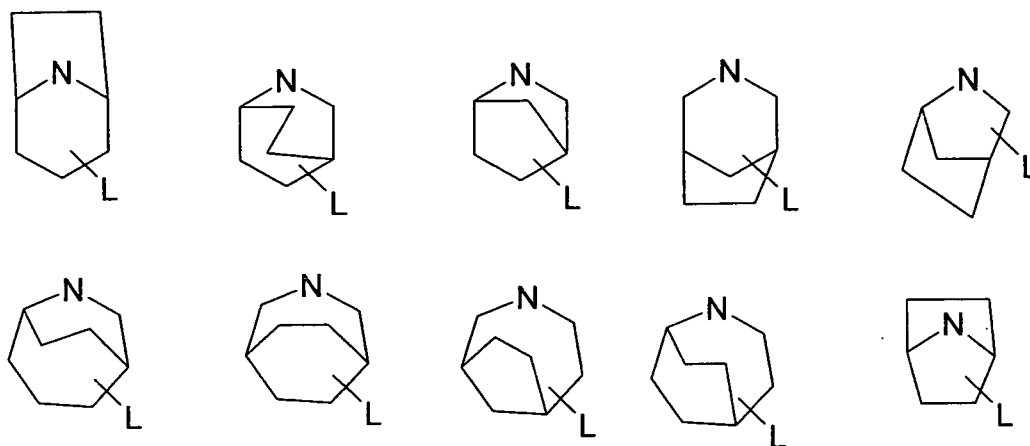
- R₂ may be bound to any carbon atom of the ring including the position where the linker
 25 group L is bound.

As examples for these embodiments, R₂ is

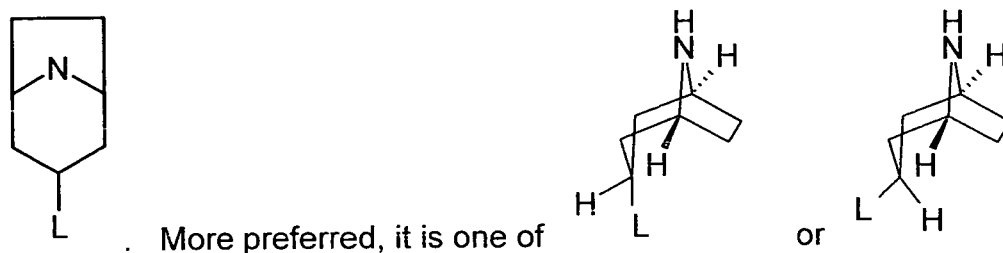


- 5 The asterisk (*) denotes where the bond is connected to the C-atom of the ring.

Examples for the embodiments wherein R₂ is a C1-C4 alkylene, which creates a second ring system with the cyclic amine, comprise



In a preferred embodiment the created ring system is selected from

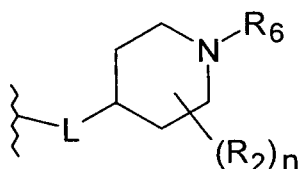


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Preferably, n is 1, 2 or 3. More preferred, n is 1 or 2. Most preferred n is 1.

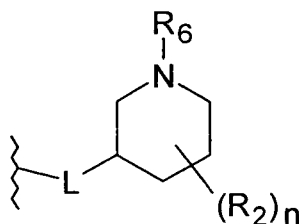
Preferably m is 2, 3 or 4. More preferred m is 3.

- 10 The linker group L may be bound to the ring in any position via a ring carbon atom. In a preferred embodiment, m is 3 and L is attached to the 4-position of the piperidine ring



or L is attached to the 3-position of the piperidine ring

23



in all their stereochemical forms.

In an especially preferred embodiment, L is attached to the 4-position of the piperidine ring.

In another embodiment, L is $O(CH_2)_p$. In a further embodiment of L, L is $S(CH_2)_p$, $S(O)(CH_2)_p$ or $SO_2(CH_2)_p$. In another embodiment L is $NH(CH_2)_p$, $N(C_1-C_6)alkyl-(CH_2)_p$, $N(C_3-C_6)cycloalkyl-(CH_2)_p$, $N[CO(C_1-C_6)alkyl]-(CH_2)_p$, $N[(C_1-C_3)alkylene-aryl]-(CH_2)_p$ or $N[(C_1-C_3)alkylene-(C_5-C_6)heterocycl]-(CH_2)_p$ with $NH(CH_2)_p$, $N(C_1-C_6)alkyl-(CH_2)_p$ being more preferred. A preferred $N(C_1-C_6)alkyl$ is $N(C_1-C_4)alkyl$, more preferably NCH_3 or NCH_2CH_3 with NCH_3 being more preferred. Even more preferred L is $O(CH_2)_p$, $S(CH_2)_p$ or $NH(CH_2)_p$. Most preferred L is O, S or NH with O being especially preferred.

Preferably p is 0, 1, 2, or 3, more preferred 0 or 1, with 0 being most preferred.

More preferably, m is 3 and L is O, S or NH and is attached to the 4-position of the piperidine ring.

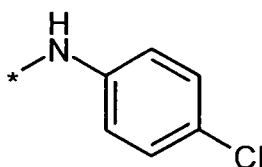
In residues R_2 to R_8 an alkyl or alkylene can optionally be substituted one or more times by halogen. Preferably alkyl or alkylene is substituted one to three times by halogen selected from chloro or bromo but may be substituted by fluoro once or more, e.g. being perfluorinated. Preferably halogen is Fluor. More preferred an alkyl or alkylene is not halogenated.

In residues R₂, R₄, R₅, R₆, R₇ and R₈ alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by a group selected independently from OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂.

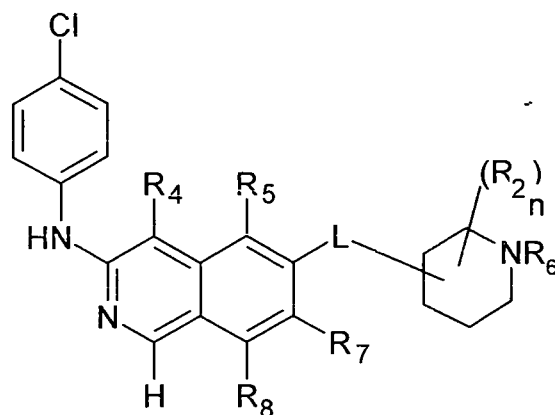
If substituted, the number of substituents is preferably between 1, 2, 3 or 4, more preferably 1 or 2 with 1 being even more preferred. Preferably an alkylene or cycloalkyl is not substituted. More preferably an alkyl, alkylene or cycloalkyl is not substituted. Preferably in R₄, R₅, R₇ and R₈ an alkyl, alkylene or cycloalkyl is not substituted. More preferred, in R₄, R₅, R₆, R₇ and R₈ an alkyl, alkylene or cycloalkyl is not substituted.

In preferred embodiments of the present invention one or more or all of the groups contained in the compounds of formula (I) can independently of each other have any of the preferred, more preferred or most preferred definitions of the groups specified above or any one or some of the specific denotations which are comprised by the definitions of the groups and specified above, all combinations of preferred definitions, more preferred or most preferred and/or specific denotations being a subject of the present invention. Also with respect to all preferred embodiments the invention includes the compounds of the formula (I) in all stereoisomeric forms and mixtures of stereoisomeric forms in all ratios, and their pharmaceutically acceptable salts.

The term “*—” in the exemplified substituents *vide supra* marks the point where the substituent is attached, which means, for example, for a R₃ substituent



and m is 3 and R₁ is H a compound of the formula



A preferred embodiment is a compound of the formula (I) wherein

5 R_1 is H, OH or NH_2 ;

R_2 is

R' ,

(C₇-C₈)alkyl,

10 (C₁-C₆)alkylene- R' ,

(C₂-C₆)alkenyl,

(C₁-C₆)alkylene-C(O) NH_2 ,

(C₁-C₆)alkylene-C(O) $NH-R'$,

(C₁-C₆)alkylene-C(O) $NH-(C_1-C_6)alkyl$,

15 (C₁-C₆)alkylene-C(O) $N[(C_1-C_6)alkyl]_2$,

(C₁-C₆)alkylene-C(O) $N[R']_2$;

(C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,

C(O) $NH-(C_1-C_6)alkyl$,

C(O) NHR' ,

20 C(O)- $NH(C_2-C_6)alkenyl$,

C(O)- $NH(C_2-C_6)alkynyl$,

C(O)- $NH(C_1-C_6)alkylene-R'$,

C(O) $N[(C_1-C_6)alkyl]R'$

$C(O)N[(C_1-C_6)alkyl]_2$,

$C(O)-(C_1-C_6)alkylene-R'$,

$C(O)O(C_1-C_6)alkylene-R'$;

- 5 or R_2 is $(C_1-C_6)alkyl$, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH_3 , $COOH$, $COOCH_3$, NH_2 , $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

- 10 or R_2 is a $(C_1-C_4)alkylene$ bound to the cyclic amine, in which the $(C_1-C_4)alkylene$ forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

R_3 is H, halogen, $(C_1-C_4)alkylene-R'$, $O-R''$ or NHR'' ;

- 15 R_4 is H, halogen or $(C_1-C_6)alkyl$;

R_5 is H, $(C_1-C_6)alkyl$, halogen, CN, $(C_2-C_6)alkenyl$, $(C_6-C_{10})aryl$, $NH-(C_6-C_{10})aryl$, $(C_1-C_6)alkylene-(C_6-C_{10})aryl$, $(C_5-C_{10})heterocyclyl$ or $(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl$;

- 20 R_6 is H, R' , $(C_1-C_8)alkyl$, $(C_1-C_6)alkylene-R'$, $(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$, $(C_1-C_6)alkylene-O-R'$, $(C_1-C_6)alkylene-CH[R']_2$, $(C_1-C_6)alkylene-C(O)NH_2$, $(C_1-C_6)alkylene-C(O)NH-R'$, $(C_1-C_6)alkylene-C(O)N[(C_1-C_4)alkyl]_2$, $C(O)(C_1-C_4)alkyl$ or $(C_1-C_6)alkylene-C(O)N[R']_2$,
- 25 $C(O)O-(C_1-C_6)alkyl$, $C(O)(C_1-C_6)alkyl$, $C(O)(C_3-C_8)cycloalkyl$, $C(O)NH-(C_1-C_6)alkyl$, $C(O)N[(C_1-C_6)alkyl]_2$, $C(O)(C_1-C_6)alkylene-C_3-C_8)cycloalkyl$, $C(O)(C_1-C_6)alkylene-C_5-C_{10})heterocyclyl$ or $C(O)(C_1-C_6)alkylene-(C_6-C_{10})aryl$.

R_7 is H, halogen, CN, $(C_1-C_6)alkyl$, $O-(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$ or R' ;

R₈ is H, halogen or (C₁-C₆)alkyl;

m is 2, 3 or 4

5 n is 1, 2 or 3,

L is S(CH₂)_p, NH(CH₂)_p or N(C₁-C₆)alkyl-(CH₂)_p, and

p is 0, 1 or 2;

10

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

15 A further preferred embodiment is a compound of the formula (I) wherein

R₁ is H or OH;

R₂ is

20

R',

(C₁-C₆)alkylene-R',

(C₂-C₆)alkenyl,

(C₁-C₆)alkylene-C(O)NH₂,

(C₁-C₆)alkylene-C(O)NH-R',

25

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

C(O)NH-(C₁-C₆)alkyl,

C(O)NHR',

C(O)-NH(C₁-C₆)alkylene-R',

C(O)-NH(C₂-C₆)alkenyl,

30

C(O)-NH(C₂-C₆)alkynyl,

or R₂ is (C₁-C₄)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

- 5 or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

R₃ is H, halogen or NHR'', wherein R'' is defined as above;

10

R₄ is H, halogen or (C₁-C₄)alkyl;

R₅ is H, (C₁-C₆)alkyl, halogen, (C₂-C₄)alkenyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl or (C₅-C₁₀)heterocyclyl;

15

R₆ is H, (C₃-C₈)cycloalkyl, (C₁-C₈)alkyl, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₃)alkylene-R', C(O)O-(C₁-C₆)alkyl, C(O)(C₁-C₆)alkyl, C(O)(C₃-C₈)cycloalkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)NH-(C₁-C₆)alkyl, C(O)N[(C₁-C₆)alkyl]₂, C(O)(C₁-C₃)alkylene-(C₃-C₈)cycloalkyl, C(O)(C₁-C₃)alkylene-(C₅-C₁₀)heterocyclyl,
 20 or C(O)(C₁-C₃)alkylene--(C₆-C₁₀)aryl;

R₇ is H, halogen, CN, (C₁-C₆)alkyl, O(C₁-C₆)alkyl, (C₂-C₆)alkenyl or R';

R₈ is H, halogen or (C₁-C₆)alkyl;

25

m is 2, 3 or 4;

n is 1, 2 or 3;

30 L is O(CH₂)_p, S(CH₂)_p or NH(CH₂)_p, and

p is 0 or 1;

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

5

An especially preferred embodiment is a compound of the formula (I) wherein

R₁ is H or OH;

10

R₂ is

C₁-C₆)alkylene-R',

(C₁-C₂)alkenyl,

(C₁-C₆)alkylene-C(O)NH-R',

15 (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

C(O)NH-(C₁-C₆)alkyl,

C(O)-NH(C₂-C₆)alkynyl,

C(O)NHR',

C(O)-NH(C₁-C₆)alkylene-R',

20

or R₂ is a (C₁-C₂)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

25 R₃ is H, NH-(C₅-C₆)heteroaryl or NH-phenyl;

R₄ is H, halogen or (C₁-C₄)alkyl;

R₅ is H, (C₁-C₄)alkyl, halogen, (C₁-C₄)alkenyl, (C₆-C₁₀)aryl, (C₁-C₂)alkyl-

30 (C₆-C₁₀)aryl or (C₅-C₆)heteroaryl;

R₆ is H, (C₃-C₈)cycloalkyl, (C₁-C₈)alkyl, (C₁-C₃)alkylene-R'; C(O)(C₁-C₆)alkyl, C(O)(C₃-C₈)cycloalkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)(C₁-C₃)alkylene-(C₅-C₁₀)heterocyclyl, or C(O)(C₁-C₃)alkylene--(C₆-C₁₀)aryl.

