Cycloalkylamine substituted isoquinolone and isoquinolinone derivatives

The present invention relates to novel isoquinolone and isoquinolinone derivatives as described in the claims, their preparation and their use in the treatment and/or 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 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 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 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 intraoccular pressure (Honjo et al. 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 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, artherosclerosis, 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 (Chitaley 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 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 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.

WO 01/64238 describes isoquinoline-5-sulfonamide derivatives optionally substituted 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.

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 Heliobacter 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-[(C_1-C_6)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 Heliobacter pylori.

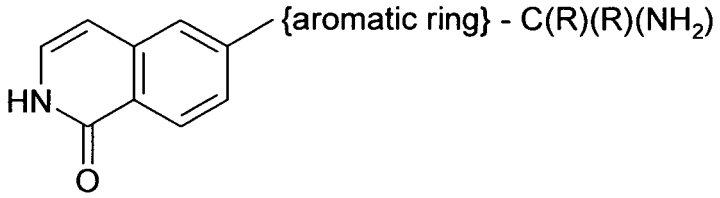
US 5,480,883 generically discloses as EGF and/or PDGF receptor inhibitors useful for inhibiting cell proliferation compounds of the formula "Ar I – X – Ar II" wherein X may be $(CHR_1)_m$-Z-$(CHR_1)_n$, e.g. Z-CH_2, wherein Z may be O, R_1 is hydrogen or alkyl, Ar I may be among others an optionally substituted isoquinolone and Ar II may be among others an optionally substituted C_{3-7} 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 $(CR^eR^f)_pOR^{43}$ wherein p may be zero, and R^{43} is e.g. a (C_3-C_{10})cycloalkyl residue optionally substituted by $NR^{51}R^{52}$, wherein $R^{51}$and R^{52} may be hydrogen, (C_1-C_6)alkyl etc.; or R^{43} is a group R^{81} defined as a 4-6 membered unsaturated or saturated monocyclic heterocylic 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 $(CR^eR^f)_pOR^{43}$ wherein p may be zero, and R^{43} is e.g. a (C_3-C_{10})cycloalkyl residue optionally substituted by $NR^{51}R^{52}$, wherein $R^{51}$and R^{52} may be hydrogen, (C_1-C_6)alkyl etc.; or R^{43} is a group R^{81}

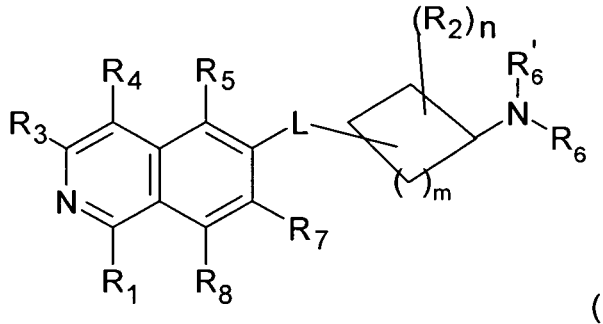
defined as a 4-6 membered unsaturated or saturated monocyclic heterocylic ring with 1, 2, 3 or 4 heteroatoms; and are substituted by a directly bound optionally substituted aryl or heteroaryl ring in the 4-position.

WO 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)



(I)

wherein

R_1 is H, OH or NH_2 ;

R_2 is H, halogen or $(C_1\text{-}C_6)$alkyl;

R_3 is

H,

halogen,

$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-R',

OH,

O-R'',

NH_2,

NHR'',

NR''R'' or

NH-C(O)-R'',

R_4 is

H,

halogen,

hydroxy,

CN,

$(C_1\text{-}C_6)$alkyl,

R',

$(C_1\text{-}C_6)$alkylene-R';

R_5 is

H,

halogen,

CN,

NO_2,

$(C_1\text{-}C_6)$alkyl,

$(C_2\text{-}C_6)$alkenyl,

R',

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

$(C_1\text{-}C_6)$alkenylene-$(C_6\text{-}C_{10})$aryl,

$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl,

CH(OH)-$(C_1\text{-}C_6)$alkyl,

NH_2,

NH-R',

$NH\text{-}SO_2H$,

$NH\text{-}SO_2\text{-}(C_1\text{-}C_6)$alkyl,

$NH\text{-}SO_2\text{-}R'$,

$NH\text{-}C(O)\text{-}(C_1\text{-}C_6)alkyl$,

$NH\text{-}C(O)\text{-}R'$,

$C(O)N[(C_1\text{-}C_6)alkyl]_2$,

$C(O)OH$, or

$C(O)O\text{-}(C_1\text{-}C_6)alkyl$;

R_6 and R_6' are independently of each other

H,

R',

$(C_1\text{-}C_8)alkyl$,

$(C_1\text{-}C_6)alkylene\text{-}R'$,

$(C_1\text{-}C_6)alkylene\text{-}O\text{-}(C_1\text{-}C_6)alkyl$,

$(C_1\text{-}C_6)alkylene\text{-}O\text{-}R'$,

$(C_1\text{-}C_6)alkylene\text{-}CH[R']_2$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)\text{-}R'$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)NH_2$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)NH\text{-}R'$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)NH\text{-}(C_1\text{-}C_6)alkyl$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)N[(C_1\text{-}C_6)alkyl]_2$,

$(C_1\text{-}C_6)alkylene\text{-}C(O)N[R']_2$;

$(C_1\text{-}C_6)alkylene\text{-}C(O)O\text{-}(C_1\text{-}C_6)alkyl$,

$C(O)O\text{-}(C_1\text{-}C_6)alkyl$,

C(O)OR'

$C(O)(C_1\text{-}C_6)alkyl$,

C(O)R',

$C(O)NH\text{-}(C_1\text{-}C_6)alkyl$,

C(O)NHR',

$C(O)N[(C_1\text{-}C_6)alkyl]R'$

$C(O)N[(C_1\text{-}C_6)alkyl]_2$,

$C(O)\text{-}(C_1\text{-}C_6)alkylene\text{-}R'$,

$C(O)O(C_1\text{-}C_6)alkylene\text{-}R'$,

or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5\text{-}C_{10})$ heterocyclyl group;

R_7 is

H,

halogen,

CN,

NO_2,

$(C_1\text{-}C_6)alkyl$,

$O\text{-}(C_1\text{-}C_6)alkyl$,

$(C_2\text{-}C_6)alkenyl$,

R',

$(C_1\text{-}C_6)alkenylene\text{-}(C_6\text{-}C_{10})aryl$,

$(C_1\text{-}C_6)alkylene\text{-}R'$,

$CH(OH)\text{-}(C_1\text{-}C_6)alkyl$,

NH_2,

NH-R',

$NH\text{-}SO_2H$,

$NH\text{-}SO_2\text{-}(C_1\text{-}C_6)alkyl$,

$NH\text{-}SO_2\text{-}R'$,

$SO_2\text{-}NH_2$,

$SO_2\text{-}NHR'$,

$NH\text{-}C(O)\text{-}(C_1\text{-}C_6)alkyl$,

NH-C(O)-R',

$C(O)N[(C_1\text{-}C_6)alkyl]_2$,

C(O)OH, or

$C(O)O-(C_1-C_6)alkyl$;

R_8 is H, halogen or $(C_1-C_6)alkyl$;

n is 1, 2, 3 or 4;

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

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

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

wherein

R' is

$(C_3-C_8)cycloalkyl$,

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

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

R'' is

$(C_3-C_8)cycloalkyl$,

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

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

$(C_1-C_6)alkyl$,

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

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

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

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

wherein R_x and R_y are independently of each other

$(C_1-C_6)alkyl$,

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

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

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

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

$(C_1\text{-}C_4)$alkylene-NH$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_4)$alkylene-N$[(C_1\text{-}C_6)\text{alkyl}]_2$,

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

$(C_1\text{-}C_4)$alkylene-N$[(C_5\text{-}C_{10})\text{heterocyclyl}]_2$;

wherein in residues R_4, R_5, R_6, R_6', R_7 and R_8 alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by OH, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

wherein in residues R_2 to R_8 alkyl or alkylene can optionally be substituted one or more times by halogen;

wherein in residues R_3 to R_8 $(C_6\text{-}C_{10})$aryl and $(C_5\text{-}C_{10})$heterocyclyl are unsubstituted or substituted one or more times by suitable groups independently selected from halogen, OH, NO_2, N_3, CN, C(O)-$(C_1\text{-}C_6)$alkyl, C(O)-$(C_1\text{-}C_6)$aryl, COOH, COO$(C_1\text{-}C_6)$alkyl, $CONH_2$, CONH$(C_1\text{-}C_6)$alkyl, CON$[(C_1\text{-}C_6)\text{alkyl}]_2$, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-OH, $(C_1\text{-}C_6)$alkylene-NH_2, $(C_1\text{-}C_6)$alkylene-NH$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-N$[(C_1\text{-}C_6)\text{alkyl}]_2$, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, O-$(C_1\text{-}C_6)$alkyl, O-C(O)-$(C_1\text{-}C_6)$alkyl, PO_3H_2, SO_3H, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$alkyl, $SO_2N[(C_1\text{-}C_6)\text{alkyl}]_2$, S-$(C_1\text{-}C_6)$alkyl, SO-$(C_1\text{-}C_6)$alkyl, SO_2-$(C_1\text{-}C_6)$alkyl, SO_2-N=CH-N$[(C_1\text{-}C_6)\text{alkyl}]_2$,