- 5 R₇ is H, halogen, CN, (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)alkenyl, phenyl, cyclopropyl, (C₅-C₆)heteroaryl;

R₈ is H, halogen or (C₁-C₄)alkyl;

- 10 m is 3

n is 1; and

L is O, S or NH;

15

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

- In an embodiment the present invention relates to a compound of formula (I) selected
20 from the group of

4. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester,
- 8, (2R,4R)-4-(Isoquinolin-6-yloxy)-2-o-tolylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester,
- 25 9. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid o-tolylamide,
10. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide,
11. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 3-methoxy-benzylamide
12. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide
- 30 13. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethyl-amide,

14. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide,
15. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (2-hydroxy-ethyl)-amide,
- 5 16. (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
17. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
18. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide,
- 10 19. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
20. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid prop-2-ynylamide,
21. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethyl-amide,
- 15 22. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide,
23. (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide,
24. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
25. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid ((R)-1-phenyl-ethyl)-amide,
- 20 26. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
27. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-hydroxy-ethyl)-amide,
- 25 28. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-amide,
29. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide,
30. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
- 30 31. (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid prop-2-ynylamide,

32. (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester,
34. (2S,4R)-2-(4-Ethyl-phenylcarbamoyl)-4-(isoquinolin-6-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester,
- 5 35. (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
38. (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
39. (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-amide,
- 10 40. (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide,
41. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
- 15 42. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide,
43. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
44. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
- 20 45. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid phenethyl-amide,
46. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid 2-chloro-benzylamide,
47. (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid isobutyl-amide,
- 25 48. (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid 3-methoxy-benzylamide,
49. (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid (2-methoxy-ethyl)-amide,
50. (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid o-tolylamide,
- 30 51. (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid isobutyl-amide,
52. 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-isoquinoline, or
69. 6-(1-benzyl-4-phenyl-piperidin-4-yloxy)-7-chloro-isoquinoline,

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts. (Cpd. number given for reference)

In another embodiment the present invention relates to a compound of formula (I)
5 selected from the group of

53 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one

72/73. 6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-7-chloro-2H-isoquinolin-1-one,

74. 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one,

75. 7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one

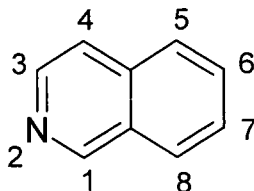
10 76. 7-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one, or

77. N6-(4-Amino-4-phenyl-cyclohexyl)-isoquinoline-1,6-diamine,

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

15 As in any embodiment of the invention, in the preceding embodiments which contain preferred, more preferred, most preferred or exemplary definitions of compounds according to the invention, one or more or all of the groups can have any of its preferred, more preferred, most preferred definitions specified above or any one or some of the specific denotations which are comprised by its definitions and are
20 specified above.

Isoquinoline substitution pattern is numbered according to IUPAC rules:



25 All references to "compound(s) of formula (I)" hereinafter refer to compound(s) of the formula (I), (II), (III), (III') and (IV) as described above, and their pharmaceutically acceptable salts, and/or to their stereoisomeric forms, polymorphs and solvates. Physiologically functional derivatives as described herein are also included.

Pharmaceutically acceptable salts of compounds of the formula (I) mean both their organic and inorganic salts as described in Remington's Pharmaceutical Sciences (17th edition, page 1418 (1985)). Because of the physical and chemical stability and the solubility, preference is given for acidic groups inter alia to sodium, potassium, calcium and ammonium salts; preference is given for basic groups inter alia to salts of maleic acid, fumaric acid, succinic acid, malic acid, tartaric acid, methanesulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or of carboxylic acids or sulfonic acids, for example as hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, acetates, lactates, maleates, fumarates, malates, gluconates, and salts of amino acids, of natural bases or carboxylic acids. The preparation of pharmaceutically acceptable salts from compounds of the formula (I) which are capable of salt formation, including their stereoisomeric forms, takes place in a manner known per se. The compounds of the formula (I) form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts with basic reagents such as hydroxides, carbonates, bicarbonates, alcoholates and ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine, diethanolamine or triethanolamine, trometamol or else basic amino acids, for example lysine, ornithine or arginine. Where the compounds of the formula (I) have basic groups, stable acid addition salts can also be prepared with strong acids. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid.

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula (I) of the invention, for

example an N-oxide, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula (I) or an active metabolite thereof.

- 5 Physiologically functional derivatives include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.
- 10 The invention relates to compounds of the formula (I), (II), (III), (III') or (VI) in the form of their stereoisomeric forms, which include racemates, racemic mixtures, pure enantiomers and diastereomers and mixtures thereof.

The compounds of the invention may also exist in various polymorphous forms, for
15 example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

If radicals or substituents may occur more than once in the compounds of the formula (I), they may all, independently of one another, have the stated meaning and be
20 identical or different.

The terms (C₁-C₂)alkyl, (C₁-C₄)alkyl, (C₁-C₆)alkyl, (C₁-C₈)alkyl and the corresponding alkylene substituents are understood as a hydrocarbon residue which can be linear, i.e. straight-chain, or branched and has 1, 2, 3, 4, 5, 6, 7 or 8
25 carbon atoms, respectively. This also applies if an alkyl group occurs as a substituent on another group, for example in an alkoxy group (O-alkyl), S-alkyl or a -O(C₁-C₆)alkylene-O-, an alkoxycarbonyl group or an arylalkyl group. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl or hexyl, the n-isomers of all these groups, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl. Alkyl or
30 alkylene groups may – if not otherwise stated – be halogenated once or more, e.g. alkyl groups may be fluorinated, e.g. perfluorinated. Examples of halogenated alkyl

groups are CF_3 and CH_2CF_3 , OCF_3 , SCF_3 , or $-\text{O}-(\text{CF}_2)_2-\text{O}-$.

The term (C_2-C_6) -alkenyl means a hydrocarbon residue whose carbon chain is straight-chain or branched and comprises 2 to 6 carbon atoms and have, depending on the chain length, 1, 2 or 3 double bonds, for example, vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl. The double bond may where possible have the E or Z orientation. The double bonds may be both internal and terminal.

10 (C_2-C_6) -alkynyl groups are hydrocarbon radicals whose carbon chain is straight-chain or branched and comprises 2 to 6 carbon atoms and have, depending on the chain length, 1 or 2 triple bonds, for example, ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butyne. The triple bonds may be both internal and terminal.

15 Halogen means fluoro, chloro, bromo or iodo.

(C_3-C_8) cycloalkyl groups are cyclic alkyl groups containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclooctyl, which can also be substituted and/or contain 1 or 2 double bonds (unsaturated cycloalkyl groups) like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

A $(\text{C}_6-\text{C}_{10})$ aryl group means an aromatic ring or a ring system which comprises two aromatic rings which are fused or otherwise linked, for example a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha- or beta-tetralon-, indanyl- or indan-1-on-yl group. A preferred $(\text{C}_6-\text{C}_{10})$ aryl group is phenyl.

A $(\text{C}_5-\text{C}_{10})$ heterocyclyl group means a mono- or bicyclic ring system in which one or more carbon atoms can be replaced by one or more heteroatoms such as, for example 1, 2 or 3 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or combinations of different hetero atoms. The heterocyclyl residues can be bound at any

positions, for example on the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position. (C₅-C₁₀)heterocyclyl groups may be (1) aromatic [= heteroaryl groups] or (2) saturated or (3) mixed aromatic/saturated.

- 5 Suitable (C₅-C₁₀)heterocyclyl group include acridinyl, azocinyl, benzimidazolyl, benzofuryl, benzomorpholinyl, benzothienyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, furanyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, chromen-2-onyl, cinnolinyl,
- 10 decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, furyl, furazanyl, homomorpholinyl, homopiperazinyl, imidazolidinyl, imidazolyl, imidazolyl, 1H-indazolyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-
- 15 oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, prolinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridonyl, pyridooxazoles, pyridoimidazoles, pyridothiazoles, pyridinyl,
- 20 pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thienyl, triazolyl, tetrazolyl and xanthenyl. Pyridyl stands both for 2-, 3- and 4-pyridyl. Thienyl stands both for 2- and 3-thienyl. Furyl stands both for 2- and 3-furyl. Also included are the
- 25 corresponding N-oxides of these compounds, for example, 1-oxy-2-, 3- or 4-pyridyl.

Substitutions in (C₅-C₁₀)heterocyclyl residues can occur on free carbon atoms or on nitrogen atoms.

- 30 Preferred examples of (C₅-C₁₀)heterocyclyl residues are pyrazinyl, pyridyl, pyrimidinyl, pyrazolyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl, benzofuryl, quinolinyl, tetrazolyl and triazolyl.

(C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl groups are unsubstituted or, if not stated otherwise, substituted one or more times, preferably one to three times, by suitable groups independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₁-C₆)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-OH, (C₁-C₆)alkylene-NH₂, (C₁-C₆)alkylene-NH(C₁-C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl; SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl, NH-C(O)O-(C₁-C₆)alkyl, NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heterocyclyl, N(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)O-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl], (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heterocyclyl, (C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, O-(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, wherein the (C₆-C₁₀)aryl or (C₅-C₁₀)heterocyclyl may be substituted one to 3 times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)O-(C₁-C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl, O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl; or wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to. Aryl or heterocyclyl substituents of (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group.

Preferred substituents for (C₆-C₁₀)aryl groups are (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, O-phenyl, phenyl, C(O)O-(C₁-C₆)alkyl, C(O)OH, C(O)-(C₁-C₄)alkyl, halogen, NO₂,

- SO₂NH₂, CN, SO₂-(C₁-C₄)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, NH-SO₂-(C₁-C₄)alkyl, NH₂, NH-C(O)-(C₁-C₄)alkyl, (C₃-C₈)cycloalkyl, (C₁-C₄)alkyl-OH, C(O)N[(C₁-C₄)alkyl]₂, CONH(C₁-C₆)alkyl, C(O)NH₂, N[(C₁-C₄)alkyl]₂, (C₁-C₄)alkylene-(C₆-C₁₀)aryl, wherein the (C₆-C₁₀)aryl may be further substituted one to three times, preferably once, by (C₁-C₄)alkyl, (C₁-C₄)alkylene-O-(C₁-C₆)alkyl, (C₆-C₁₀)aryl O-(C₁-C₆)alkyl-(C₆-C₁₀)aryl, or may be vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to. More preferred substituents for (C₆-C₁₀)aryl are halogen, CN, phenyl, O-phenyl, NH-C(O)-(C₁-C₄)alkyl especially NH-C(O)-CH₃, C(O)-(C₁-C₄)alkyl especially C(O)-CH₃, (C₁-C₄)alkyl especially CH₃ or CF₃, O-(C₁-C₄)alkyl especially O-CH₃, SO₂-NH₂, SO₂-(C₁-C₄)alkyl especially SO₂-CH₃ or SO₂-CF₃ or SO₂-N=CH-N[(C₁-C₄)alkyl]₂ especially SO₂-N=CH-N[(CH₃)₂.
- 15 In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl groups carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position.
- 20 The above statements relating to phenyl groups correspondingly apply to divalent groups derived from phenyl groups, i.e. phenylene which can be unsubstituted or substituted 1,2-phenylene, 1,3-phenylene or 1,4-phenylene. The above statements also correspondingly apply to the aryl subgroup in arylalkylene groups. Examples of arylalkylene groups which can also be unsubstituted or substituted in the aryl subgroup as well as in the alkylene subgroup, are benzyl, 1-phenylethylene, 2-phenylethylene, 3-phenylpropylene, 4-phenylbutylene, 1-methyl-3-phenyl-propylene.

- Preferred substituents for (C₅-C₁₀)heterocyclyl groups are (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, (C₁-C₄)alkylene-phenyl, halogen, (C₁-C₄)alkylene-O-(C₁-C₄)alkyl,
- 30

(C₅-C₁₀)heterocyclyl, (C₁-C₄)alkylene-N[(C₁-C₄)alkyl]₂, or (C₆-C₁₀)aryl, wherein the (C₆-C₁₀)aryl may be further substituted by (C₁-C₄)alkyl, O-(C₁-C₆)alkyl, halogen, (C₁-C₄)alkylene-O-(C₁-C₆)alkyl, O-(C₁-C₆)alkyl-(C₆-C₁₀)aryl, or may be vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to. More preferred substituents for (C₅-C₁₀)heterocyclyl groups are (C₁-C₄)alkyl, halogen or phenyl, wherein the phenyl may be further substituted one to three times, preferably once, by halogen, (C₁-C₄)alkyl or O-(C₁-C₄)alkyl.

- 10 The general and preferred substituents of (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl groups may be combined with the general and preferred definitions of R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, n, m, L and p as described above.

The present invention therefore also relates to the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs for the production of pharmaceuticals for the treatment and/or prevention of diseases associated with Rho-kinase and/or Rho-kinase mediated phosphorylation of myosin light chain phosphatase, i.e. for the treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, retinopathy, and glaucoma, peripheral circulatory disorder, peripheral occlusive arterial disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, including hypertension-induced, non-hypertension-induced, and diabetic nephropathies, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, e.g. neuropathic pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood

vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy such as osteoporosis, infection of digestive tracts with bacteria, sepsis, cancer development and progression, e.g. cancers of the breast, colon, prostate, ovaries, brain and lung and their metastases.

5

The present invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula (I) and/or its pharmaceutically acceptable salts and a pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances (or vehicles) and/or additives (or excipients).

10

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

20

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carrier substances and/or additives being used in addition to the compound(s) of the formula (I) and/or its (their) pharmaceutically acceptable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of

25

30

glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 to about 90 % by weight of the compounds of the formula (I) and/or their pharmaceutically acceptable salts and/or their prodrugs. The amount of the active ingredient of the formula (I) and/or its pharmaceutically acceptable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 to about 1000 mg, preferably from about 1 to about 500 mg.

In addition to the active ingredients of the formula (I) and/or their pharmaceutically acceptable salts and to carrier substances, the pharmaceutical preparations can contain one or more additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula (I) and/or their pharmaceutically acceptable salts. In case a pharmaceutical preparation contains two or more compounds of the formula (I) the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency.

The flexibility permitted with respect to the choice of substituents in the compounds of the formula (I) allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula (I) and/or its pharmaceutically acceptable salts, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

When using the compounds of the formula (I) the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for

achieving the desired results in an adult weighing about 75 kg is from about 0.01 to about 100 mg/kg, preferably from about 0.1 to about 50 mg/kg, in particular from about 0.1 to about 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts,
5 into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

Furthermore, the compounds of the formula (I) can be used as synthesis intermediates
10 for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

In general, protective groups that may still be present in the products obtained in the
15 coupling reaction are then removed by standard procedures. For example, tert-butyl protecting groups, in particular a tert-butoxycarbonyl group which is a protection form of an amino group, can be deprotected, i. e. converted into the amino group, by treatment with trifluoroacetic acid. As already explained, after the coupling reaction also functional groups can be generated from suitable precursor groups. In addition, a
20 conversion into a pharmaceutically acceptable salt or a prodrug of a compound of the formulae (I) can then be carried out by known processes.

In general, a reaction mixture containing a final compound of the formula (I) or an intermediate is worked up and, if desired, the product is then purified by customary
25 processes known to those skilled in the art. For example, a synthesized compound can be purified using well known methods such as crystallization, chromatography or reverse phase-high performance liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound. Similarly, well known methods such as amino acid sequence analysis,
30 NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

Accordingly, the following examples are part of and intended to illustrate but not to limit the present invention.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein.

Method A:

10 Stationary phase: Col YMC Jsphere 33 x 2
Gradient: ACN+0,05% TFA : water + 0.05% TFA
5:95(0 min) to 95:5(3.4 min) to 95:5(4.4 min)
Flow 1 mL/min

15 Method B:

Stationary phase: Col YMC Jsphere 33 x 2
Gradient: ACN+0,05% TFA : water + 0.05% TFA
5:95(0 min) to 95:5(2.5 min) to 95:5(3.0 min)
Flow 1 mL/min

20 Method C:

Stationary phase: Col YMC Jsphere ODS H80 20 x 2
Gradient: ACN : water+0.05% TFA
4:96(0 min) to 95:5(2.0 min) to 95:5(2.4 min)
25 Flow 1 mL/min

Method D:

Stationary phase: Col YMC Jsphere 33 x 2.1
Gradient: Grad ACN+0.08% FA:water+0.1%FA (Formic Acid)
30 5:95 (0min) to 95:5 (2.5min) to 95:5 (3min)
Flow 1.3 mL/min

Method E:

Stationary phase: Col YMC Jsphere 33 x 2
Gradient: ACN+0,05% TFA : water+0.05% TFA
5:95(0 min) to 95:5(2.5 min) to 95:5(3.2 min)
5 Flow 1.3 mL/min

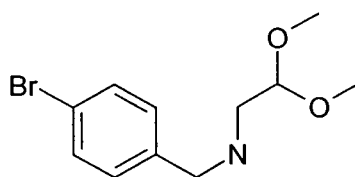
Method F:

Stationary phase: Col YMC-Pack Pro C18 RS 33 x 2.1
Gradient: Grad ACN+0.1% FA : water+0.1%FA (Formic Acid)
10 5:95(0min) to 95:5(2.5min) to 95:5(3min)
Flow 1.3 mL/min

Method G:

Stationary phase: Col Waters XBridge 4
15 Gradient: Grad water+0.1% FA : ACN+0.08%FA (Formic Acid)
97:3(0min) to 40:60(3.5min) to 2:98(5min)
Flow 1.3 mL/min

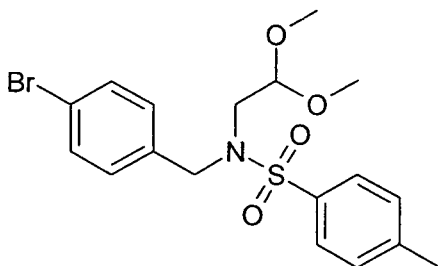
(4-Bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1)



20 50 g (270.2 mmol) 4-bromobenzaldehyde were dissolved in 200 ml toluene and 28.4 g (270.2 mmol) aminoacetaldehyde dimethylacetal were added. After the addition of 5.1 g (27.0 mmol) p-toluenesulfonic acid monohydrate, the reaction mixture was heated under reflux in a Dean Stark apparatus. After 4 h, the reaction was cooled to room
25 temperature and washed with saturated NaHCO₃-solution (2x) and H₂O. The combined aqueous layers were extracted with toluene and the combined organic layers were dried with MgSO₄ and evaporated. The residue was dissolved in 200 ml ethanol and 5.11 g (135.1 mmol) sodium borohydride were added in small portions. After stirring for 2 h at room temperature and standing overnight, 5.0 ml acetic acid were added and
30 the solvent was removed i. vac. The residue was taken up in dichloromethane and

washed (2x) with H₂O. After drying with MgSO₄ and evaporation, 60.5 g of the title compound were obtained, which were used without further purification. R_t = 0.80 min (Method C). Detected mass: 274.1/276.1 (M+H⁺).

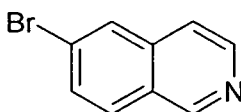
5 N-(4-Bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2)



60.5 g (4-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1, crude product) were dissolved in 270 ml dichloromethane / pyridine (8:1). At 0 °C a solution of 76.0 g (386.4 mmol) p-toluenesulfonylchloride in 100 ml dichloromethane were added and the solution was stirred at room temperature. After 3 h, the reaction mixture was washed twice with 2 N HCl and saturated NaHCO₃-solution. The organic layer was dried with MgSO₄ and evaporated. Final silicagel chromatography (heptane/ethyl acetate 4:1) gave 59.9 g of the title compound. R_t = 1.82 min (Method C). Detected mass: 396.1/398.1 (M-OMe⁻).

15

6-Bromo-isoquinoline (3)

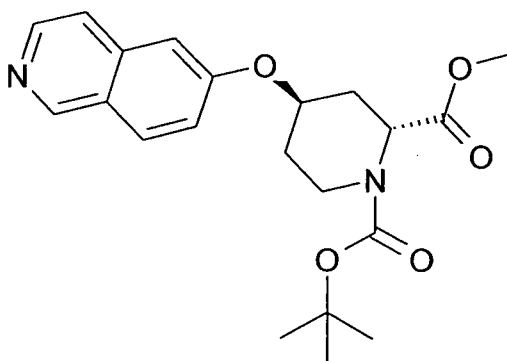


To a mechanically stirred suspension of 95.2 g (699.5 mmol) AlCl₃ in 400 ml dichloromethane a solution of 59.9 g (139.8 mmol) N-(4-Bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2) in 400 ml dichloromethane was added and the reaction was stirred at room temperature for 4 h. After standing overnight, the reaction mixture was poured on ice, the organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined dichloromethane solutions were washed with 1 N NaOH (2x) and saturated NaHCO₃-solution (2x). After drying with MgSO₄ and evaporation of the solvent, the crude product was purified by silicagel chromatography (heptane/ethyl acetate 1:1) to yield

17.5 g of the title compound. $R_t = 0.68$ min (Method C). Detected mass: 208.1/210.1 ($M+H^+$).

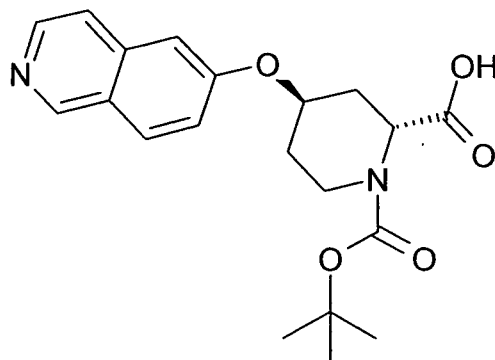
(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-

5 methyl ester (4)



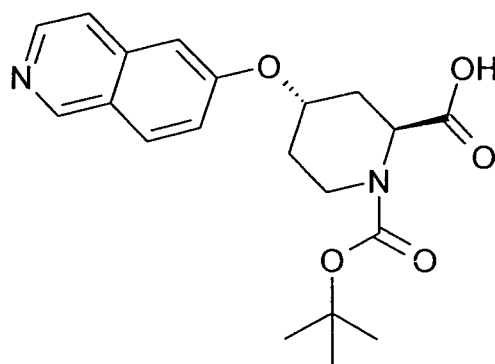
145 mg of 6-Hydroxyisoquinoline and 311 mg of (2R,4S)-4-Hydroxy-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester and 341 mg of triphenylphosphine
10 were suspended in 3.5 ml of THF and 171 μ l DIPEA were added. At 0°C 261 mg DEAD were added slowly and the mixture was allowed to come to room temperature and stirred until no further increase in product could be monitored. After Evaporation the mixture was subjected to chromatography on silica gel (50 to 80% ethylacetate in Heptane) to give (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester as an colorless oil.
15

(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (5)



6.9 g crude (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (4) in 100 ml of methanol were treated with 10 ml of 2 N NaOH and stirred over night. After Evaporation the mixture was subjected to preparative HPLC. Lyophilisation gave (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester as the trifluoroacetate as a white solid.

(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (6)

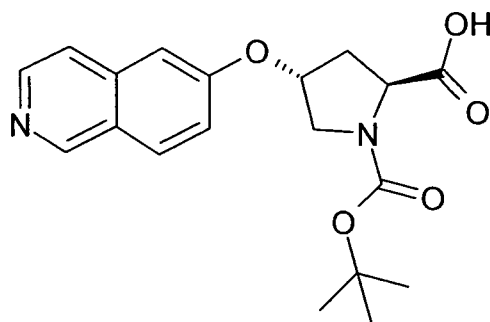


10

Starting from 6-Hydroxyisoquinoline and (2S,4R)-4-Hydroxy-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester could be obtained as the trifluoroacetate, using a similar method as described for the synthesis of (5).

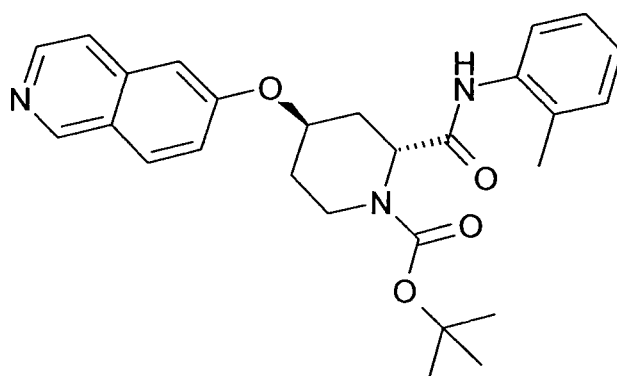
15

(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (7)



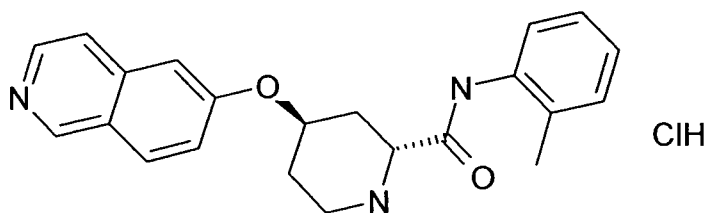
Starting from 6-Hydroxyisoquinoline and (2R,4S)-4-Hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester could be obtained as the trifluoroacetate.

- 5 (2R,4R)-4-(Isoquinolin-6-yloxy)-2-o-tolylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester (8)



- 28 mg 2-Mehtylaniline und 98 mg (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester trifluoroacetate (5) were dissolved in 0.5 ml of DMF. 32 mg HOBT and 88.0 μ l N-methylmorpholine were added follow by 44 mg EDC (free base) in 2 mol of dichloromethane. After stirring over night all volatiles were removed and the mixture subjected to preparative HPLC. Lyophilisation gave (2R,4R)-4-(Isoquinolin-6-yloxy)-2-o-tolylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester as the trifluoroacetate.

(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid o-tolylamide (9)



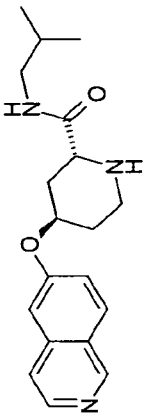
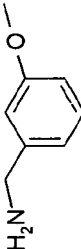
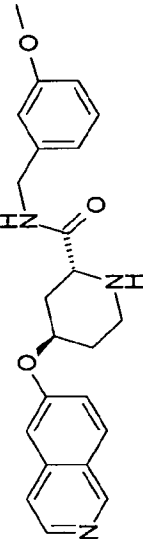
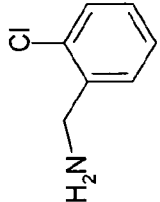
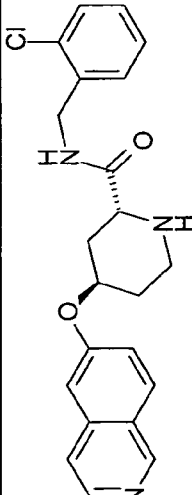
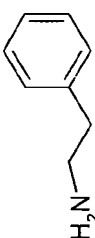
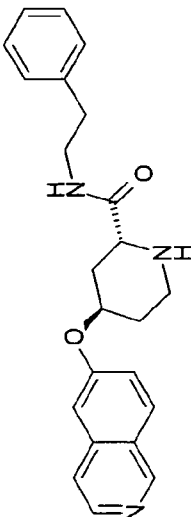
- (2R,4R)-4-(Isoquinolin-6-yloxy)-2-o-tolylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester trifluoroacetate (8) was dissolved in 4 N HCl in dioxane and stirred for 2 h at rt. Evaporation gave (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid o-

tolylamide as the hydrochloride. $R_t = 0.77$ min (Method B). Detected mass: 362.2 ($M+H^+$).

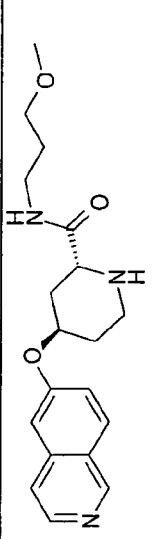
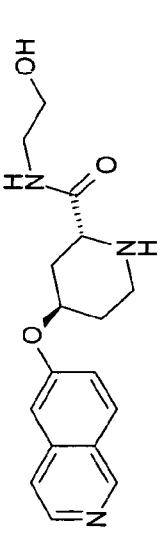
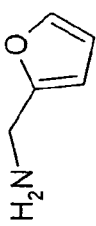
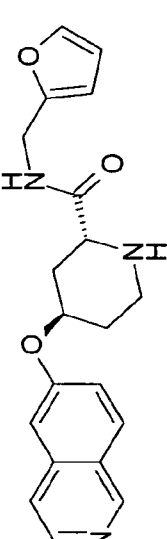
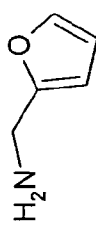
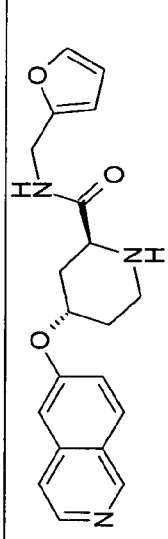
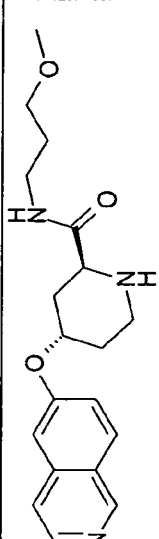
5 The compounds described in the following table were obtained in a similar fashion as described for compound 8 and 9 respectively. All compounds were measured using method A (Table 1).