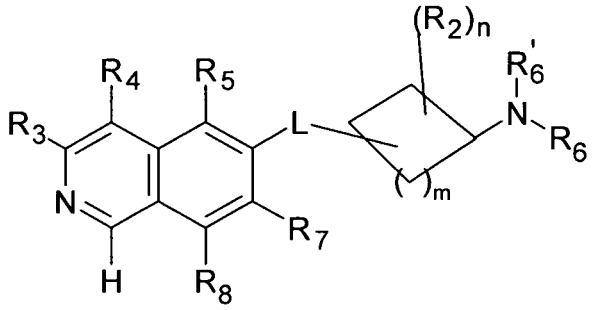
C(NH)(NH_2), NH_2, NH-$(C_1\text{-}C_6)$alkyl, N$[(C_1\text{-}C_6)\text{alkyl}]_2$, NH-C(O)-$(C_1\text{-}C_6)$alkyl, NH-C(O)O-$(C_1\text{-}C_6)$alkyl,

NH-SO_2-$(C_1\text{-}C_6)$alkyl, NH-SO_2-$(C_6\text{-}C_{10})$aryl, NH-SO_2-$(C_5\text{-}C_{10})$heterocyclyl, N$(C_1\text{-}C_6)$alkyl-C(O)-$(C_1\text{-}C_6)$alkyl, N$(C_1\text{-}C_6)$alkyl-C(O)O-$(C_1\text{-}C_6)$alkyl,

$N(C_1\text{-}C_6)$alkyl-C(O)-NH-$(C_1\text{-}C_6)$alkyl],
$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, O-$(C_6\text{-}C_{10})$aryl,
O-$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$heterocyclyl,
$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, or O-$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl,
wherein the $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heterocyclyl may be substituted one to three times by a group independently selected from halogen, OH, NO_2, CN, O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, NH_2, NH$(C_1\text{-}C_6)$alkyl, N[$(C_1\text{-}C_6)$alkyl]$_2$, SO_2CH_3, COOH, C(O)O-$(C_1\text{-}C_6)$alkyl, $CONH_2$, $(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-O-$(C_6\text{-}C_{10})$aryl, or O-$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl;
or wherein $(C_6\text{-}C_{10})$aryl is vicinally substituted by a O-$(C_1\text{-}C_4)$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 $(C_6\text{-}C_{10})$aryl and $(C_5\text{-}C_{10})$heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group;

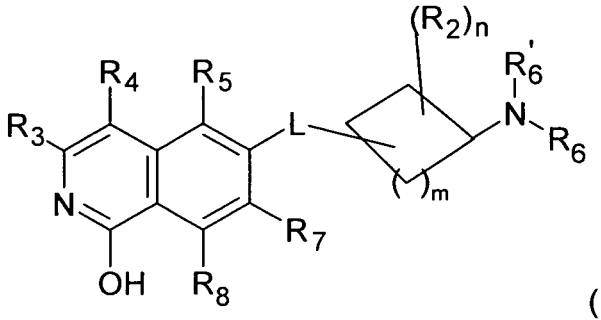
or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts thereof.

In one embodiment of the present invention R_1 is H and the compound is characterized by the formula (II)



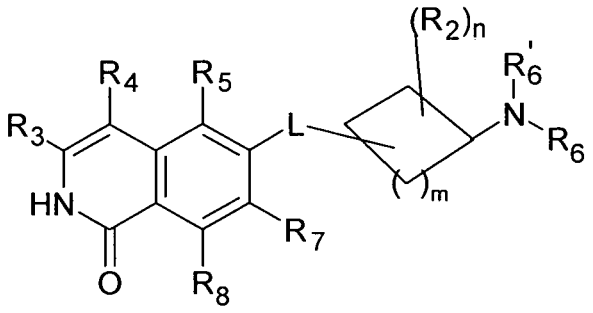
(II)

In another embodiment of the present invention R_1 is OH and the compound is characterized by the formula (III)



(III)

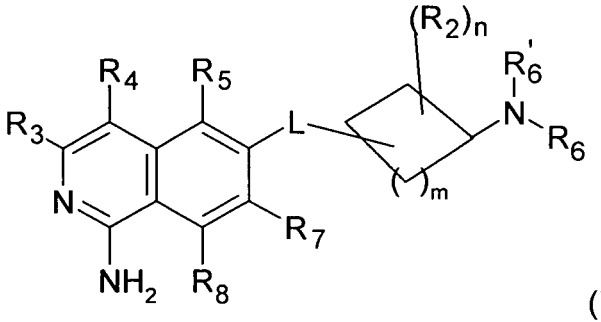
The isoquinoline derivative of formula (I), wherein R_1 is OH, include the corresponding tautomeric 1-isoquinolone derivative which is characterized by the formula (III´)



(III´)

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

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



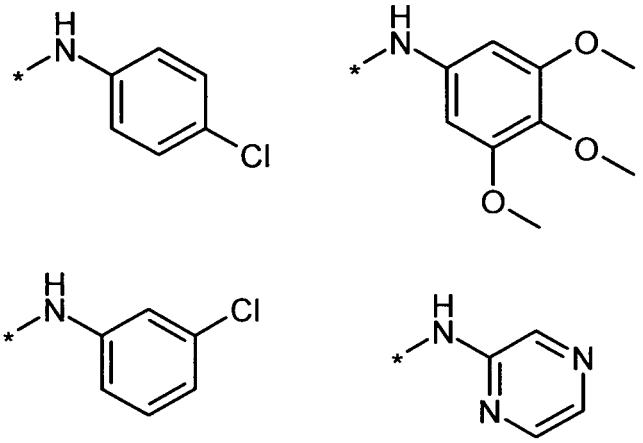
(IV)

The following embodiments refer to the compounds of formula (I), (II), (III), (III´) and (IV).

R_1 is preferably H or OH;

R_3 is preferably H, halogen, $(C_1\text{-}C_4)$alkylene-R', O-R'' or NHR''. More preferred, R_3 is H or NHR''. Most preferred, R_3 is H, NH-$(C_5\text{-}C_6)$heterocyclyl or NH-phenyl, especially preferred are H, NH-$(C_5\text{-}C_6)$heteroaryl containing one or more N atoms or NH-phenyl. Most especially preferred, R_3 is H.

Examples of R_3 substituents are



Preferably, R_4 is H, halogen or $(C_1\text{-}C_6)$alkyl. More preferred, R_4 is H, halogen or $(C_1\text{-}C_4)$alkyl. Most preferred, R_4 is H.

Preferably, R_5 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, R', NH-$(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkylene-R'. More preferably, R_5 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, R', NH-$(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkylene-R'. Most preferably, R_5 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_2)$alkyl-$(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heteroaryl. Especially preferred, R_5 is H, halogen, phenyl, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_6)$heteroaryl. Most especially preferred R_5 is H, halogen, methyl, ethyl, vinyl, phenyl, thienyl or pyridyl.

Examples of R_5 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, R_5 is H, halogen, methyl, or ethyl, most preferred R_5 is H.

Preferably, R_6 and R_6' are independently of each other
H, (C_1-C_6)alkyl, R', (C_1-C_4)alkylene-(C_3-C_8)cycloalkyl, (C_1-C_4)alkylene-(C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-(C_6-C_{10})aryl, (C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_1-C_4)alkylene-C(O)-(C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-C(O)-(C_6-C_{10})aryl, (C_1-C_6)alkylene-C(O)N$[(C_1-C_6)$alkyl$]_2$, (C_1-C_6)alkylene-C(O)NH-(C_1-C_6)alkyl, (C_1-C_6)alkylene-C(O)O-(C_1-C_6)alkyl, C(O)R' C(O)(C_1-C_6)alkyl, C(O)O-(C_1-C_6)alkyl, C(O)NH-(C_1-C_6)alkyl, C(O)N$[(C_1-C_6)$alkyl$]_2$, or C(O)(C_1-C_6)alkylene-R', or
R_6 and R_6', together with the N-atom to which they are attached, form a (C_5-C_{10})heterocyclyl group.

In a further preferred embodiment, R_6 and R_6' are independently of each other
H, (C_1-C_6)alkyl, (C_5-C_{10})heterocyclyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl , (C_1-C_4)alkylene-(C_3-C_8)cycloalkyl, (C_1-C_4)alkylene-(C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-(C_6-C_{10})aryl, (C_1-C_6)alkylene-O-(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)NH-(C_1-C_6)alkyl, (C_1-C_6)alkylene-C(O)O-(C_1-C_6)alkyl, 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, C(O)(C_1-C_6)alkylene-(C_6-C_{10})aryl, or
R_6 and R_6', together with the N-atom to which they are attached form a (C_5-C_{10})heterocyclyl group.

In a more preferred embodiment, R_6 is H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl or (C_1-C_4)alkylene-(C_3-C_6)cycloalkyl, and
R_6' is H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_5-C_{10})heterocyclyl, (C_5-C_{10})aryl, (C_1-C_4)alkylene-(C_3-C_8)cycloalkyl, (C_1-C_4)alkylene-(C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-(C_6-C_{10})aryl, (C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (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-

$C(O)O$-$(C_1$-$C_6)$alkyl, $C(O)O$-$(C_1$-$C_6)$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, $C(O)(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$heterocyclyl group.

In a further more preferred embodiment, R_6 is H, $(C_1$-$C_6)$alkyl and R_6' is H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_6$-$C_{10})$aryl,$(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, $(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylene-$C(O)N[(C_1$-$C_4)$alkyl$]_2$, $(C_1$-$C_6)$alkylene-$C(O)NH$-$(C_1$-$C_6)$alkyl, $C(O)(C_1$-$C_6)$alkyl, $C(O)(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, or
R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$heterocyclyl group.