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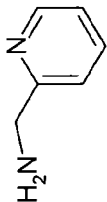
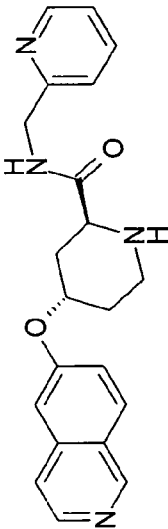
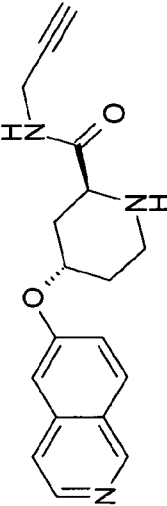
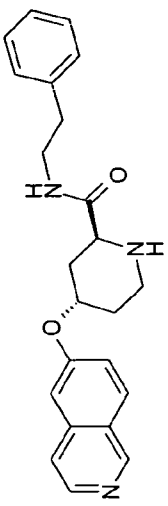
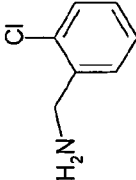
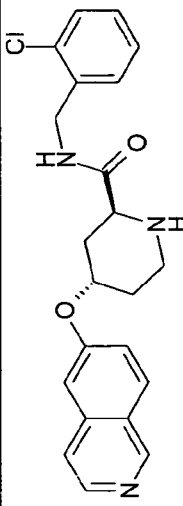
Table 1

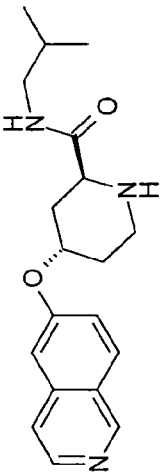
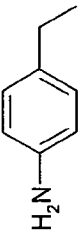
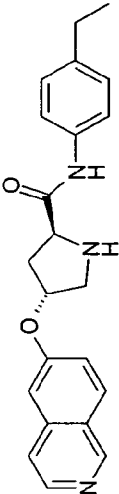
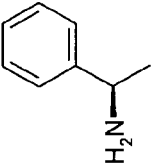
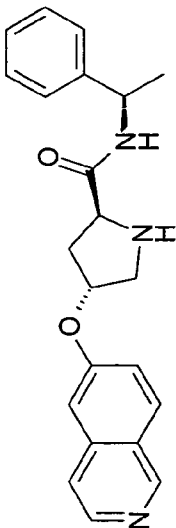
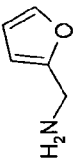
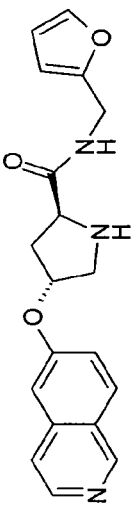
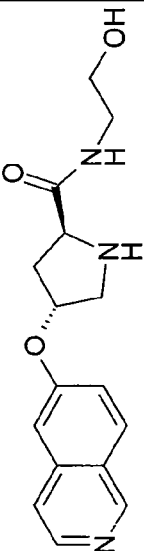
Cmpd. No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
10	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide			0.74	328.2
11	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 3-methoxy-benzylamide			0.79	392.2
12	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide			0.87	396.2
13	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethyl-amide			0.84	376.2

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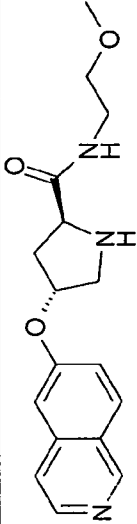
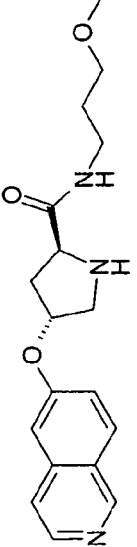
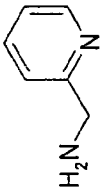
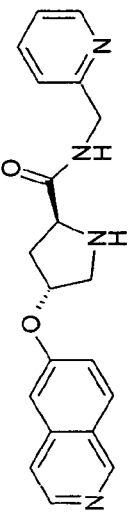
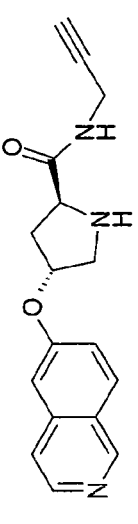
Cmpd. No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
14	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide			0.48	344.3
15	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (2-hydroxy-ethyl)-amide			0.16	316.3
16	(2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide			0.64	352.3
17	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide			0.57	352.2
18	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide			0.49	344.3

53

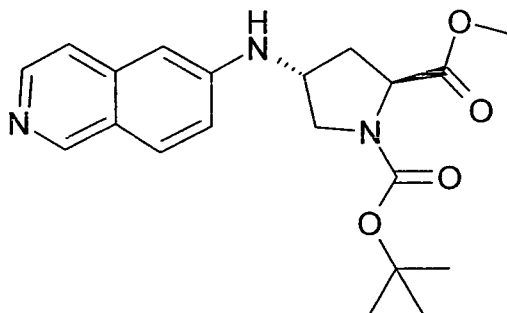
Cmpd. No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
19	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide			0.42	363.2
20	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid prop-2-ynylamide			0.42	310.2
21	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethylamide			0.84	376.3
22	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide			0.87	396.2

Cmpd. No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
23	(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide			0.74	328.3
24	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide			1.01	362.2
25	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid ((R)-1-phenyl-ethyl)-amide			0.81	362.2
26	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide			0.58	338.2
27	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-hydroxy-ethyl)-amide			0.17	302.2

55

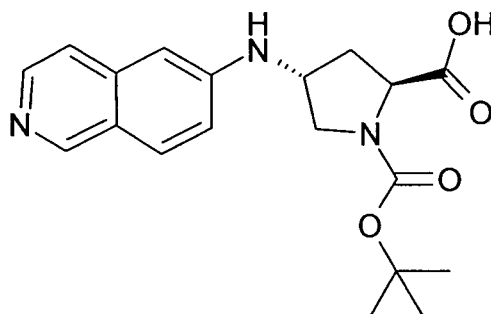
Cmpd. No.	Chemical Name	Amine	Product	R _f [min]	Mass [M+H ⁺]
28	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-amide			0.39	316.2
29	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide			0.44	330.2
30	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide			0.21	349.2
31	(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid prop-2-ynylamide			0.40	296.2

(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (32)



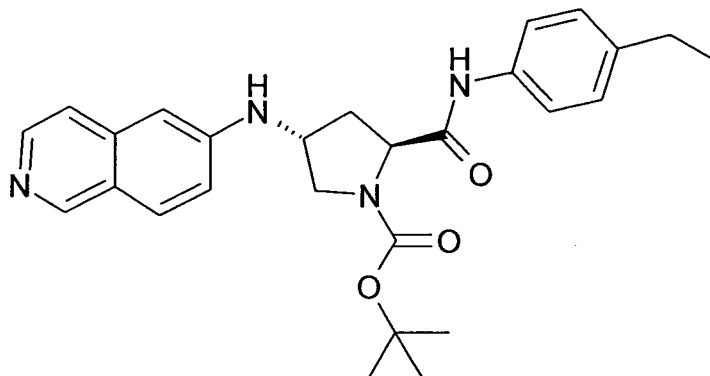
124 mg of 6-bromoisoquinoline (3), 488 mg of cesium carbonate and 202 mg (2S,4R)-4-amino-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester hydrochloride were dissolved in 6 ml of DMF and degassed. 46 mg Palladium acetate and 132 mg of Xanthphos were added and the mixture was stirred at 100°C for 5 h. After cooling to rt the mixture was filtrated, evaporated and the residue was purified by chromatography on silica gel (50% ethyl acetate in heptane to 100% ethyl acetate). To obtain (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester as a colourless oil.

(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (33)



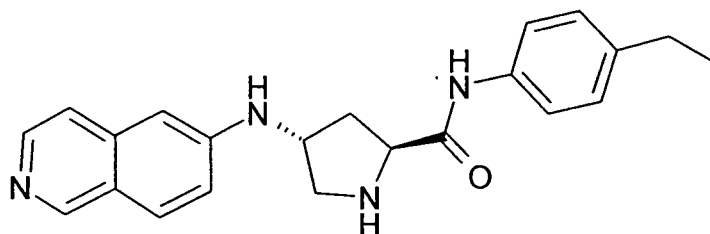
1.4 g of (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (32) were dissolved in 15 ml of methanol and treated with 3.4 ml of 2 N NaOH at rt until saponification was complete. After evaporation the residue was

subjected to preparative HPLC and lyophilized to obtain (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester as the trifluoroacetate. (2S,4R)-2-(4-Ethyl-phenylcarbamoyl)-4-(isoquinolin-6-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester (34)



94 mg (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (33) and 32 mg 4-ethylaniline were dissolved in 0.5 ml DMF and a solution of 33 mg HOAT in 0.5 ml DMF and 100 μ l DIPEA were added, followed by 112 mg PyBroP in 2 ml dichloromethane. After stirring over night all volatiles were evaporated and the mixture purified by preparative HPLC to obtain (2S,4R)-2-(4-ethyl-phenylcarbamoyl)-4-(isoquinolin-6-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester as the trifluoroacetate salt.

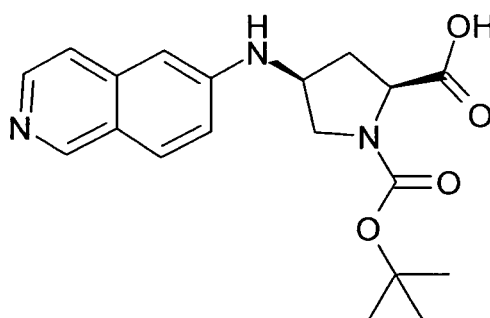
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide (35)



(2S,4R)-2-(4-Ethyl-phenylcarbamoyl)-4-(isoquinolin-6-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester trifluoroacetate was dissolved in 4 N HCl in dioxane and stirred for 2 h at rt. Evaporation gave (2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic

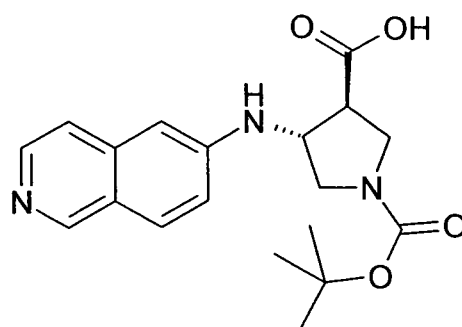
acid (4-ethyl-phenyl)-amide as the hydrochloride salt. $R_t = 1.05$ min (Method A).
Detected mass: 361.2 ($M+H^+$).

(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester
(36)



In analogy to the preparation of (33), (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester was prepared as the trifluoroacetate from 6-bromoisquinoline (3) and (2S,4S)-4-Amino-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester hydrochloride.

(3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester
(37)

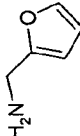
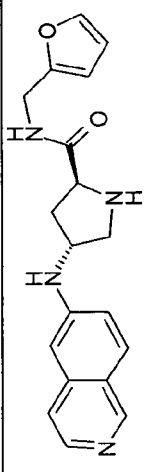
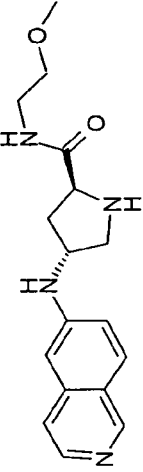
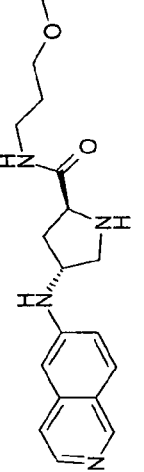
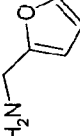
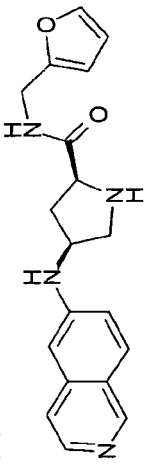
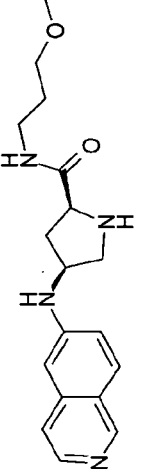


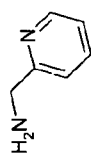
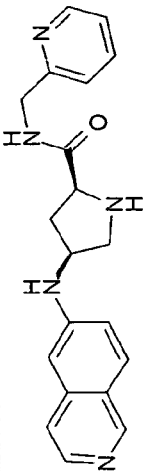
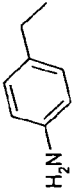
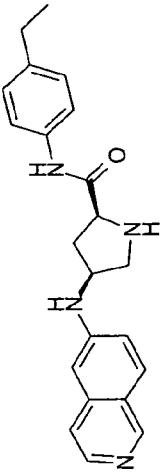
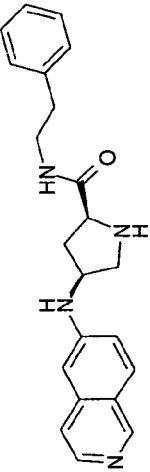
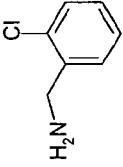
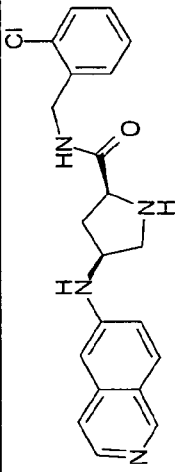
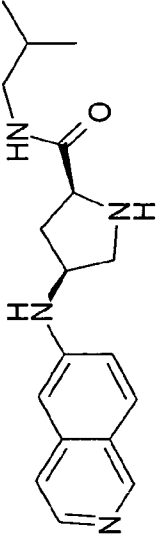
In analogy to the preparation of (33), (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester was prepared as the trifluoroacetate from 6-Bromoisquinoline and (3S,4R)-4-Amino-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

The compounds described in the following table 2 were obtained in a similar fashion as described for compound 34 and 35. All compounds were measured using method A.

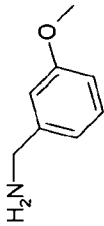
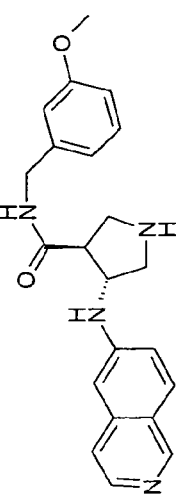
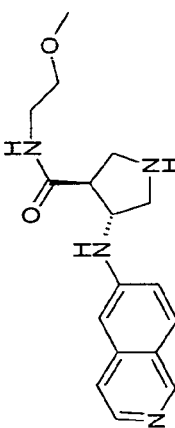
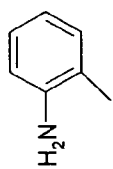
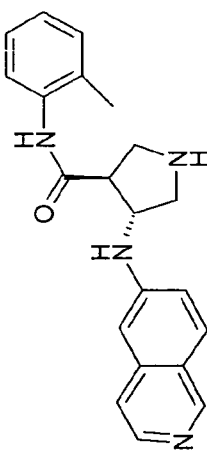
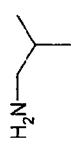
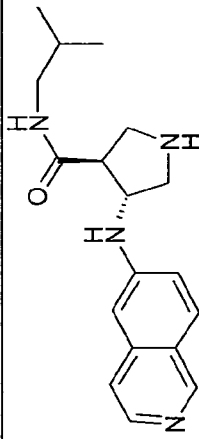
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Table 2

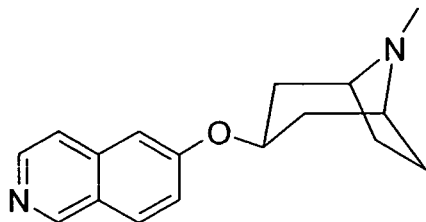
Compound No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
38	(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide			0.67	337.2
39	(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-amide			0.46	315.2
40	(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide			0.60	329.3
41	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide			0.60	337.2
42	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide			0.55	329.2

Compound No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
43	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide			0.16	348.2
44	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide			0.96	361.3
45	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid phenethyl-amide			0.82	361.3
46	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid 2-chloro-benzylamide			0.84	381.2
47	(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid isobutyl-amide			0.67	313.3

62

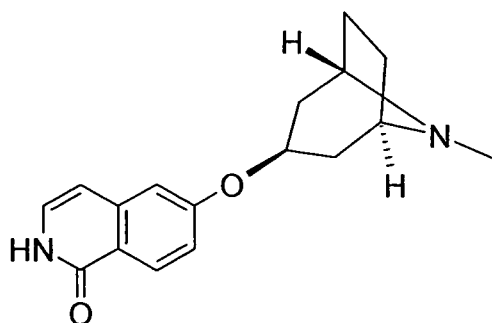
Compound No.	Chemical Name	Amine	Product	R _t [min]	Mass [M+H ⁺]
48	(3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid 3-methoxy-benzylamide			0.83	377.2
49	(3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid (2-methoxy-ethyl)-amide			0.68	315.1
50	(3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid o-tolylamide			0.86	347.1
51	(3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid isobutylamide			0.75	313.2

6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-isoquinoline (52)



625 mg of triphenyl phosphine were dissolved in 20 mL of dry dichloromethane, 0.095 mL of diethyl azodicarboxylate were added and the solution was shaken for 20 minutes. 69 μ L of triethyl amine, 72.6 mg of 6-hydroxy isoquinoline and 67.1 mg of tropine were added and the mixture was shaken overnight. The reaction mixture was filtered, the remainders washed thoroughly with dichloromethane and the combined organic layer was extracted twice with 1N sodium hydroxide and water, respectively. The organic layer was dried, evaporated to dryness and the crude material was purified by HPLC. The product was dissolved in 2N HCl and lyophilized to give 23 mg of 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-isoquinoline (52) as the hydrochloride. $R_t = 0.52$ min (Method A). Detected mass: 269.2 ($M+H^+$).

15 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one (53)

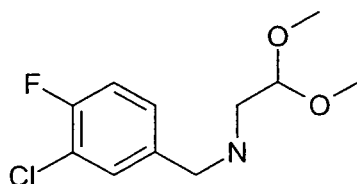


8 mL of dry dichloromethane were added to 814 mg (1.73 mmol) of polystyrene bound triphenyl phosphine. At 0°C 234 μ L (1.48 mmol) of diethyl azodicarboxylate were added. 200 mg (1.24 mmol) of 6-hydroxy-2H-isoquinolinone (66), 210 mg (1.49 mmol) of tropine and 261 μ L of triethylamine were added and the reaction mixture was allowed to warm to room temperature and stirred overnight. Another 279 mg of PS-triphenyl phosphine, 43 mg of tropine, 26 μ L of diethyl azodicarboxylate and 2 mL of dry

dichloromethane were added and stirring was continued overnight. The solids were filtered off and washed with THF. The mixture was evaporated and purified by flash chromatography to give 158 mg of 6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one (53). $R_t = 0.79$ min (Method B). Detected mass: 279.2 ($M+H^+$).

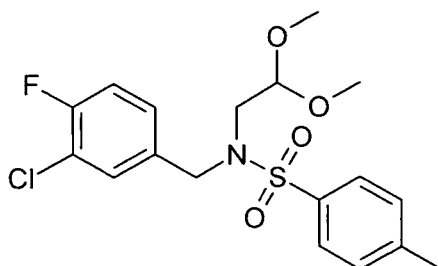
5

3-Chloro-4-fluoro-benzyl)-(2,2-dimethoxy-ethyl)-amine (54)



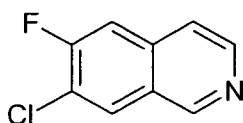
100 g (0.63 mol) of 3-chloro-4-fluoro-benzaldehyde were dissolved in 300 ml of toluene and 66.3 g (0.63 mol) of aminoacetaldehyd-dimethylacetal were added at room
10 temperature. After adding 12.0 g (0.06 mol) of p-toluenesulfonic acid monohydrate, the reaction was heated in a Dean-Stark apparatus for 3 h. The solution was then cooled to room temperature and washed twice with saturated NaHCO_3 -solution and water. The aqueous solutions were extracted with toluene. The combined organic layers were dried with MgSO_4 and evaporated. The obtained imine-intermediate was dissolved
15 directly in 300 mL of ethanol and 11.93 g (0.32 mol) of sodium borohydride were added in small portions. After stirring overnight, 10 mL of acetic acid were added and the solvent was removed i. vac. The residue was dissolved in dichloromethane and washed twice with water. After drying with MgSO_4 and evaporation of the solvent, 147.0 g of crude product were obtained as a yellow oil, which was used without further
20 purification. $R_t = 0.81$ min (Method C). Detected mass: 248.2 ($M+H^+$).

N-(3-Chloro-4-fluoro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (55)



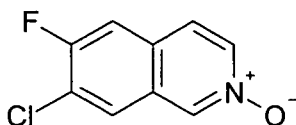
147.0 g (3-Chloro-4-fluoro-benzyl)-(2,2-dimethoxy-ethyl)-amine (54, crude product) were dissolved in 540 ml of dichloromethane/pyridine (8:1). At 0 °C a solution of 145.8 g (1.04 mol) p-toluenesulfonylchloride in 200 ml of dichloromethane was added. After 5 h at room temperature additional 20 ml of pyridine, 29.16 g (0.15 mol) p-toluene-sulfonylchloride and a catalytic amount of DMAP were added. The solution was stirred at room temperature for 7 h and then refluxed for additional 4 h. Again 29.16 g (0.15 mol) p-toluene-sulfonylchloride and a catalytic amount of DMAP were added and the mixture was stirred overnight. For workup, the solution was washed twice with 2 N HCl and twice with saturated NaHCO₃-solution. The organic layer was dried with MgSO₄ and evaporated. Final silicagel chromatography (heptane/ethyl acetate 4:1) gave 155 g of the title compound as a yellow oil. R_t = 1.80 min (Method B). Detected mass: 370.2 (M-OMe⁻).

7-Chloro-6-fluoro-isoquinoline (56)



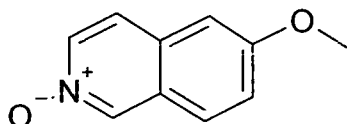
343.6 (2.54 mol) of AlCl₃ were suspended in 1.1 l of dichloromethane and were stirred for 30 min with a mechanical stirrer. To this suspension, a solution of 204 g (0.51 mol) (N-(3-chloro-4-fluoro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (55) was added and the mixture was stirred at room temperature for 5 h. After standing overnight, the reaction suspension was poured on ice, the organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The combined organic layers were washed twice with 1 N NaOH and saturated NaHCO₃-solution, dried with MgSO₄ and evaporated. The obtained crude product was purified by silicagel chromatography (heptane/ethyl acetate 1:1), which gave 61.3 g of the title compound. R_t = 0.73 min (Method B). Detected mass: 182.1 (M+H⁺).

7-Chloro-6-fluoro-isoquinoline 2-oxide (57)



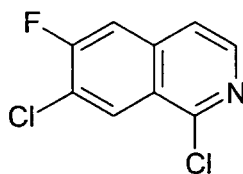
25 g (137.7 mmol) of 7-Chloro-6-fluoro-isoquinoline (56) were dissolved in 500 ml of dichloromethane. At room temperature 50.9 g (206.5 mmol) of 3-chloro-peroxy benzoic acid (70 %) were added and the mixture was stirred at room temperature until complete conversion was achieved. For workup, the precipitate was filtered off and washed with dichloromethane. The filtrate was washed twice with NaHCO₃-solution. The layers were separated and the aqueous phase was extracted twice with dichloromethane. The organic phases were dried with MgSO₄ and evaporated. The so obtained solid material (18.4 g) was used without further purification. $R_t = 0.87$ min (Method C). Detected mass: 198.1/200.1 (M+H⁺).

6-Methoxy-isoquinoline 2-oxide (58)



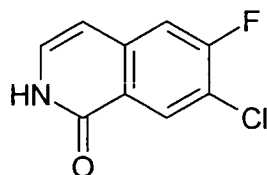
Starting from 4-methoxy-benzaldehyde, 6-methoxy-isoquinoline 2-oxide (58) was prepared following a similar route as described for 7-chloro-6-fluoro-isoquinoline 2-oxide (57). $R_t = 0.70$ min (Method C). Detected mass: 176.1 (M+H⁺).

1,7-Dichloro-6-fluoro-isoquinoline (59)



2.6 g (12.0 mmol) of 7-Chloro-6-fluoro-isoquinoline 2-oxide (57) were heated in 40 ml of POCl₃ at reflux for 4 h. After the mixture has cooled down to room temperature, it was poured on ice. The aqueous solution was extracted three times with dichloromethane. The combined organic layers were dried with MgSO₄ and evaporated to yield 2.91 g of the title compound, which was used without further purification. $R_t = 2.34$ min (Method A). Detected mass: 216.0/218.0 (M+H⁺).

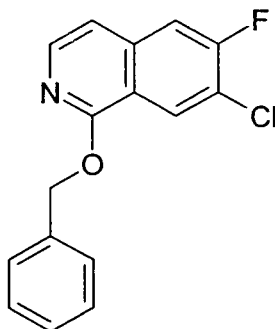
7-Chloro-6-fluoro-2H-isoquinolin-1-one (60)



41.1 g 1,7-dichloro-6-fluoro-isoquinoline (59) were dissolved in 670 ml of acetic acid. After addition of 148.8 g of ammonium acetate, the solution was stirred at 100 °C. After 3 h, the solvent was removed under reduced pressure and the residue was poured into water. The aqueous phase was extracted three times with dichloromethane, the combined organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to dryness. The crude product was crystallized from ethyl acetate : heptane to yield 14.85 g of the desired product.

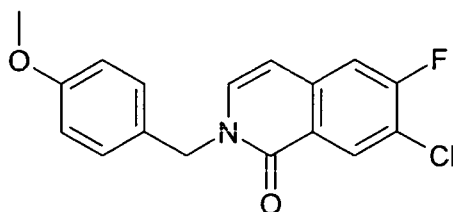
Another 4.5 g could be obtained upon evaporation and silica gel chromatography of the mother liquor. The precipitate was filtered and dried to yield 9.91 g (83%) of the title compound. $R_t = 1.33$ min (Method B). Detected mass: 198.0 ($M+H^+$).

1-Benzyloxy-7-chloro-6-fluoro-isoquinoline (61)



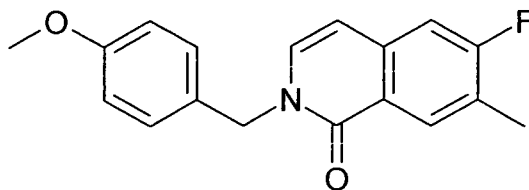
14.74 g (74.6 mmol) of 7-chloro-6-fluoro-2H-isoquinolin-1-one (60) were dissolved in 150 ml of toluene. After addition of 30.86 g (111.9 mmol) of silver carbonate and 15.31 g (89.5 mmol) of benzyl bromide, the mixture was stirred at 80 °C for 3 h. After cooling down to room temperature, the reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane and washed with water, dried with magnesium sulfate and evaporated. Final purification by MPLC gave 11.63 g of the title compound. $R_t = 2.51$ min (Method B). Detected mass: 288.1/290.1 ($M+H^+$).

7-Chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (62)



10 g of 7-chloro-6-fluoro-2H-isoquinolin-1-one (60) were suspended in 100 mL of DMF. 19.75 g of cesium carbonate and 7.55 mL of p-methoxy benzyl chloride were added successively and the mixture was stirred for 2h. The mixture was poured on ice/water and the formed precipitate was filtered off, washed with water and dried in vacuum to give 13.67 g of the title compound. $R_t = 1.96$ min (Method B). Detected mass: 318.1 ($M+H^+$).

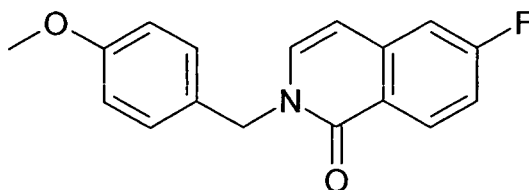
10 6-Fluoro-2-(4-methoxy-benzyl)-7-methyl-2H-isoquinolin-1-one (63)



Starting from 3-methyl-4-fluoro benzaldehyde, the title compound was prepared following a similar sequence as described for 7-chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (62). $R_t = 1.83$ min (Method B). Detected mass: 298.1 ($M+H^+$).

15

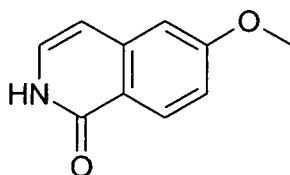
6-Fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (64)



Starting from 4-fluoro benzaldehyde, the title compound was prepared following a similar sequence as described for 7-chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (62). $R_t = 1.72$ min (Method B). Detected mass: 284.1 ($M+H^+$).

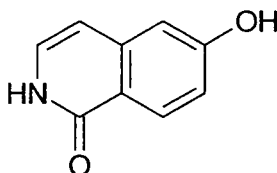
20

6-Methoxy-2H-isoquinolin-1-one (65)



5.2 g of 6-Methoxy-isoquinoline 2-oxide (58) was heated in 120 mL of acetic anhydride
5 at 100°C for 3h. The reaction mixture was evaporated and the residue was taken up in
2 M NaOH and heated at 100°C for another hour. The mixture was allowed to cool
down and the pH was adjusted by addition of 2N HCl to 6. The aqueous layer was
extracted several times with methyl-tert.butyl ether, the combined organic layer was
dried over sodium sulphate and evaporated. The crude material was purified by silica
10 gel chromatography to yield 3.26 g of the desired product.
 $R_t = 0.93$ min (Method C). Detected mass: 176.1 ($M+H^+$).

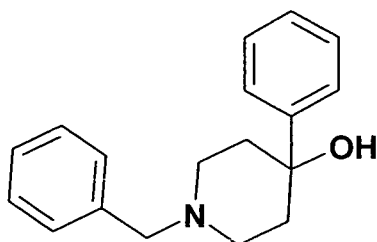
6-Hydroxy-2H-isoquinolin-1-one (66)



15 2.54 g of 6-Methoxy-2H-isoquinolin-1-one (65) were dissolved in 50 mL of dry
dichloromethane and at 0°C 2.74 mL of boron tribromide were carefully added. The
mixture was allowed to stir at room temperature for 18h and was then poured on
ice/water. The organic layer was separated, washed with brine, dried over sodium
sulphate and evaporated to dryness. The crude material was purified by silica gel
20 chromatography to yield 1.96 g of the desired product.
 $R_t = 0.64$ min (Method C). Detected mass: 162.2 ($M+H^+$).

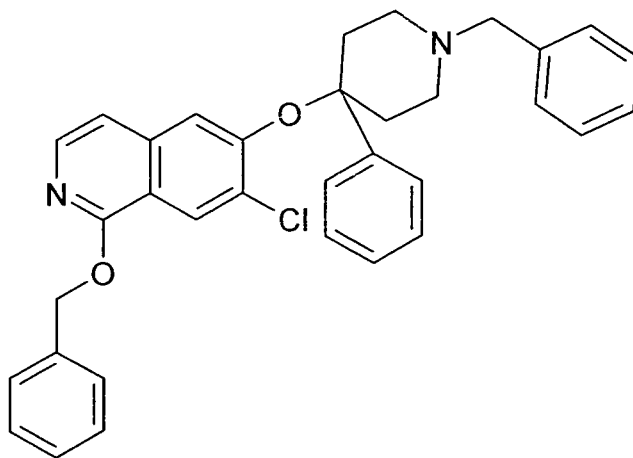
1-Benzyl-4-phenyl-piperidin-4-ol (67)

70



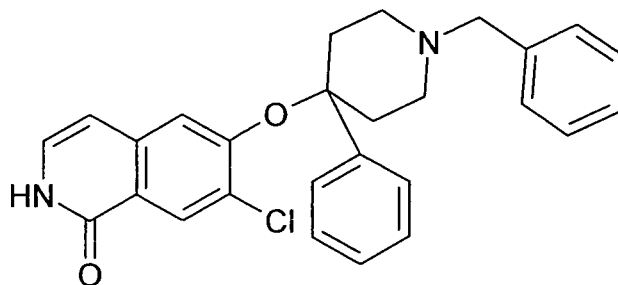
A solution of phenylmagnesium chloride in THF (25%, 33mL) was added at -10°C to a solution of 1-Benzylpiperidone (10g, dissolved in THF). The mixture was warmed to room temperature, stirred for 4h and quenched by addition of 20% ammonium chloride solution. The mixture was extracted three times with methyl tert. butyl ether and the combined organic layer was dried over sodium sulfate and evaporated to dryness. The crude product was purified by silica gel chromatography to give 14.3 g of the desired product as an orange oil. $R_t = 1.09$ min (Method B). Detected mass: 268.1 ($M+H^+$).