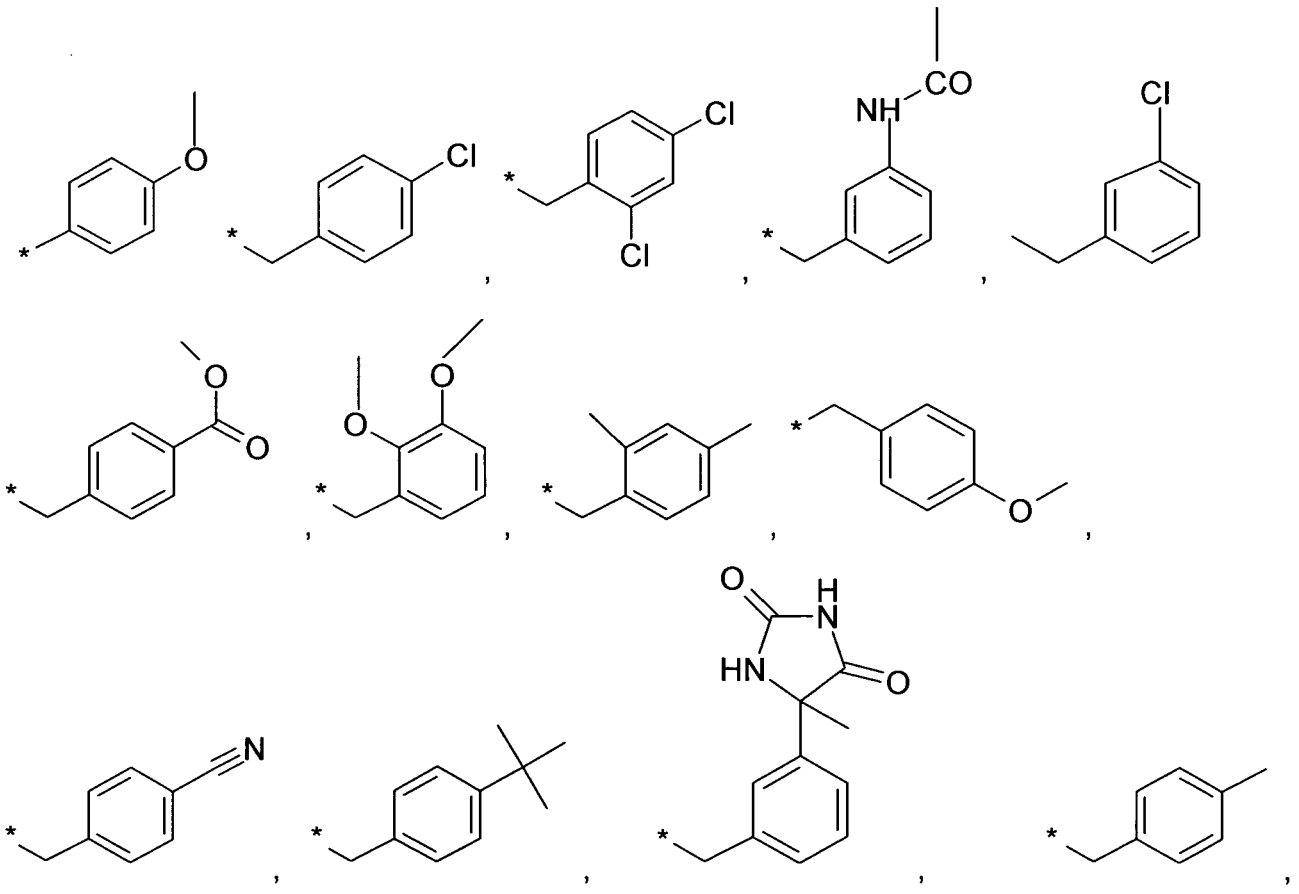
In a further even more preferred embodiment, R_6 is H, $(C_1$-$C_6)$alkyl and R_6' is H,
$(C_1$-$C_6)$alkyl;
$(C_3$-$C_8)$cycloalkyl;
$(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl;
$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl;
$(C_1$-$C_4)$alkylene-$C(O)N[(C_1$-$C_4)$alkyl$]_2$;
$(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl, or
$(C_1$-$C_4)$alkylene-$(C_6$-$C_{10})$aryl;
$C(O)(C_1$-$C_4)$alkyl;
$C(O)(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl;
or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_6)$heterocyclyl group.

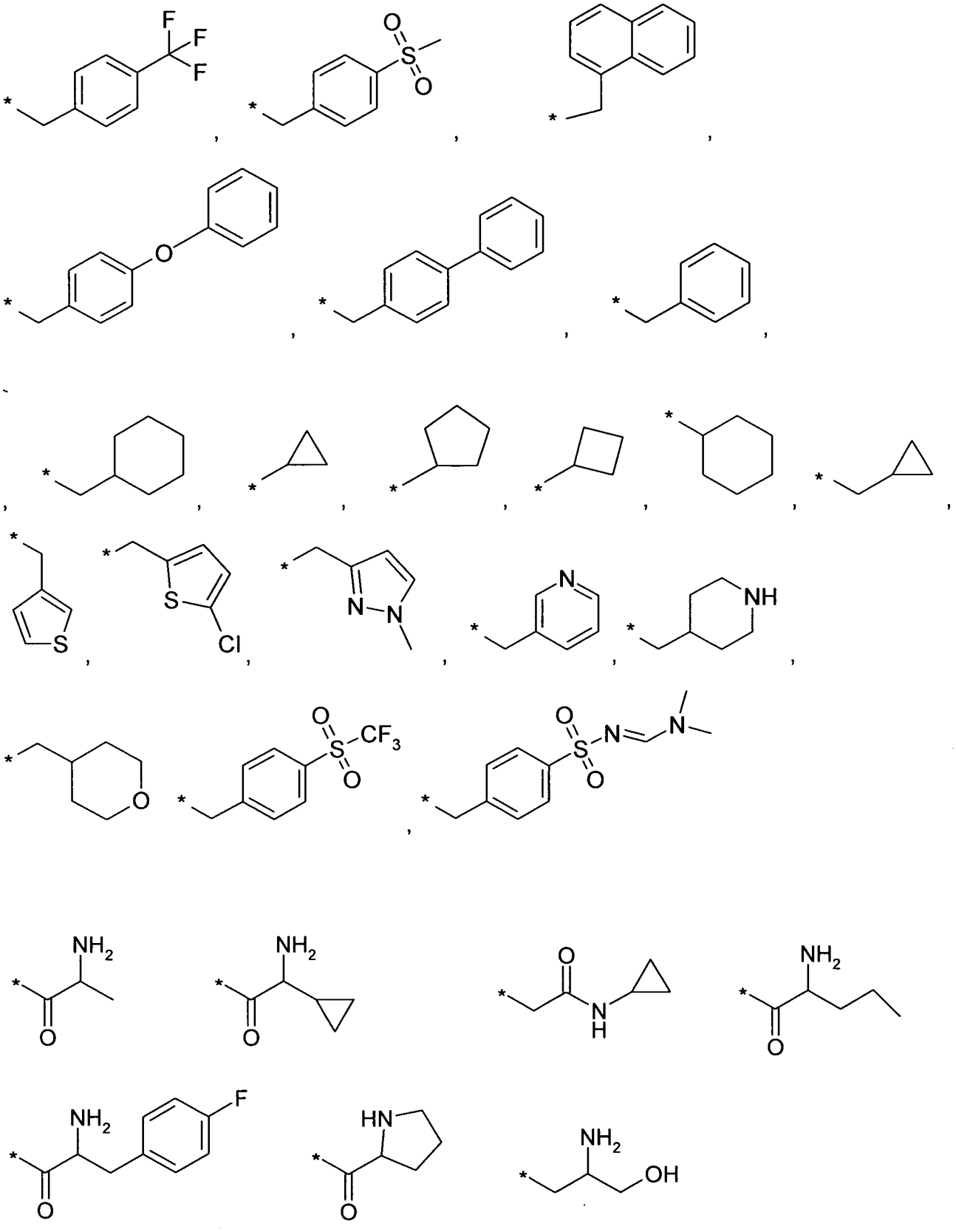
Preferably the formed heterocyclyl group is morpholino, piperidino, pyrrolidino or piperazino. More preferably the heterocyclyl group is morpholino or piperazinyl.