1-Benzyl-4-phenylpiperidin-4-ol (67)



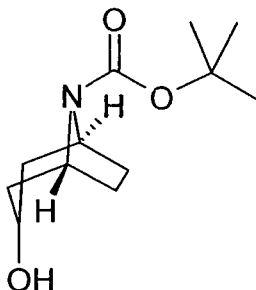
566 mg of 1-Benzyl-4-phenylpiperidin-4-ol (67) were dissolved in 6 ml of dry dimethyl acetamide. 48 mg of sodium hydride (95%) were added and after 1h of stirring, 580 mg of 1-benzyl-4-phenylpiperidin-4-ol (67), dissolved in 6 ml of dry dimethyl acetamide were added. The course of the reaction was monitored by LCMS and 50 mg of sodium hydride were added several times until no further conversion could be observed. 10 mL of water were added. The resulting precipitate was purified by silica gel chromatography to give 930 mg of the desired product, sufficiently pure for further conversion. $R_t = 1.62$ min (Method C). Detected mass: 536.2 ($M+H^+$).

6-(1-Benzyl-4-phenyl-piperidin-4-yl oxy)-7-chloro-2H-isoquinolin-1-one (69)



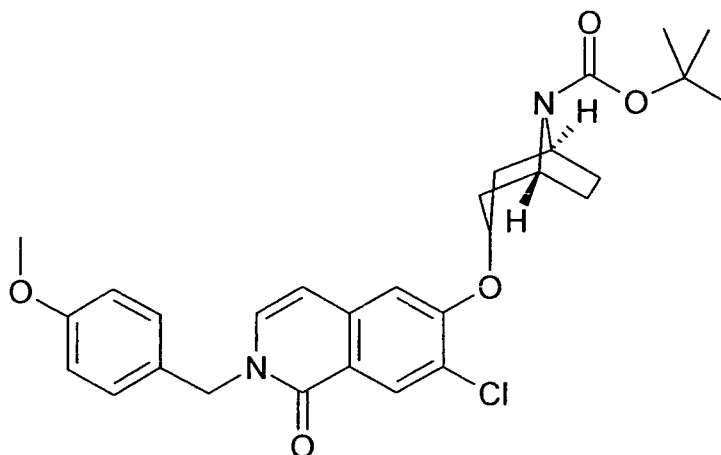
920 mg of 1-Benzyloxy-6-(1-benzyl-4-phenyl-piperidin-4-yloxy)-7-chloro-isoquinoline (68) were suspended in 1M HCl and dissolved by addition of methanol. After stirring overnight, the solution was diluted with water, extracted with methyl tert. butyl ether and the aqueous layer was lyophilized. The product was purified by crystallization to give 98 mg of the desired product as a white solid as the hydrochloride. $R_t = 1.46$ min (Method A). Detected mass: 445.3 ($M+H^+$).

3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (70)



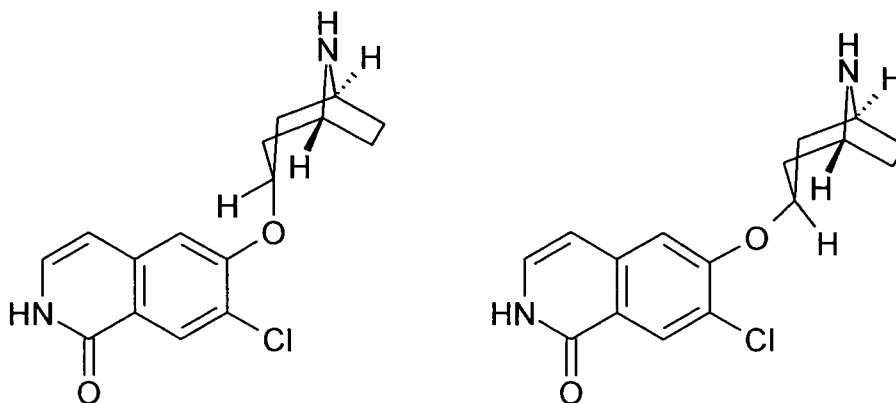
To a 0 °C cold solution of 2.00 g *N*-Boc-nortropinone in 50 mL of methanol was added portionwise 672 mg of sodium borohydride. The reaction mixture was stirred at 0 °C for 1 h. The solvent was evaporated, the crude product was taken up in dichloromethane and treated with sat. sodium bicarbonate solution. The phases were separated and the aqueous phase extracted twice with dichloromethane. The organic phases were combined, dried over magnesium sulfate and concentrated to give 3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (70) as diastereomeric mixture. $R_t = 1.11$ min, 1.17 min (Method C). Detected mass: 128.0 ($M\text{-Boc}+H^+$).

3-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-yloxy]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (71)



528 mg of sodium hydride (60%) were suspended in 8 mL of dimethyl acetamide and 1.00 g of 3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (70), dissolved in 4 mL of dimethyl acetamide, were added dropwise. After 1h, 1.40 g of 7-Chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (62), dissolved in another 8 mL of dimethyl acetamide, were added. The reaction mixture was stirred at room temperature until the reaction was complete. 30 mL of water were added, the resulting suspension extracted three times with a mixture of dichloromethane and 2-propanol (3:1) and the combined organic layers were evaporated. Water was added and the crude product was subjected to lyophilization to remove remainders of dimethyl acetamide. The obtained crude product was purified by silica gel chromatography to yield 1.85 g of the title compound as a mixture of diastereoisomers (71). $R_t = 1.95$ min, 2.03 min (Method C). Detected mass: 525.0 ($M+H^+$).

15 6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-7-chloro-2H-isoquinolin-1-one (72, 73)



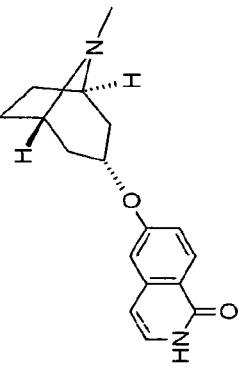
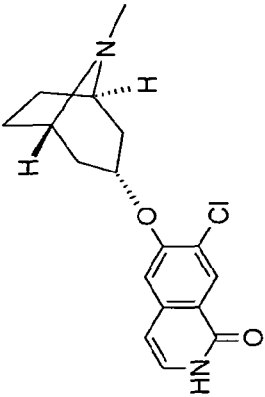
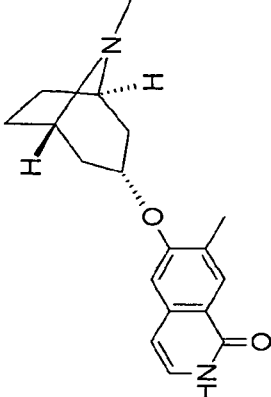
1.70 g of 3-[7-chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-yloxy]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (71) were dissolved in 6 mL

of TFA and heated in a microwave oven at 150 °C for 1 h. Methanol was added and the reaction mixture was evaporated. The pure diastereomers were obtained as hydrochlorides by separation of the mixture via preparative HPLC and lyophilization of the residues from 2N HCl and water, respectively. Stereoisomer 1 (72): $R_t = 0.81$ min (Method A). Detected mass: 305.2 ($M+H^+$). Stereoisomer 2 (73): $R_t = 0.88$ min (Method A). Detected mass: 305.2 ($M+H^+$), 346.2 ($M-NH_3+H^+$).

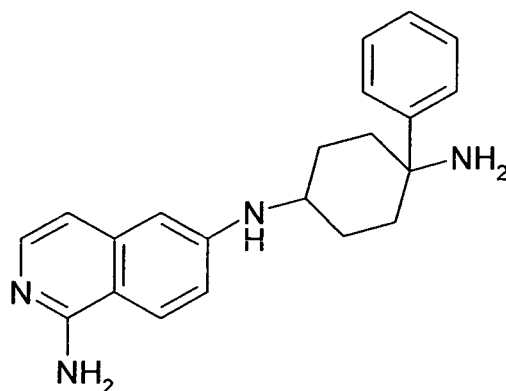
The following products were synthesized in a similar fashion as described for the synthesis of 72/73 using the designated isoquinolinone starting material and tropinone as aminoalcohol component. HCl salts of the compounds could be obtained by taking up the evaporated crude product or chromatographed material in 1M HCl, washing of the aqueous phase with dichloromethane and subsequent lyophilization, followed by twice taking up in water and lyophilization again, eventually followed by recrystallization from isopropanol

74

Table 3

Compound No.	Chemical Name	Isoquinolinone	Product	R _t [min]	Mass [M+H ⁺]	Method
74	6-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one	64		0.77	285.2	B
75	7-Chloro-6-(8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one	62		0.99	319.1	B
76	7-Methyl-6-(8-methyl-8-azabicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one	63		0.85	299.1	B

N6-(4-Amino-4-phenyl-cyclohexyl)-isoquinoline-1,6-diamine (77)



100 mg (0.278 mmol) of (6-amino-isoquinolin-1-yl)-di-carbamic acid tert-butyl ester
were dissolved in 0.5 ml of methanol. After addition of molecular sieves 4 Å, 56.3 mg
5 (0.57 mmol) of triethyl amine, 167 mg (2.78 mmol) of acetic acid and 241 mg (0.835
mmol) of (4-oxo-1-phenyl-cyclohexyl)-carbamic acid tert-butyl ester were added, and
the mixture was stirred for 1h. Then a solution of 52.4 mg (0.835 mmol) of sodium
cyano borohydride was added dropwise and the mixture was stirred at 70 °C until no
further conversion was observed. The solution was filtered and the solvent was
10 removed under reduced pressure. The residue was dissolved in dichloromethane,
washed with 1 N NaOH and sat. sodium chloride solution, dried with magnesium
sulfate and evaporated. The crude product was stirred in 4 N HCl/dioxane, evaporated,
dissolved in water and freeze dried to yield 2.7 mg of the desired product as its
hydrochloride. $R_t = 2.22$ min (Method G). Detected mass: 333.3 ($M+H^+$).

Determination of Rho-Kinase activity

To measure Rho-kinase inhibition, IC₅₀ values were determined according to the following protocol:

5

Active human recombinant ROCK II (N-terminal His6-tagged recombinant human ROCK-II residues 11-552) was purchased from Upstate Ltd., Dundee, UK. The peptide substrate, Fluorescein-AKRRRLSSLRA-COOH, was obtained from JPT Peptide Technologies, Berlin, Germany. Adenosine-5'-triphosphate (ATP), bovine serum albumine (BSA), dimethylsulphoxide (DMSO), 4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid (Hepes), Brij-35 and dithiothreitol (DTT) were purchased from Sigma-Aldrich, Munich, Germany. Tris(hydroxymethyl)-aminomethane (Tris), magnesium chloride, NaOH, 1M HCl and EDTA were obtained from Merck Biosciences, Darmstadt, Germany. "Complete" protease inhibitor was from Roche Diagnostics, Mannheim, Germany.

15

Test compounds were diluted to the appropriate concentrations in buffer 1 (25 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 2 mM DTT, 0.02 % (w/v) BSA and 3 % DMSO). The ROCK II enzyme was diluted to a concentration of 100 ng/ml in buffer 2 (25 mM Tris-HCl, pH 7.4, 5 mM MgCl₂, 2 mM DTT and 0.02 % (w/v) BSA). The peptide substrate and ATP were diluted to concentrations of 3 µM and 120 µM, respectively, in the buffer 2. Two µl of the compound solution were mixed with 2 µl of the diluted enzyme in a 384-well small volume microtiter plate (Greiner, Bio-One, Frickenhausen, Germany), and the kinase reaction was initiated by addition of 2 µl of the solution containing peptide substrate and ATP. After 60 min incubation at 32 °C, the reaction was stopped by addition of 20 µl of a solution containing 100 mM Hepes-NaOH, pH 7.4, 0.015 % (v/v) Brij-35, 45 mM EDTA and 0.227 % chip coating reagent 1 (Caliper Lifescience Inc, Hopkinton, MA). Phosphorylation of the substrate peptide was then detected on a Caliper 3000 instrument essentially as described by Pommereau et al (J. Biomol. Screening 9(5), 409-416, 2004). Separation conditions were as follows: Pressure -1.3 psi, upstream voltage -1562 V, downstream voltage -500 V, sample sip time 200 ms. Positive controls (buffer 1 instead of compound) and negative controls (buffer 1 instead of compound and buffer 2 instead of ROCK II) were run in parallel on each plate.

30

The following products/compounds were tested in said assay by using the respective form (salt or free base) obtained as in the examples described above and the following activities were measured.

Compound No.	pIC ₅₀
21	++++
22	+++++
27	++++
31	+++++
41	++++
45	+++++
48	+++++
49	++++
50	+++++
69	++++
75	+++++
76	+++++

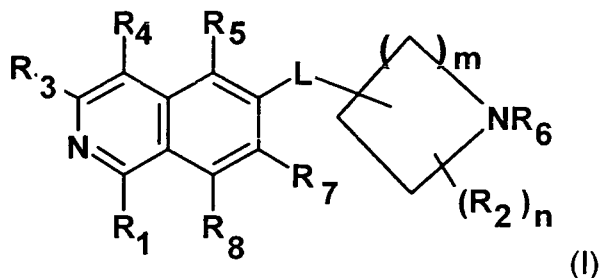
5

The given activity is denoted as the negative decadal logarithm of the IC₅₀ (pIC₅₀) as follows:

	+: pIC ₅₀ ≤ 3.0
10	++: 3.0 ≤ pIC ₅₀ < 4.0
	+++ 4.0 ≤ pIC ₅₀ < 5.0
	++++: 5.0 ≤ pIC ₅₀ < 6.0
	+++++: 6.0 ≤ pIC ₅₀

Claims

1. A compound of the formula (I)



- 5 wherein

R_1 is H, OH or NH_2 .