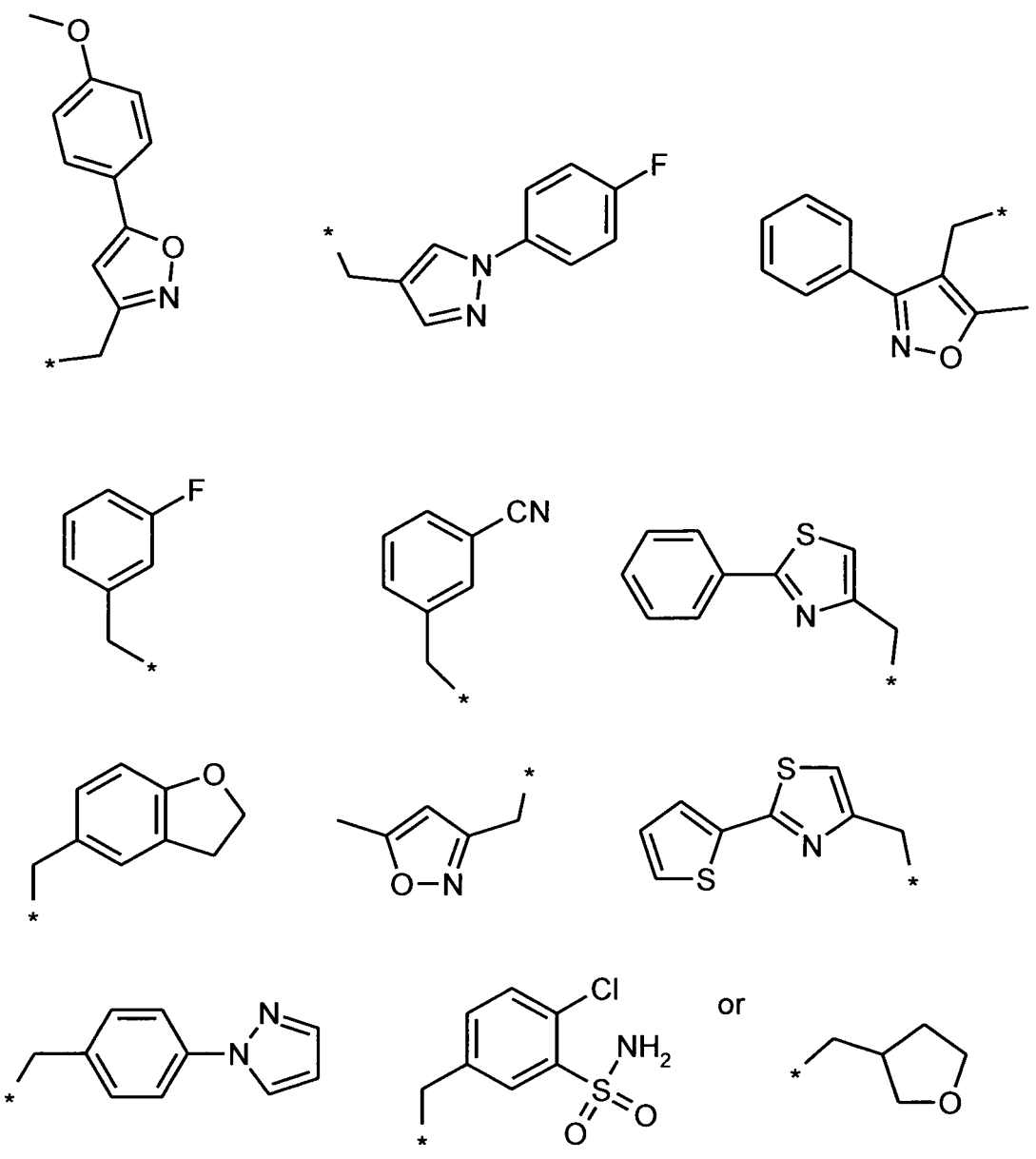
In a most preferred embodiment, R_6 is H, $(C_1\text{-}C_6)$alkyl and R_6' is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl.

In a further most preferred embodiment, R_6 is H and R_6' is H, preferably unsubstituted $(C_1\text{-}C_6)$alkyl, or preferably unsubstituted $(C_3\text{-}C_8)$cycloalkyl. Especially preferred, R_6 and R_6' are H.

As examples for these embodiments, R_6 or R_6' are, independently from each other, hydrogen, methyl, ethyl, propyl, isopropyl, 3-methyl-butyl, 2-methyl-propyl, butyl, pentyl, 3,3,3-trifuoropropyl, 4,4,4-trifluorobutyl or a substituent selected from the group consisting of







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

Preferably, R_7 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, O-$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, R' or $(C_1\text{-}C_6)$alkylene-$(C_3\text{-}C_8)$cycloalkyl. More preferred, R_7 is H, halogen, CN, $(C_1\text{-}C_4)$alkyl, O-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, phenyl, cyclopropyl or $(C_5\text{-}C_6)$heteroaryl. Most preferably, R_7 is H, fluoro, chloro, bromo, methyl, ethyl,

methoxy, phenyl, nitrile, cyclopropyl, thienyl or vinyl, most especially preferred R_7 is H, fluoro, chloro, methyl or methoxy. More particular preferred R_7 is H.

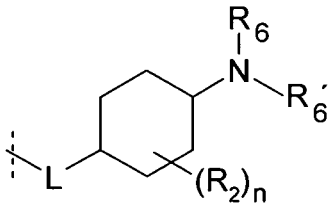
R_8 is preferably H, halogen or $(C_1$-$C_4)$alkyl. More preferred, R_8 is H, Cl, F, methyl or ethyl. Most preferred R_8 is H.

Preferably, R_2 is H, halogen or $(C_1$-$C_4)$alkyl. Preferably, R_2 is H or $(C_1$-$C_2)$alkyl. More preferred, R_2 is H, methyl or ethyl. Most preferred R_2 is H. R_2 may be bound to any carbon atom of the ring including the position where the linker group L is bound.

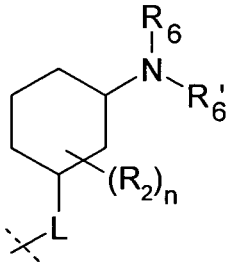
Preferably, n is 1, 2 or 3. More preferred, n is 1 or 2. Most preferred n is 1.

Preferably m is 2, 3 or 4. More preferred m is 3. In a further embodiment m is 1, 2, 4 or 5.

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 amino cyclohexane ring



or L is attached to the 3-position of the amino cyclohexane ring



in all their stereochemical forms.

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

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 $NH(CH_2)p$, $N(C_1\text{-}C_6)$alkyl-$(CH_2)p$, $N(C_3\text{-}C_6)$cycloalkyl-$(CH_2)p$ $N[CO(C_1\text{-}C_6)alkyl]\text{-}(CH_2)p$, $N[(C_1\text{-}C_3)$alkylene-aryl$]\text{-}(CH_2)p$ or $N[(C_1\text{-}C_3)$alkylene-$(C_1\text{-}C_6)$heterocyclyl$]\text{-}(CH_2)p$ with $NH(CH_2)p$, $N(C_1\text{-}C_6)$alkyl-$(CH_2)p$ being more preferred. A preferred $N(C_1\text{-}C_6)$alkyl is $N(C_1\text{-}C_4)$alkyl, more preferably methyl or ethyl with methyl being more preferred. Even more preferred L is $S(CH_2)p$ or $NH(CH_2)p$. A preferred $N(C_1\text{-}C_6)$alkyl is $N(C_1\text{-}C_4)$alkyl, more preferably NCH_3 or NCH_2CH_3 with NCH_3 being more preferred. Most preferred L is S or NH.

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 S or NH and is attached to the 4-position of the amino cyclohexane ring.

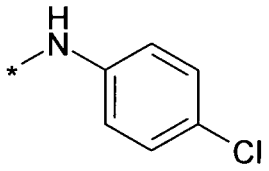
In residues R_2 to R_8 an alkyl or alkylene can optionally be substituted one or more times by halogen. Preferably alkyl or alkylene is substituted one to three times by halogen selected from chloro or bromo but may be substituted by fluoro once or more, e.g. being perfluorinated. Preferably halogen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

In residues R_4, R_5, R_6 ,R_6', R_7 and R_8 alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by a group selected independently from OH, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$. 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 alkyl, alkylene or cycloalkyl in R_4, R_5, R_7 and R_8 are not

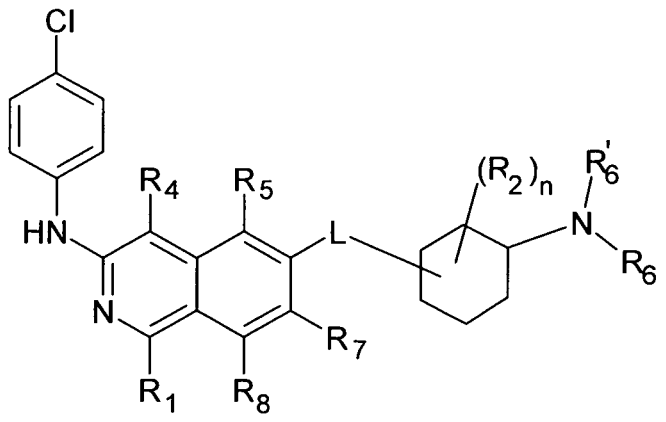
substituted. In a further embodiment alkyl, alkylene or cycloalkyl in R_4, R_5, R_6, R_6', R_7 and R_8 are not substituted.

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 R_3 substituent



and m is 3 a compound of the formula



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

R_1 is H or OH

R_2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

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

R_4 is H, halogen or $(C_1\text{-}C_6)$alkyl;

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

R_6 and R_6' are independently of each other H, R', $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_6)$alkylene-R', $(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-O-R', $(C_1\text{-}C_6)$alkylene-CH[R']$_2$, $(C_1\text{-}C_6)$alkylene-C(O)NH_2, $(C_1\text{-}C_6)$alkylene-C(O)NH-R', $(C_1\text{-}C_6)$alkylene-C(O)N[$(C_1\text{-}C_4)$alkyl]$_2$, $(C_1\text{-}C_6)$alkylene-C(O)N[R']$_2$, C(O)O-$(C_1\text{-}C_6)$alkyl, C(O)$(C_1\text{-}C_6)$alkyl, C(O)$(C_3\text{-}C_8)$cycloalkyl, C(O)$(C_5\text{-}C_{10})$heterocyclyl, C(O)NH-$(C_1\text{-}C_6)$alkyl, C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$, C(O)-$(C_1\text{-}C_6)$alkylene-$C_3\text{-}C_8)$cycloalkyl, C(O)$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, C(O)$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5\text{-}C_6)$heterocyclyl group.

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

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

m is 2, 3 or 4

n is 1, 2 or 3, and

L is $S(CH_2)p$, $NH(CH_2)p$ or $N(C_1\text{-}C_6)alkyl\text{-}(CH_2)p$; and

p is 0, 1 or 2;

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

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

R_1 is H or OH;

R_2 is H or $(C_1\text{-}C_4)alkyl$;

R_3 is H, halogen or NHR", wherein R" is defined as above;

R_4 is H, halogen or $(C_1\text{-}C_4)alkyl$;

R_5 is H, $(C_1\text{-}C_6)alkyl$, halogen, $(C_2\text{-}C_4)alkenyl$, $(C_6\text{-}C_{10})aryl$, $(C_1\text{-}C_6)alkylene\text{-}(C_6\text{-}C_{10})aryl$ or $(C_5\text{-}C_{10})heterocyclyl$;

R_6 and R_6' are independently of each other H, $(C_3\text{-}C_8)cycloalkyl$, $(C_1\text{-}C_8)alkyl$, $(C_1\text{-}C_6)alkylene\text{-}O\text{-}(C_1\text{-}C_6)alkyl$, $(C_1\text{-}C_3)alkylene$-R'; $C(O)(C_1\text{-}C_6)alkyl$, $C(O)(C_3\text{-}C_8)cycloalkyl$, $C(O)(C_5\text{-}C_{10})heterocyclyl$, $C(O)(C_1\text{-}C_6)alkylene\text{-}(C_3\text{-}C_8)cycloalkyl$, $C(O)(C_1\text{-}C_6)alkylene\text{-}(C_5\text{-}C_{10})heterocyclyl$ or $C(O)(C_1\text{-}C_6)alkylene\text{-}(C_6\text{-}C_{10})aryl$;

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

R_8 is H, halogen or $(C_1\text{-}C_6)alkyl$;

m is 2, 3 or 4

n is 1, 2 or 3; and

L is $S(CH_2)p$ or $NH(CH_2)p$,

p is 0 or 1;
or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

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

R_1 is H or OH;

R_2 is H, $(C_1\text{-}C_4)$alkyl;

R_3 is H, NH-$(C_5\text{-}C_6)$heteroaryl or NH-phenyl;

R_4 is H, halogen or $(C_1\text{-}C_4)$alkyl;

R_5 is H, $(C_1\text{-}C_4)$alkyl, halogen, $(C_1\text{-}C_4)$alkenyl, $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_2)$alkyl-$(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_6)$heteroaryl;

R_6 is H, $(C_3\text{-}C_6)$cycloalkyl or $(C_1\text{-}C_4)$alkyl;

R_6' is H, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_3)$alkylene-R', C(O)O-$(C_1\text{-}C_6)$alkyl, C(O)$(C_1\text{-}C_6)$alkyl, C(O)$(C_3\text{-}C_6)$cycloalkyl, C(O)$(C_5\text{-}C_6)$heterocyclyl, C(O)$(C_1\text{-}C_3)$alkylene-$(C_3\text{-}C_6)$cycloalkyl, C(O)$(C_1\text{-}C_3)$alkylene-$(C_5\text{-}C_6)$heterocyclyl, or C(O)$(C_1\text{-}C_3)$alkylene-phenyl;

R_7 is H, halogen, CN, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, phenyl, cyclopropyl, $(C_5$-$C_6)$heteroaryl;

R_8 is H, halogen or $(C_1$-$C_4)$alkyl;

m is 3

n is 1; and
L is S or NH;

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

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

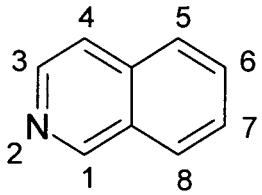
26. [4-(Isoquinolin-6-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester,
35. N-Isoquinolin-6-yl-cyclohexane-1,4-diamine,
36. 6-trans-(4-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one,
37. 6-cis-(4-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one,
38. 6-cis-(4-Amino-cyclohexyl-amino)-7-chloro-2H-isoquinolin-1-one,
39. 6-trans-(4-Amino-cyclohexyl-amino)-7-chloro-2H-isoquinolin-1-one,
40. 6-cis-(2-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one,
43. 6-trans-(2-Amino-cyclohexylamino)-2H-isoquinolin-1-one,
44. 6-cis-(4-Diethyl-amino-cyclohexylamino)-2H-iso-quinolin-1-one,
45. 6-cis-(4-Ethyl-amino-cyclohexylamino)-2H-isoquinolin-1-one,
46. 6-cis-(4-Dipropyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one,
47. 6-cis-(4-Propyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one,
48. 6-cis-(4-Benzyl-amino-cyclohexylamino)-2H-iso-quinolin-1-one,
49. 6-cis-(4-Isopropyl-amino-cyclohexylamino)-2H-iso-quinolin-1-one,
50. 6-cis-[4-(3-Chloro-benzylamino)-cyclohexylamino]-2H-isoquinolin-1-one,
51. 6-cis-[4-(4-Chloro-benzylamino)-cyclohexylamino]-2H-isoquinolin-1-one,
52. 6-cis-{4-[(Piperidin-4-ylmethyl)-amino]-cyclohexylamino}-2H-isoquinolin-1-one,

53. 6-cis-(4-Cyclopropylamino-cyclohexylamino)-2H-isoquinolin-1-one,
54. 6-cis-(4-Dicyclopropyl-amino-cyclohexylamino)-2H-isoquinolin-1-one,
55. 7-Chloro-6-cis-(4-isopropylamino-cyclohexylamino)-2H-isoquinolin-1-one,
56. 7-Chloro-6-cis-(4-diethylamino-cyclohexylamino)-2H-isoquinolin-1-one,
57. 7-Chloro-6-trans-(4-isopropylamino-cyclohexylamino)-2H-isoquinolin-1-one,
61. cis-4-(7-Chloro-isoquinolin-6-ylsulfanyl)-cyclohexylamine,
62. cis-4-(7-Bromo-isoquinolin-6-ylsulfanyl)-cyclohexylamine, or
64. 6-cis-(4-Amino-cyclohexylsulfanyl)-7-chloro-2H-isoquinolin-1-one,

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

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 specified above.

Isoquinoline substitution pattern is numbered according to IUPAC rules:



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, methylsulfonic 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.

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.

The invention relates to compounds of the formula (I) 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 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 identical or different.

The terms $(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_8)$alkyl and the corresposponding 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 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$(C_1\text{-}C_6)$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 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 -O-$(CF_2)_2$-O-.

Alkenyl are, 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.

Alkynyl are, for example, ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl.

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 bounds (unsaturated cycloalkyl groups) like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

A (C_6-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 (C_6-C_{10})aryl group is phenyl.

A (C_5-C_{10})heterocyclyl group means a mono- or bicyclic ring system in which one or more carbon atom can be replaced by one or more heteroatoms such as, for example, e.g. 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. (C_5-C_{10})heterocyclyl groups may be (1) aromatic [= heteroaryl groups] or (2) saturated or (3) mixed aromatic/saturated.

Suitable (C_5-C_{10})heterocyclyl groups include acridinyl, azocinyl, benzimidazolyl, benzofuryl, benzomorpholinyl, benzothienyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, furanyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, chromen-2-onyl, cinnolinyl,

decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, furyl, furazanyl, homomorpholinyl, homopiperazinyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-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, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 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 corresponding N-oxides of these compounds, for example, 1-oxy-2-, 3- or 4-pyridyl.

Substitutions in (C_5-C_{10})heterocyclyl residues can occur on free carbon atoms or on nitrogen atoms.

Preferred examples of (C_5-C_{10})heterocyclyl residues are pyrazinyl, pyridyl, pyrimidinyl, pyrazolyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl, benzofuryl, quinolinyl, tetrazolyl and triazolyl. A preferred (C_5-C_{10})heterocyclyl is (C_5-C_6)heterocyclyl.

(C_6-C_{10})aryl and (C_5-C_{10})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, NO_2, N_3, CN, C(O)-(C_1-C_6)alkyl, C(O)-(C_1-C_6)aryl, COOH, COO(C_1-C_6)alkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$, (C_3-C_8)cycloalkyl, (C_1-C_6)alkyl, (C_1-C_6)alkylene-OH, (C_1-C_6)alkylene-NH_2, (C_1-C_6)alkylene-NH(C_1-C_6)alkyl, (C_1-C_6)alkylene-N[(C_1-C_6)alkyl]$_2$,

$(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, O-$(C_1\text{-}C_6)$alkyl, O-C(O)-$(C_1\text{-}C_6)$alkyl, PO_3H_2, SO_3H, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$alkyl, $SO_2N[(C_1\text{-}C_6)\text{alkyl}]_2$, S-$(C_1\text{-}C_6)$alkyl; SO-$(C_1\text{-}C_6)$alkyl, SO_2-$(C_1\text{-}C_6)$alkyl, SO_2-N=CH-$N[(C_1\text{-}C_6)\text{alkyl}]_2$, $C(NH)(NH_2)$, NH_2, NH-$(C_1\text{-}C_6)$alkyl, $N[(C_1\text{-}C_6)\text{alkyl}]_2$, NH-C(O)-$(C_1\text{-}C_6)$alkyl, NH-C(O)O-$(C_1\text{-}C_6)$alkyl, NH-$SO_2$-$(C_1\text{-}C_6)$alkyl, NH-$SO_2$-$(C_6\text{-}C_{10})$aryl, NH-$SO_2$-$(C_5\text{-}C_{10})$heterocyclyl, N$(C_1\text{-}C_6)$alkyl-C(O)-$(C_1\text{-}C_6)$alkyl, N$(C_1\text{-}C_6)$alkyl-C(O)O-$(C_1\text{-}C_6)$alkyl, N$(C_1\text{-}C_6)$alkyl-C(O)-NH-$(C_1\text{-}C_6)$alkyl], $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, O-$(C_6\text{-}C_{10})$aryl, O-$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, O-$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, wherein the $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heterocyclyl may be substituted one to 3 times by a group independently selected from halogen, OH, NO_2, CN, O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, NH_2, $NH(C_1\text{-}C_6)$alkyl, $N[(C_1\text{-}C_6)\text{alkyl}]_2$, SO_2CH_3, COOH, C(O)O-$(C_1\text{-}C_6)$alkyl, $CONH_2$, $(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-O-$(C_6\text{-}C_{10})$aryl, O-$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl; or wherein $(C_6\text{-}C_{10})$aryl is vicinally substituted by a O-$(C_1\text{-}C_4)$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 $(C_6\text{-}C_{10})$aryl and $(C_5\text{-}C_{10})$heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group.