R_2 is

R' ,

- 10 (C₇-C₈)alkyl,

(C₁-C₆)alkylene- R' ,

(C₂-C₆)alkenyl,

(C₂-C₆)alkynyl,

(C₁-C₆)alkylene-O- R' ,

- 15 (C₁-C₆)alkylene-CH[R']₂,

(C₁-C₆)alkylene-C(O)- R' ,

(C₁-C₆)alkylene-C(O)NH₂,

(C₁-C₆)alkylene-C(O)NH- R' ,

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

- 20 (C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,

(C₁-C₆)alkylene-C(O)N[R']₂;

(C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,

C(O)O-(C₁-C₆)alkyl,

C(O)OR'

- 25 C(O)(C₁-C₆)alkyl,

C(O)R',

C(O)NH-(C₁-C₆)alkyl,

C(O)NHR',

C(O)-NH(C₂-C₆)alkenyl,

C(O)-NH(C₂-C₆)alkynyl,

5 C(O)-NH(C₁-C₆)alkylene-R',

C(O)N[(C₁-C₆)alkyl]R'

C(O)N[(C₁-C₆)alkyl]₂,

C(O)-(C₁-C₆)alkylene-R',

C(O)O(C₁-C₆)alkylene-R';

10

or R₂ is (C₁-C₆)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

15 or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

R₃ is

20

H,

halogen,

(C₁-C₆)alkyl,

(C₁-C₆)alkylene-R',

OH,

25

O-R'',

NH₂,

NHR'',

NR''R'' or

NH-C(O)-R'',

30

R₄ is

H,
halogen,
hydroxy,
CN,
5 (C₁-C₆)alkyl,
R',
(C₁-C₆)alkylene-R';

R₅ is

- 10 H,
halogen,
CN,
NO₂,
(C₁-C₆)alkyl,
15 (C₂-C₆)alkenyl,
R',
(C₁-C₆)alkylene-(C₆-C₁₀)aryl,
(C₁-C₆)alkenylene-(C₆-C₁₀)aryl,
(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl,
20 CH(OH)-(C₁-C₆)alkyl,
NH₂,
NH-R',
NH-SO₂H,
NH-SO₂-(C₁-C₆)alkyl,
25 NH-SO₂-R',
NH-C(O)-(C₁-C₆)alkyl,
NH-C(O)-R',
C(O)N[(C₁-C₆)alkyl]₂,
C(O)OH, or
30 C(O)O-(C₁-C₆)alkyl;

R₆ is

H,

R',

(C₁-C₈)alkyl,

5 (C₁-C₆)alkylene-R',

(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-O-R',

(C₁-C₆)alkylene-CH[R']₂,

(C₁-C₆)alkylene-C(O)-R',

10 (C₁-C₆)alkylene-C(O)NH₂,

(C₁-C₆)alkylene-C(O)NH-R',

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,

(C₁-C₆)alkylene-C(O)N[R']₂;

15 (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,

C(O)O-(C₁-C₆)alkyl,

C(O)OR',

C(O)(C₁-C₆)alkyl,

C(O)R',

20 C(O)NH-(C₁-C₆)alkyl,

C(O)NHR',

C(O)N[(C₁-C₆)alkyl]R'

C(O)N[(C₁-C₆)alkyl]₂,

C(O)-(C₁-C₆)alkylene-R',

25 C(O)O(C₁-C₆)alkylene-R';

R₇ is

H,

halogen,

- CN,
NO₂,
(C₁-C₆)alkyl,
O-(C₁-C₆)alkyl,
5 (C₂-C₆)alkenyl,
R',
(C₁-C₆)alkenylene-(C₆-C₁₀)aryl,
(C₁-C₆)alkylene-R',
CH(OH)-(C₁-C₆)alkyl,
10 NH₂,
NH-R',
NH-SO₂H,
NH-SO₂-(C₁-C₆)alkyl,
NH-SO₂-R',
15 SO₂-NH₂,
SO₂-NHR',
NH-C(O)-(C₁-C₆)alkyl,
NH-C(O)-R',
C(O)N[(C₁-C₆)alkyl]₂,
20 C(O)OH, or
C(O)O-(C₁-C₆)alkyl;

R₈ is H, halogen or (C₁-C₆)alkyl;

- 25 n is 1, 2, 3 or 4;

m is 1, 2, 3, 4 or 5; and

L is $O(CH_2)_p$, $S(CH_2)_p$, $S(O)(CH_2)_p$, $S(O)(CH_2)_p$, $SO_2(CH_2)_p$, $NH(CH_2)_p$, $N(C_1-C_6)alkyl-(CH_2)_p$, $N(C_3-C_6)cycloalkyl-(CH_2)_p$, $N[CO(C_1-C_6)alkyl]-(CH_2)_p$ or $N[(C_1-C_3)alkylene-R']-(CH_2)_p$;

5 p is 0, 1, 2, 3, or 4;

wherein

R' is

$(C_3-C_8)cycloalkyl$,

10 $(C_5-C_{10})heterocyclyl$,

$(C_6-C_{10})aryl$;

R'' is

$(C_3-C_8)cycloalkyl$,

15 $(C_5-C_{10})heterocyclyl$,

$(C_6-C_{10})aryl$,

$(C_1-C_6)alkyl$,

$(C_1-C_6)alkylene-R'$,

$(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$,

20 $(C_1-C_6)alkylene-O-R'$, or

$(C_1-C_6)alkylene-NR_xR_y$; and

wherein R_x and R_y are independently of each other

$(C_1-C_6)alkyl$,

$(C_5-C_{10})heterocyclyl$,

25 $(C_6-C_{10})aryl$,

$(C_1-C_4)alkylene-(C_5-C_{10})heterocyclyl$,

$(C_1-C_4)alkylene-(C_6-C_{10})aryl$,

$(C_1-C_4)alkylene-NH(C_1-C_6)alkyl$,

$(C_1-C_4)alkylene-N[(C_1-C_6)alkyl]_2$,

30 $(C_1-C_4)alkylene-N[(C_6-C_{10})aryl]_2$, or

(C₁-C₄)alkylene-N[(C₅-C₁₀)heterocyclyl]₂;

wherein in residues R₂, R₄, R₅, R₆, R₇ and R₈ alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by OH, OCH₃, COOH, COOCH₃, NH₂,
 5 NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

wherein in residues R₂ to R₈ alkyl or alkylene can optionally be substituted one or more times by halogen;

- 10 wherein in residues R₂ to R₈ (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl are unsubstituted or substituted one or more times by suitable groups independently selected from halogen, OH, NO₂, N₃, CN, C(O)-(C₁-C₆)alkyl, C(O)-(C₁-C₆)aryl, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₃-C₈)cycloalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkylene-OH, (C₁-C₆)alkylene-NH₂,
 15 (C₁-C₆)alkylene-NH(C₁-C₆)alkyl, (C₁-C₆)alkylene-N[(C₁-C₆)alkyl]₂, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, O-(C₁-C₆)alkyl, O-C(O)-(C₁-C₆)alkyl, PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)alkyl, SO₂N[(C₁-C₆)alkyl]₂, S-(C₁-C₆)alkyl; SO-(C₁-C₆)alkyl, SO₂-(C₁-C₆)alkyl, SO₂-N=CH-N[(C₁-C₆)alkyl]₂, C(NH)(NH₂), NH₂, NH-(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, NH-C(O)-(C₁-C₆)alkyl,
 20 NH-C(O)O-(C₁-C₆)alkyl, NH-SO₂-(C₁-C₆)alkyl, NH-SO₂-(C₆-C₁₀)aryl, NH-SO₂-(C₅-C₁₀)heterocyclyl, N(C₁-C₆)alkyl-C(O)-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)O-(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)-NH-(C₁-C₆)alkyl], (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, O-(C₆-C₁₀)aryl,
 25 O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heterocyclyl, (C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, or O-(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, wherein the (C₆-C₁₀)aryl or (C₅-C₁₀)heterocyclyl may be substituted one to three times by a group independently selected from halogen, OH, NO₂, CN, O-(C₁-C₆)alkyl, (C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, N[(C₁-C₆)alkyl]₂, SO₂CH₃, COOH, C(O)O-(C₁-

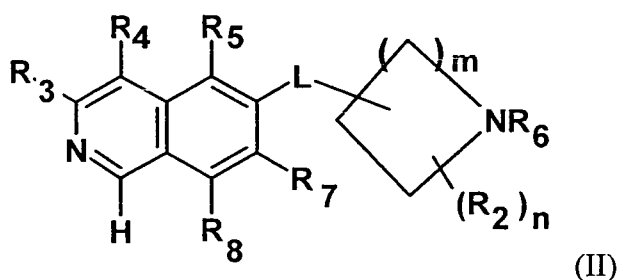
C₆)alkyl, CONH₂, (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-(C₆-C₁₀)aryl, or O-(C₁-C₆)alkylene-(C₆-C₁₀)aryl;

or wherein (C₆-C₁₀)aryl is vicinally substituted by a O-(C₁-C₄)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to;

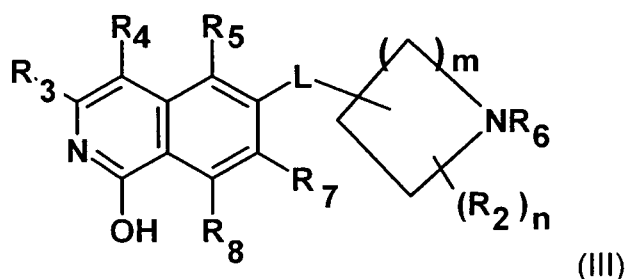
and wherein aryl or heterocyclyl substituents of (C₆-C₁₀)aryl and (C₅-C₁₀)heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group; and

or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

2. A compound of formula (I) according to claim 1, wherein R₁ is H and is characterized by the formula (II)

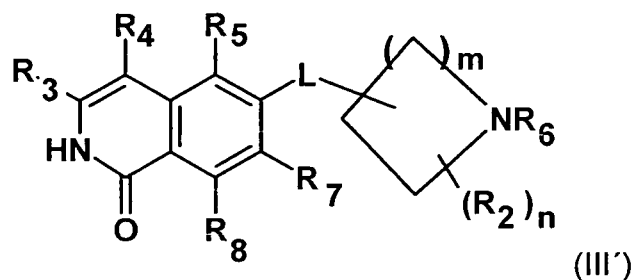


3. A compound of formula (I) according to claim 1, wherein R₁ is OH, and is characterized by the formula (III)



4. A compound of formula (I) according to claim 1 or claim 3, wherein R₁ is OH and is characterized by the formula (III')

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5. A compound according to claim 1 wherein R_1 is NH_2 .

5 6. A compound according to one of claims 1 to 5, wherein R_3 is H, halogen, (C_1-C_4) alkylene- R' , $O-R''$ or NHR'' .

7. A compound according to one of claims 1 to 6, wherein R_3 is H or NHR'' .

10 8. A compound according to one of claims 1 to 7, wherein R_3 is H; $NH-(C_5-C_6)$ heterocyclyl, or NH -phenyl.

9. A compound according to one of claims 1 to 8, wherein R_3 is H.

15 10. A compound according to one of claims 1 to 9, wherein R_8 is H, halogen or (C_1-C_4) alkyl.

11. A compound according to one of claims 1 to 10, wherein R_8 is H, Cl, F, methyl or ethyl.

20

12. A compound according to one of claims 1 to 11, wherein R_8 is H.

13. A compound according to one of claims 1 to 12, wherein R_4 is H, halogen or (C_1-C_6) alkyl.

25

14. A compound according to one of claims 1 to 13, wherein R₄ is H, halogen or (C₁-C₄)alkyl.

15. A compound according to one of claims 1 to 14, wherein R₄ is H.

5

16. A compound according to one of claims 1 to 15, wherein R₅ is H, halogen, CN, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, R', NH-(C₆-C₁₀)aryl or (C₁-C₆)alkylene-R'.

17. A compound according to one of claims 1 to 16, wherein R₅ is H, halogen,
10 (C₁-C₆)alkyl, (C₂-C₆)alkenyl, R', NH-(C₆-C₁₀)aryl or (C₁-C₆)alkylene-R'.

18. A compound according to one of claims 1 to 17, wherein R₅ is H, halogen,
(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl, NH-(C₆-C₁₀)aryl, (C₁-C₂)alkyl-(C₆-
C₁₀)aryl or (C₅-C₁₀)heteroaryl.

15

19. A compound according to one of claims 1 to 18, wherein R₅ is H, halogen,
(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl, or (C₅-C₁₀)heteroaryl.

20. A compound according to one of claims 1 to 19, wherein R₅ is H, halogen,
20 methyl, ethyl, vinyl, phenyl, thienyl, or pyridyl.

21. A compound according to one of claims 1 to 20, wherein R₅ is H, halogen,
methyl, or ethyl.

25 22. A compound according to one of claims 1 to 21, wherein R₅ is H.

23. A compound according to one of claims 1 to 16, wherein R₇ is H, halogen, CN,
(C₁-C₆)alkyl, O-(C₁-C₆)alkyl, (C₂-C₆)alkenyl, R' or
(C₁-C₆)alkylene-(C₃-C₈)cycloalkyl.

30

24. A compound according to one of claims 1 to 23, wherein R₇ is H, halogen, CN, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, (C₁-C₄)alkenyl, phenyl, cyclopropyl or (C₅-C₆)heteroaryl.
- 5 25. A compound according to one of claims 1 to 24, wherein R₇ is H, fluoro, chloro, bromo, methyl, ethyl, methoxy, phenyl, nitrile, cyclopropyl, thienyl or vinyl.
26. A compound according to one of claims 1 to 25, wherein R₇ is H, fluoro, chloro, bromo, methyl or methoxy.
- 10 27. A compound according to one of claims 1 to 26, wherein R₇ is H.
28. A compound according to one of claims 1 to 27, wherein m is 2, 3, or 4.
29. A compound according to one of claims 1 to 28, wherein m is 3.
- 15 30. A compound according to one of claims 1 to 29, wherein R₂ is R', (C₇-C₈)alkyl, (C₁-C₆)alkylene-R', (C₁-C₆)alkenyl, (C₁-C₆)alkylene-C(O)NH₂, (C₁-C₆)alkylene-C(O)NH-R', (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂, (C₁-C₆)alkylene-C(O)N[R']₂, (C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl, C(O)NH-(C₁-C₆)alkyl, C(O)NHR', C(O)-NH(C₂-C₆)alkenyl, C(O)-NH(C₂-C₆)alkynyl, C(O)-NH(C₁-C₆)alkylene-R', C(O)N[(C₁-C₆)alkyl]R', C(O)N[(C₁-C₆)alkyl]₂, C(O)-(C₁-C₆)alkylene-R', C(O)O(C₁-C₆)alkylene-R';
- 20 or R₂ is (C₁-C₆)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂, CONHCH₃ or CON(CH₃)₂;

or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

5 31. A compound according to one of claims 1 to 30, wherein R₂ is

R',

(C₁-C₆)alkylene-R',

(C₂-C₆)alkenyl,

(C₁-C₆)alkylene-C(O)NH₂,

10 (C₁-C₆)alkylene-C(O)NH-R',

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

C(O)NH-(C₁-C₆)alkyl,

C(O)NHR',

C(O)-NH(C₂-C₆)alkenyl,

15 C(O)-NH(C₂-C₆)alkynyl,

C(O)-NH(C₁-C₆)alkylene-R',

or R₂ is (C₁-C₃)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂,

20 CONHCH₃ or CON(CH₃)₂;

or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

25

32. A compound according to one of claims 1 to 31, wherein R₂ is

R',

(C₁-C₆)alkylene-R',

(C₂-C₆)alkenyl,

30 (C₁-C₆)alkylene-C(O)NH-R',

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,
 C(O)NH-(C₁-C₆)alkyl,
 C(O)NHR',
 C(O)-NH(C₂-C₆)alkynyl,

5 C(O)-NH(C₁-C₆)alkylene-R',

or R₂ is a (C₁-C₂)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

10

33. A compound according to one of claims 1 to 32, wherein n is 1, 2 or 3.

34. A compound according to one of claims 1 to 33, wherein n is 1 or 2.

35. A compound according to one of claims 1 to 34, wherein n is 1.

15

36. A compound according to one of claims 1 to 35, wherein

R₆ is

H,

(C₁-C₆)alkyl,

20 R',

(C₁-C₄)alkylene-(C₅-C₁₀)aryl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,

(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

25 (C₁-C₄)alkylene-C(O)-(C₅-C₁₀)heterocyclyl,

(C₁-C₄)alkylene-C(O)-(C₆-C₁₀)aryl,

(C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,

30 C(O)O-(C₁-C₆)alkyl,

C(O)(C₁-C₆)alkyl,

C(O)R',

C(O)NH-(C₁-C₆)alkyl,

C(O)N[(C₁-C₆)alkyl]₂, or

5 C(O)(C₁-C₆)alkylene-R'.

37. A compound according to any of claims 1 to 36, wherein R₆ is

H,

(C₁-C₆)alkyl,

10 (C₅-C₁₀)heterocyclyl,

(C₃-C₈)cycloalkyl,

(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,

15 (C₁-C₄)alkylene-(C₆-C₁₀)aryl,

(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)O-(C₁-C₆)alkyl,

20 C(O)O-(C₁-C₆)alkyl,

C(O)(C₁-C₆)alkyl,

C(O)(C₅-C₁₀)heterocyclyl,

C(O)(C₃-C₈)cycloalkyl

C(O)NH-(C₁-C₆)alkyl,

25 C(O)N[(C₁-C₆)alkyl]₂,

C(O) (C₁-C₆)alkylene-(C₃-C₈)cycloalkyl,

C(O) (C₁-C₆)alkylene- C₅-C₁₀)heterocyclyl, or

C(O) (C₁-C₆)alkylene--(C₆-C₁₀)aryl:

38. A compound according to any of claims 1 to 37, wherein

R₆ is

H,

(C₁-C₆)alkyl,

5 (C₃-C₈)cycloalkyl,

(C₅-C₁₀)heterocyclyl,

(C₅-C₁₀)aryl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,

(C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,

10 (C₁-C₄)alkylene-(C₆-C₁₀)aryl,

(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

(C₁-C₆)alkylene-C(O)N[(C₁-C₆)alkyl]₂,

C(O)O-(C₁-C₆)alkyl,

15 C(O)(C₁-C₆)alkyl,

C(O)(C₃-C₈)cycloalkyl,

C(O)-(C₅-C₁₀)heterocyclyl,

C(O)NH-(C₁-C₆)alkyl,

C(O)N[(C₁-C₆)alkyl]₂,

20 C(O)(C₁-C₆)alkylene-(C₃-C₈)cycloalkyl,

C(O)(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, or

C(O)(C₁-C₆)alkylene--(C₆-C₁₀)aryl.