Preferred substituents for $(C_6\text{-}C_{10})$aryl groups are $(C_1\text{-}C_4)$alkyl, O-$(C_1\text{-}C_4)$alkyl, O-phenyl, phenyl, C(O)O-$(C_1\text{-}C_6)$alkyl, C(O)OH, C(O)-$(C_1\text{-}C_4)$alkyl, halogen, NO_2, SO_2NH_2, CN, SO_2-$(C_1\text{-}C_4)$alkyl, SO_2-N=CH-$N[(C_1\text{-}C_6)\text{alkyl}]_2$, NH-$SO_2$-$(C_1\text{-}C_4)$alkyl, NH_2, NH-C(O)-$(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_4)$alkyl-OH, $C(O)N[(C_1\text{-}C_4)\text{alkyl}]_2$, $CONH(C_1\text{-}C_6)$alkyl, $C(O)NH_2$, $N[(C_1\text{-}C_4)\text{alkyl}]_2$, $(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl, wherein the $(C_6\text{-}C_{10})$aryl may be further substituted one to three times, preferabyl once, by $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkylene-O-$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl O-$(C_1\text{-}C_6)$alkyl-$(C_6\text{-}C_{10})$aryl, or may be vicinally substituted by a

O-(C_1-C_4)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 (C_6-C_{10})aryl are halogen, CN, phenyl, O-phenyl, NH-C(O)-(C_1-C_4)alkyl especially NH-C(O)-CH_3, C(O)-(C_1-C_4)alkyl especially C(O)-CH_3, C(O)-O(C_1-C_4)alkyl especially C(O)-OCH_3, (C_1-C_4)alkyl especially CH_3 or CF_3, O-(C_1-C_4)alkyl especially O-CH_3, SO_2-NH_2, SO_2-(C_1-C_4)alkyl especially SO_2-CH_3 or SO_2-CF_3; or SO_2-N=CH-N[(C_1-C_4)alkyl]$_2$ especially SO_2-N=CH-N[(CH_3)$_2$.

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.

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 (C_5-C_{10})heterocyclyl groups are (C_1-C_4)alkyl, O-(C_1-C_4)alkyl, (C_1-C_4)alkylene-phenyl, halogen, (C_1-C_4)alkylene-O-(C_1-C_4)alkyl, (C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-N[(C_1-C_4)alkyl]$_2$, or (C_6-C_{10})aryl, wherein the (C_6-C_{10})aryl may be further substituted by halogen, (C_1-C_4)alkyl, O(C_1-C_4)alkyl, (C_1-C_4)alkylene-O-(C_1-C_6)alkyl, O-(C_1-C_6)alkyl-(C_6-C_{10})aryl, or may be vicinally substituted by a O-(C_1-C_4)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 $(C_5$-$C_{10})$heterocyclyl groups are $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, halogen or phenyl, wherein the phenyl may be further substituted one to three times, preferably once, by halogen, $(C_1$-$C_4)$alkyl or O-$(C_1$-$C_4)$alkyl.

The general and preferred substituents of $(C_6$-$C_{10})$aryl and $(C_5$-$C_{10})$heterocyclyl groups may be combined with the general and preferred definitions of R_1, R_2, R_3, R_4, R_5, R_6, R_6', R_7, R_8, n, m and L 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 arterial occlusive 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.

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).

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.

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 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,

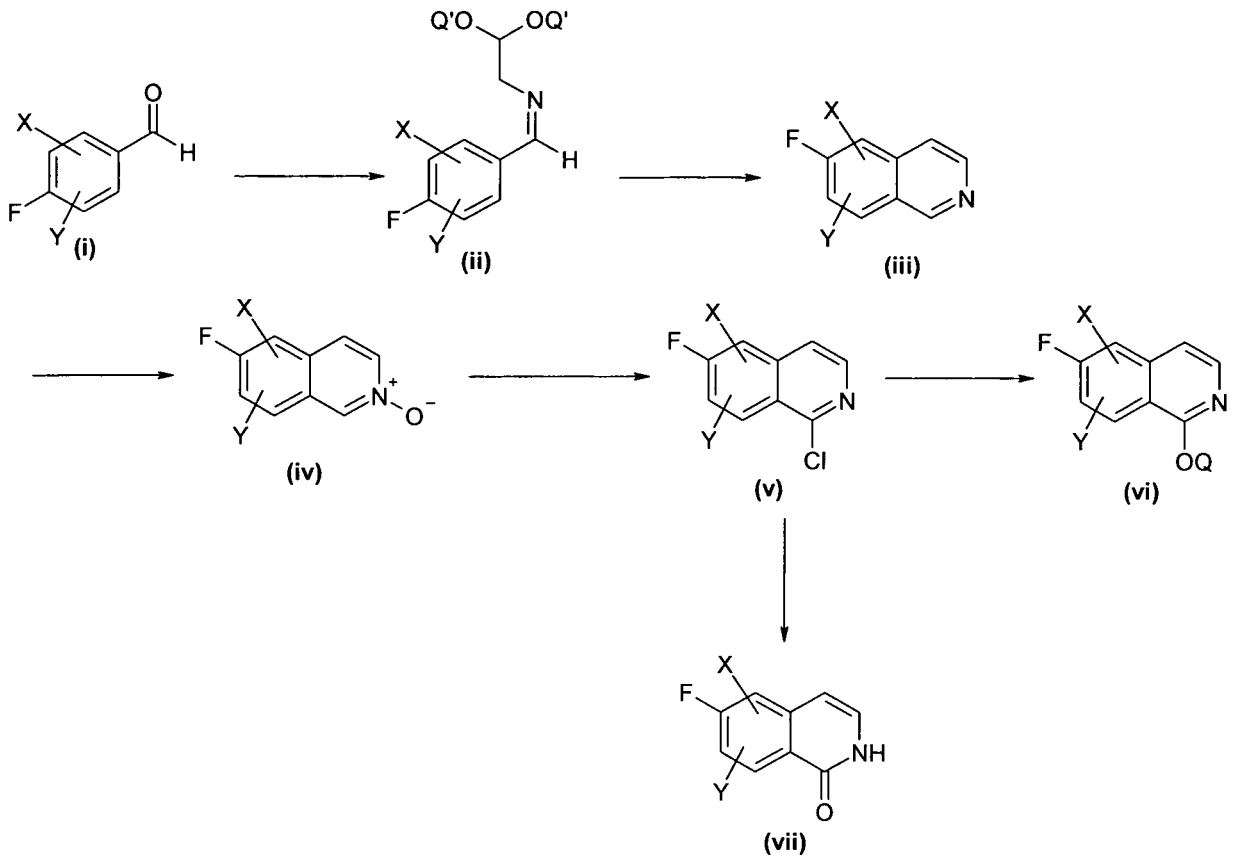
into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

Furthermore, the compounds of the formula (I) can be used as synthesis intermediates 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 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 conversion into a pharmaceutically acceptable salt or a prodrug of a compound of the formulae (I) or (I') can then be carried out by known processes.

In general, a reaction mixture containing a final compound of the formula (I) or (I') or an intermediate is worked up and, if desired, the product is then purified by customary 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, NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

Isoquinolines and isoquinolinones can by synthesized via a variety of methods. The following general schemes illustrate some of the possible ways to access isoquinolones, but do not limit the present invention.

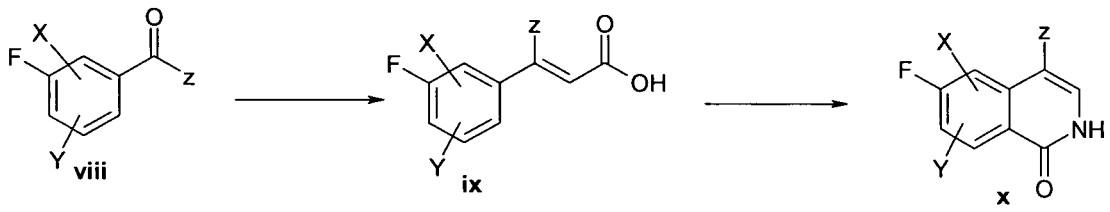


Scheme 1:

A suitably substituted aldehyde, for example substituted by X or Y being independently from each other hydrogen, alkyl, alkoxy or halide attached in a suitable position, can be reacted with a suitable compound such as for example an actal of aminoacetaldehyde for example in a solvent like THF, chloroform or toluene under acid catalysis by toluene sulfonic acid or another appropriate acid to give imine (ii) wherein Q' can be for instance methyl or ethyl, which in turn can be cyclized by different methods to the isoquinoline (iii). For example this can be done by Lewis acid catalysis by suitable Lewis acids like titanium tetrachloride, ferrous halides, aluminium halides etc. at temperatures ranging from ambient to 100 °C or by reducing the imine to the corresponding amine by action of a suitable reducing agent like sodium borohydride, converting the amine into an amide or sulphonamide by reaction with a suitable acid chloride and subsequent cyclization to the isoquinoline by action of an appropriate lewis acid. The isoquinoline (iii) itself can then be converted to the corresponding N-oxide (iv) by action of a suitable oxidative agent like hydrogen peroxide, m-chloro perbenzoic acid or others at room temperature or elevated temperature. The N-oxide (iv) can then be converted into the 1-chloro-isoquinoline derivative (v) by reacting it

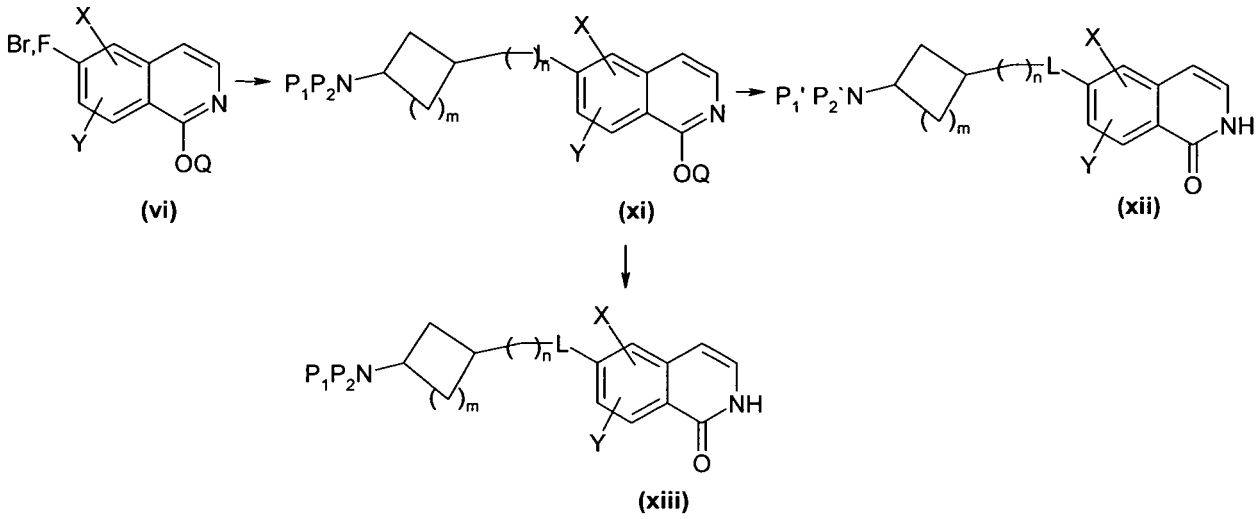
with a reagent like phosphorous oxy chloride in or without presence of phosphorous pentachloride. The derivative (v) can then be turned into suitable 1-alkoxy-derivatives by reacting it with various alcohols Q-OH like methanol, ethanol or benzyl alcohol in the presence of a suitable base like sodium hydride and in a suitable solvent like dimethyl formamide, dimethyl acetamide or others. Alternatively (v) can be directly converted into the isoquinolinone derivative (vii) by reacting it with a reagent like ammonium acetate.

Employing suitable bromo derivatives in the described reaction sequences, 6-bromo isoquinolines or bromo isoquinolones can be obtained.



Scheme 2

Alternatively isoquinolines can be obtained by reacting suitable 3-formylated or acylated fluorobenzenes (viii), wherein z is for example H or alkyl like methyl or ethyl, with a reagent like triethyl phosphono acetate in the presence of a suitable base like sodium hydride to give the corresponding cinnamic acid ester, which subsequently is cleaved by action of a suitable base like potassium hydroxide, sodium hydroxide or lithium hydroxide in a suitable solvent to deliver acid (ix). (ix) can then be converted in the corresponding acid chloride by well known methods, which can be transferred into the acid azide by reaction with sodium azide in a suitable solvent like ether, chloroform or acetone in or without the presence of water. The corresponding azide then can be converted into isoquinolinone (x) by reacting it in a suitable solvent like diphenylmethane or dipenylether at suitable temperature.



Scheme 3:

The above obtained 6-fluoro-isoquinolones (or the corresponding isoquinolines iii, alternatively), for example (vi), can be reacted with suitable P_1 / P_2 substituted thiols or amines wherein P_1 / P_2 are independently from each other for example hydrogen, alkyl or a protecting group like for example Boc or phthaloyl in the presence of base such as DBU, cesium carbonate or sodium hydride to give the corresponding alkylthio or alkylamino substituted derivatives (xi). Eventually, this conversion can already be performed at earlier stages of the synthesis (e.g. by reacting a suitable intermediate). It is understood, that this may require in case of unprotected isoquinolones protection on the nitrogen or oxygen of the isoquinolone moiety by suitable methods, like reaction with suitably substituted alkyl or benzyl halides in the presence of base.

In case of amine substitutions, reaction may also be accomplished by reacting a suitable bromo-derivative with the given amine in the presence of a palladium catalyst like palladium acetate, a ligand like e.g. BINAP and a base like cesium carbonate.

The products like (xi) obtained via this method can then either be liberated or, if a suitable amino functionality is present, be reacted with suitable aldehydes or ketones in the presence of a reducing agent like sodium triacetoxy borohydride, sodium borohydride or sodium cyanoborohydride in a suitable solvent and in the presence of a water withdrawing agent like molecular sieves or a suitable ortho ester. This amino group may have to be liberated in an initial step like for example acidic removal of Boc-

groups. Furthermore an amino group can be acylated by reacting it with a suitable acid chloride in the presence of a base like triethyl amine or Hünig's base or by reacting it with a suitable carboxylic acid in the presence of a base like triethylamine or Hünig's base and a coupling reagent like EDC, PyBOP or TOTU.

In case of use of protected isoquinolones, cleavage of the used protection groups is required to liberate the desired isoquinolone (xii). This liberation, however, can be performed before or after the reductive amination step, depending on the nature of the used aldehyde / ketone and the protection group used.

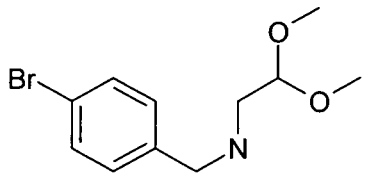
Isoquinolone derivatives like (xii) can be obtained as free bases or as various salts like for example hydrochlorides, hydrobromides, phosphates, trifluoroacetates, sulfates or fumarates. The salts obtained can be converted into the corresponding free base by either subjecting them to ion exchange chromatography or for example by alkaline aqueous treatment and subsequent extraction with suitable organic solvents like for example methyl tert. butyl ether, chloroform, ethyl acetate or isopropanol / dichloromethane mixtures and subsequent evaporation to dryness.

The general methods for the preparation of isoquinoline derivatives as described above can be readily adapted to the preparation of the compounds of the formula (I). In the following examples the preparation of the compounds of the present invention is outlined in more detail.

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

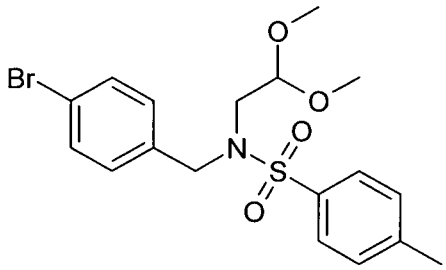
It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein.

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



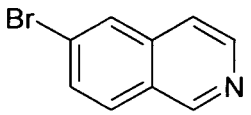
50 g (270.2 mmol) 4-bromobenzaldehyde were dissolved in 200 ml toluene and 28.4 g (270.2 mmol) aminoacetaldehyde dimethylacetal were added. After the addition of 5.1 g (27.0 mmol) p-toluenesulfonic acid monohydrate, the reaction mixture was heated under reflux in a Dean Stark apparatus. After 4 h, the reaction was cooled to room temperature and washed with saturated $NaHCO_3$-solution (2x) and H_2O. The combined aqueous layers were extracted with toluene and the combined organic layers were dried with $MgSO_4$ 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 the solvent was removed i. vac. The residue was taken up in dichloromethane and washed (2x) with H_2O. After drying with $MgSO_4$ and evaporation, 60.5 g of the title compound were obtained (crude product), which were used without further purification. R_t = 0.80 min (Method C). Detected mass: 274.1/276.1 ($M+H^+$).

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



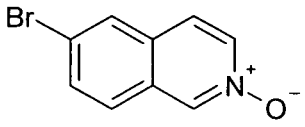
60.5 g (4-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1, crude product) were dissolved in 270 ml dichloromethane/pyridin (8:1). At 0 °C a solution of 76.0 g (386.4 mmol) p-toluenesulfonylchloride in 100 ml dichloromethane were added and the solution was stirred at room temperature. After 3 h, the reaction mixture was washed twice with 2 N HCl and saturated $NaHCO_3$-solution. The organic layer was dried with $MgSO_4$ and evaporated. Final silicagel chromatography (heptane/ethylacetate 4:1) gave 59.9 g of the title compound. R_t = 1.82 min (Method C). Detected mass: 396.1/398.1 ($M-OMe^-$).

6-Bromo-isoquinoline (3)



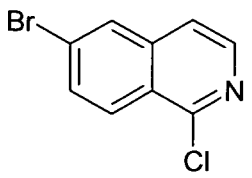
To a mechanically stirred suspension of 95.2 g (699.5 mmol) $AlCl_3$ in 400 ml dichloromethane a solution of 59.9 g (139.8 mmol) N-(4-Bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2) in 400 ml dichloromethane was added and the reaction was stirred at room temperature for 4 h. After 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 $NaHCO_3$-solution (2x). After drying with $MgSO_4$ 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 ($M+H^+$).

6-Bromo-isoquinoline-2-oxide (4)



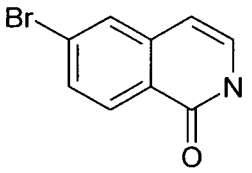
To a solution of 51.0 g (245.1 mmol) 6-bromo-isoquinoline (3) in 800 ml dichloromethane were added under mechanical stirring 90.6 g (367.6 mmol) 3-chloro-benzenecarboperoxoic acid (70%). After stirring for 4 h at room temperature and standing overnight, saturated $NaHCO_3$-solution was added until two clear layers were obtained. The dichloromethane solution was separated and washed with saturated NaCl-solution. The aqueous layers were extracted with a chloroform/isopropanol (3:1) mixture and the organic layers were combined, washed again with saturated NaCl-solution, dried with $MgSO_4$ and evaporateed. The obtained crude product (53.0 g) was used without further purification. R_t = 0.89 min (Method C). Detected mass: 226.2 ($M+H^+$).