39. A compound according to any of claims 1 to 38, wherein

25 R₆ is

H,

(C₁-C₆)alkyl,

(C₃-C₈)cycloalkyl,

(C₆-C₁₀)aryl,

(C₁-C₄)alkylene-(C₃-C₈)cycloalkyl,
 (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl,
 (C₁-C₄)alkylene-(C₆-C₁₀)aryl,
 (C₁-C₄)alkylene-O-(C₁-C₄)alkyl,

- 5 C(O)(C₁-C₆)alkyl,
 C(O)(C₃-C₈)cycloalkyl,
 C(O)-(C₅-C₁₀)heterocyclyl,
 C(O)(C₁-C₄)alkylene- (C₅-C₁₀)heterocyclyl, or
 C(O)(C₁-C₄)alkylene--(C₆-C₁₀)aryl.

10

40. A compound according to any of claims 1 to 39, wherein
 R₆ is

H;
 (C₁-C₆)alkyl;

15

(C₃-C₈)cycloalkyl;
 (C₁-C₄)alkylene-(C₃-C₈)cycloalkyl;
 (C₁-C₄)alkylene-(C₅-C₁₀)heterocyclyl wherein heterocyclyl is unsubstituted or
 substituted one or more times by (C₁-C₄)alkyl;
 (C₁-C₄)alkylene-(C₆-C₁₀)aryl wherein aryl is unsubstituted or substituted one or more
 20 times by halogen, (C₁-C₄)alkyl, O-(C₁-C₄)alkyl, SO₂-(C₁-C₄)alkyl or SO₂-N[(C₁-
 C₆)alkyl]₂.

41. A compound according to any of claims 1 to 40, wherein R₆ is H, (C₁-C₆)alkyl
 or (C₃-C₈)cycloalkyl.

25

42. A compound according to any of claims 1 to 41, wherein R₆ is H, unsubstituted
 (C₁-C₆)alkyl or unsubstituted (C₃-C₈)cycloalkyl.

43. A compound according to any of claims 1 to 42, wherein R₆ is H.

44. A compound according to one of claims 1 to 43, wherein m is 3 and L is attached to the 3-position or to the 4-position of the piperidine ring.

45. A compound according to one of claims 1 to 44, wherein m is 3 and L is attached to the 4-position of the piperidine ring.

46. A compound according to one of claims 1 to 45, wherein L is $S(CH_2)_p$, $S(O)(CH_2)_p$ or $SO_2(CH_2)_p$.

47. A compound according to one of claims 1 to 45, wherein L is $NH(CH_2)_p$ or $N(C_1-C_6)alkyl-(CH_2)_p$.

48. A compound according to one of claims 1 to 45, wherein L is $O(CH_2)_p$.

49. A compound according to one of claims 1 to 48, wherein p is 0.

50. A compound according to claim 1, wherein R_1 is H or OH;

R_2 is R' , $(C_7-C_8)alkyl$, $(C_1-C_6)alkylene-R'$, $(C_2-C_6)alkenyl$, $(C_1-C_6)alkylene-C(O)NH_2$, $(C_1-C_6)alkylene-C(O)NH-R'$, $(C_1-C_6)alkylene-C(O)NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkylene-C(O)N[(C_1-C_6)alkyl]_2$, $(C_1-C_6)alkylene-C(O)N[R']_2$; $(C_1-C_6)alkylene-C(O)O-(C_1-C_6)alkyl$, $C(O)NH-(C_1-C_6)alkyl$, $C(O)NHR'$, $C(O)-NH(C_1-C_6)alkenyl$, $C(O)-NH(C_1-C_6)alkynyl$, $C(O)-NH(C_1-C_6)alkylene-R'$, $C(O)N[(C_1-C_6)alkyl]R'$, $C(O)N[(C_1-C_6)alkyl]_2$, $C(O)-(C_1-C_6)alkylene-R'$, $C(O)O(C_1-C_6)alkylene-R'$;

or R_2 is $(C_1-C_6)alkyl$, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH_3 , $COOH$, $COOCH_3$, NH_2 , $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

5 R₃ is H, halogen, (C₁-C₄)alkylene-R', O-R'' or NHR'';

R₄ is H, halogen or (C₁-C₆)alkyl;

10 R₅ is H, (C₁-C₆)alkyl, halogen, CN, (C₂-C₆)alkenyl, (C₆-C₁₀)aryl, NH-(C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl, (C₅-C₁₀)heterocyclyl or (C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl;

15 R₆ is H, R', (C₁-C₈)alkyl, (C₁-C₆)alkylene-R', (C₁-C₆)alkylene-O-(C₁-C₆)alkyl, (C₁-C₆)alkylene-O-R', (C₁-C₆)alkylene-CH[R']₂, (C₁-C₆)alkylene-C(O)NH₂, (C₁-C₆)alkylene-C(O)NH-R', (C₁-C₆)alkylene-C(O)N[(C₁-C₄)alkyl]₂, (C₁-C₆)alkylene-C(O)N[R']₂; C(O)O-(C₁-C₆)alkyl, C(O)(C₁-C₆)alkyl, C(O)(C₃-C₈)cycloalkyl, C(O)NH-(C₁-C₆)alkyl, C(O)N[(C₁-C₆)alkyl]₂, C(O)(C₁-C₆)alkylene-C₃-C₈cycloalkyl, C(O)(C₁-C₆)alkylene-C₅-C₁₀heterocyclyl, or C(O)(C₁-C₆)alkylene--(C₆-C₁₀)aryl;

20 R₇ is H, halogen, CN, (C₁-C₆)alkyl, O-(C₁-C₆)alkyl, (C₂-C₆)alkenyl or R';

R₈ is H, halogen or (C₁-C₆)alkyl;

m is 2, 3 or 4

25

n is 1, 2 or 3,

L is O(CH₂)_p, S(CH₂)_p, NH(CH₂)_p or N(C₁-C₆)alkyl-(CH₂)_p, and

30 p is 0, 1 or 2.

51. A compound according to claim 1, wherein

R₁ is H or OH;

5 R₂ is R', (C₁-C₆)alkylene-R', (C₂-C₆)alkenyl, (C₁-C₆)alkylene-C(O)NH₂, (C₁-C₆)alkylene-C(O)NH-R', C(O)-NH(C₂-C₆)alkynyl, (C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl, C(O)NH-(C₁-C₆)alkyl, C(O)NHR', C(O)-NH(C₁-C₆)alkylene-R',
 or R₂ is (C₁-C₃)alkyl, provided that in said alkyl residue at least one hydrogen is substituted by OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃, N(CH₃)₂, CONH₂,
 10 CONHCH₃ or CON(CH₃)₂;

or R₂ is a (C₁-C₄)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene forms a second bond to a different carbon atom of the cyclic amine ring and forms, together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

15 R₃ is H, halogen or NHR'', wherein R'' is defined as above;

R₄ is H, halogen or (C₁-C₄)alkyl;

R₅ is H, (C₁-C₆)alkyl, halogen, (C₂-C₄)alkenyl, (C₆-C₁₀)aryl, (C₁-C₆)alkylene-(C₆-C₁₀)aryl or (C₅-C₁₀)heterocyclyl;

R₆ is H, (C₃-C₈)cycloalkyl, (C₁-C₈)alkyl, (C₁-C₃)alkylene-R', C(O)O-(C₁-C₆)alkyl, C(O)(C₁-C₆)alkyl, C(O)(C₃-C₈)cycloalkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)NH-(C₁-C₆)alkyl, C(O)N[(C₁-C₆)alkyl]₂, C(O)(C₁-C₆)alkylene-(C₃-C₈)cycloalkyl,
 25 C(O)(C₁-C₆)alkylene-(C₅-C₁₀)heterocyclyl, or
 C(O)(C₁-C₆)alkylene--(C₆-C₁₀)aryl;

R₇ is H, halogen, CN, (C₁-C₆)alkyl, O(C₁-C₆)alkyl, (C₂-C₆)alkenyl or R';

30 R₈ is H, halogen or (C₁-C₆)alkyl;

m is 2, 3 or 4

n is 1, 2 or 3;

5 L is O(CH₂)_p, S(CH₂)_p or NH(CH₂)_p, and

p is 0 or 1.

52. A compound according to claim 1, wherein

10

R₁ is H or OH;

R₂ is

R',

15 (C₁-C₆)alkylene-R',

(C₂-C₆)alkenyl,

(C₁-C₆)alkylene-C(O)NH-R',

(C₁-C₆)alkylene-C(O)NH-(C₁-C₆)alkyl,

C(O)NH-(C₁-C₆)alkyl,

20 C(O)NHR',

C(O)-NH(C₂-C₆)alkynyl,

C(O)-NH(C₁-C₆)alkylene-R',

or R₂ is a (C₁-C₂)alkylene bound to the cyclic amine, in which the (C₁-C₄) alkylene
25 forms a second bond to a different carbon atom of the cyclic amine ring and forms,
together with carbon atoms of cyclic amine, a second, 4-8 membered ring;

R₃ is H, NH-(C₅-C₆)heteroaryl or NH-phenyl;

30 R₄ is H, halogen or (C₁-C₄)alkyl;

R₅ is H, (C₁-C₄)alkyl, halogen, (C₁-C₄)alkenyl, (C₆-C₁₀)aryl, (C₁-C₂)alkyl-(C₆-C₁₀)aryl or (C₅-C₆)heteroaryl;

R₆ is H, (C₃-C₈)cycloalkyl, (C₁-C₈)alkyl, (C₁-C₃)alkylene-R'; C(O)(C₁-C₆)alkyl,
 5 C(O)(C₃-C₈)cycloalkyl, C(O)-(C₅-C₁₀)heterocyclyl, C(O)(C₁-C₃)alkylene-(C₅-C₁₀)heterocyclyl or C(O)(C₁-C₃)alkylene--(C₆-C₁₀)aryl;

R₇ is H, halogen, CN, (C₁-C₄)alkyl, O(C₁-C₄)alkyl, (C₁-C₄)alkenyl, phenyl, cyclopropyl, (C₅-C₆)heteroaryl;

10 R₈ is H, halogen or (C₁-C₄)alkyl;

m is 3;

n is 1; and

15

L is O, NH or S.

53. A compound according to claim 1 selected from the group of
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-
 20 methyl ester,
 (2R,4R)-4-(Isoquinolin-6-yloxy)-2-o-tolylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester,
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid o-tolylamide,
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide,
 25 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 3-methoxy-benzylamide
 (11),
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide (12),
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethyl-amide,
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide,
 30 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (2-hydroxy-ethyl)-amide,
 (2R,4R)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide,

- (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (3-methoxy-propyl)-amide,
(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid prop-2-ynylamide,
5 (2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid phenethyl-amide,
(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid 2-chloro-benzylamide,
(2S,4S)-4-(Isoquinolin-6-yloxy)-piperidine-2-carboxylic acid isobutyl-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid ((R)-1-phenyl-ethyl)-
10 amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-hydroxy-ethyl)-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-amide,
15 (2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
(2S,4R)-4-(Isoquinolin-6-yloxy)-pyrrolidine-2-carboxylic acid prop-2-ynylamide,
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-
methyl ester,
(2S,4R)-2-(4-Ethyl-phenylcarbamoyl)-4-(isoquinolin-6-ylamino)-pyrrolidine-1-carboxylic
20 acid tert-butyl ester,
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-
amide,
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (2-methoxy-ethyl)-
25 amide,
(2S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-
amide,
(2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (furan-2-ylmethyl)-
amide,
30 (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (3-methoxy-propyl)-
amide,

- (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide,
 (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid (4-ethyl-phenyl)-amide,
 (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid phenethyl-amide,
 5 (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid 2-chloro-benzylamide,
 (2S,4S)-4-(Isoquinolin-6-ylamino)-pyrrolidine-2-carboxylic acid isobutyl-amide,
 (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid 3-methoxy-benzylamide,
 (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid (2-methoxy-ethyl)-
 10 amide,
 (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid o-tolylamide,
 (3S,4R)-4-(Isoquinolin-6-ylamino)-pyrrolidine-3-carboxylic acid isobutyl-amide,
 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-isoquinoline, or
 6-(1-benzyl-4-phenyl-piperidin-4-yloxy)-7-chloro-isoquinoline,
 15 or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

54. A compound according to claim 1 selected from the group of
 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one,
 20 6-(8-Aza-bicyclo[3.2.1]oct-3-yloxy)-7-chloro-2H-isoquinolin-1-one,
 6-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one ,
 7-Chloro-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one,
 7-Methyl-6-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yloxy)-2H-isoquinolin-1-one , or
 N6-(4-Amino-4-phenyl-cyclohexyl)-isoquinoline-1,6-diamine,
 25 or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

55. Use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as claimed in one of claims 1 to 54 for producing a medicament.

- 30 56. Use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as claimed in one of claims 1 to 54 for producing a medicament for the

- treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, retinopathy, glaucoma, peripheral circulatory disorder, peripheral occlusive arterial disease (PAOD), coronary heart disease, angina pectoris, heart hypertrophy, heart failure, ischemic diseases, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, nephropathy, renal failure, fibroid kidney, renal glomerulosclerosis, organ hypertrophy, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, thrombotic disorders, stroke, cerebral vasospasm, cerebral ischemia, pain, neuronal degeneration, spinal cord injury, Alzheimer's disease, premature birth, erectile dysfunction, endocrine dysfunctions, arteriosclerosis, prostatic hypertrophy, diabetes and complications of diabetes, metabolic syndrome, blood vessel restenosis, atherosclerosis, inflammation, autoimmune diseases, AIDS, osteopathy, infection of digestive tracts with bacteria, sepsis or cancer development and progression.
57. A medicament comprising an effective amount of at least one compound as claimed in any of claims 1 to 54 and/or a pharmacologically acceptable salt thereof, physiologically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.