6-Bromo-1-chloro-isoquinoline (5)



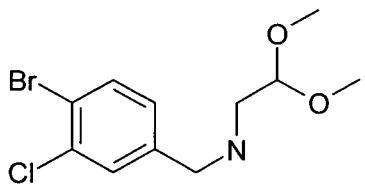
53.0 g (236.5 mmol) 6-bromo-isoquinoline-2-oxide (4) were heated in 400 ml $POCl_3$ under reflux conditions in two portions. After 4 h, the reaction was cooled to room temperature and poured carefully on ice with mechanical stirring. The aqueous solution was extracted three times with dichloromethane. The combined organic layers were dried with $MgSO_4$ and evaporated, which gave 42.8 g of the title compound, which was used without further purification. R_t = 1.64 min (Method C). Detected mass: 242.1/244.2 ($M+H^+$).

6-Bromo-2H-isoquinolin-1-one (6)



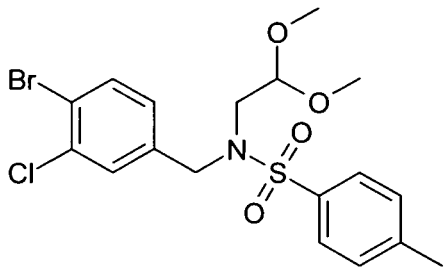
To a solution of 42.8 g (173.5 mmol) 6-bromo-1-chloro-isoquinoline (5) in 700 ml acetic acid were added 133.6 g (1.74 mol) ammonium acetate. After stirring at 100 °C for 3 h, the solution was cooled to room temperature and the solvent was removed i. vac. to a small volume. The residue was poured on H_2O and the suspension was stirred for some minutes. The precipitate was isolated by filtration and dried, to yield 28.2 g of the title compound. R_t = 1.30 min (Method B). Detected mass: 224.0 ($M+H^+$).

(4-Bromo-3-chloro-benzyl)-(2,2-dimethoxy-ethyl)-amine (7)



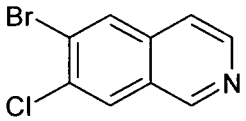
Starting from 4-bromo-3-chloro-benzaldehyde, the title compound was prepared by the methode described for (4-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1). R_t = 0.94 min (Method C). Detected mass: 308.3/310.3 ($M+H^+$).

N-(4-Bromo-3-chloro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (8)



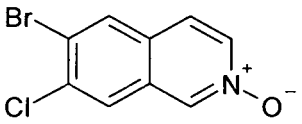
The title compound was prepared by the protocol described for N-(4-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2), starting from (4-bromo-3-chloro-benzyl)-(2,2-dimethoxy-ethyl)-amine (7). R_t = 1.93 min (Method C). Detected mass: 430.3/432.3 ($M\text{-}OMe^-$).

6-Bromo-7-chloro-isoquinoline (9)



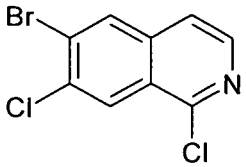
Starting from N-(4-bromo-3-chloro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (8), the title compound was synthesized by the protocol described for 6-bromo-isoquinoline (3). R_t = 1.02 min (Method C). Detected mass: 242.2/244.2 ($M+H^+$).

6-Bromo-7-chloro-isoquinoline-2-oxide (10)



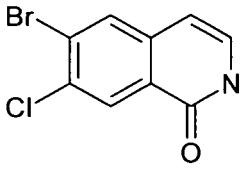
The title compound was prepared by the method described for 6-bromo-isoquinoline 2-oxide (4), starting with 6-bromo-7-chloro-isoquinoline (9). R_t = 1.05 min (Method C). Detected mass: 258.1/260.2 ($M+H^+$).

6-Bromo-1,7-dichloro-isoquinoline (11)



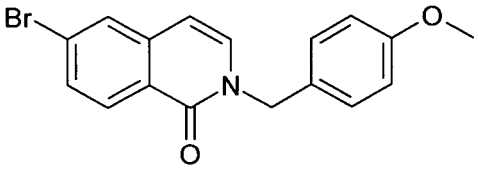
Starting with 6-bromo-7-chloro-isoquinoline-2-oxide (10), the desired 6-bromo-1,7-dichloro-isoquinoline was prepared by the method, described for 6-bromo-1-chloro-isoquinoline (5). R_t = 1.85 min (Method C). Detected mass: 276.1/278.2 ($M+H^+$).

6-Bromo-7-chloro-2H-isoquinolin-1-one (12)



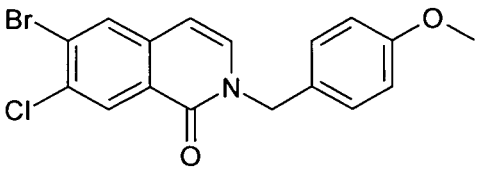
The title compound was prepared by the method, described for 6-bromo-2H-isoquinolin-1-one (6), starting from 6-bromo-1,7-dichloro-isoquinoline (11). R_t = 1.26 min (Method C). Detected mass: 258.2/260.2 ($M+H^+$).

6-Bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (13)



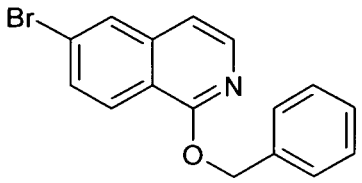
28.18 g (125.8 mmol) 6-bromo-2H-isoquinolin-1-one (6) were dissolved in 200 ml dimethylacetamide and 7.55 g (188.7 mmol) sodium hydride (60%) were added at room temperature. After stirring for 30 minutes, 29.94 g (188.7 mmol) 4-methoxy-benzylchloride were added and stirring was continued at room temperature until complete conversion was detected. The solvent was removed under reduced pressure, the residue taken up in saturated $NaHCO_3$-solution and extracted three times with dichloromethane. The organic layers were dried with $MgSO_4$ and evaporated. Final purification was achieved by silicagel chromatography. R_t = 1.93 min (Method B). Detected mass: 344.1 ($M+H^+$).

6-Bromo-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (14)



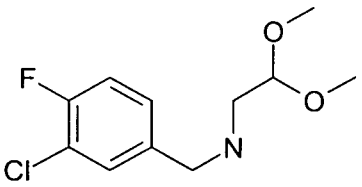
Starting from 6-bromo-7-chloro-2H-isoquinolin-1-one (12), the title compound was prepared by the method described for 6-bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (13). R_t = 2.12 min (Method B). Detected mass: 378.1/380.1 ($M+H^+$).

1-Benzyloxy-6-bromo-isoquinoline (15)



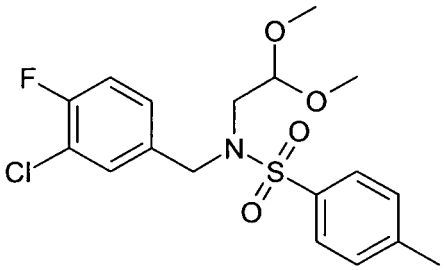
To a solution of 3.93 g (17,5 mmol) 6-bromo-2H-isoquinolin-1-one (6) in 150 ml toluene were added 12.13 g (44.0 mmol) Ag_2CO_3 and 3.60 g (21.1 mmol) benzylbromide. The reaction mixture was refluxed for 1.5 h and then cooled to room temperature. The solution was filtered. The filtrate was washed with H_2O and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and evaporated. Final purification was achieved by preparative HPLC. R_t = 2.47 min (Method B). Detected mass: 314.1/316.5 ($M+H^+$).

(4-Fluoro-3-chloro-benzyl)-(2,2-dimethoxy-ethyl)-amine (16)



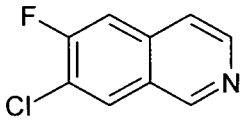
Starting from 4-fluoro-3-chloro-benzaldehyde, the title compound was prepared by the methode described for (4-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1). R_t = 0.81 min (Method C). Detected mass: 248.2 ($M+H^+$).

N-(4-Fluoro-3-chloro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (17)



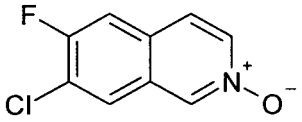
The title compound was prepared by the protocol described for N-(4-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2), starting from (4-fluoro-3-chloro-benzyl)-(2,2-dimethoxy-ethyl)-amine (16). R_t = 1.80 min (Method C). Detected mass: 370.2 ($M\text{-}OMe^-$).

6-Fluoro-7-chloro-isoquinoline (18)



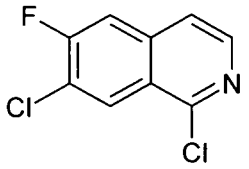
Starting from N-(4-fluoro-3-chloro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (17), the title compound was synthesized by the protocol described for 6-bromo-isoquinoline (3). R_t = 0.73 min (Method C). Detected mass: 182.1 ($M+H^+$).

6-Fluoro-7-chloro-isoquinoline-2-oxide (19)



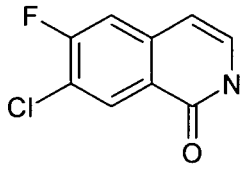
The title compound was prepared by the method, described for 6-bromo-isoquinoline-2-oxide (4), starting with 6-fluoro-7-chloro-isoquinoline (18). R_t = 0.87 min (Method C). Detected mass: 198.1 ($M+H^+$).

6-Fluoro-1,7-dichloro-isoquinoline (20)



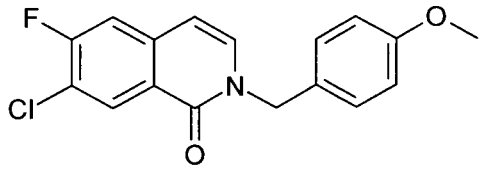
Starting with 6-fluoro-7-chloro-isoquinoline-2-oxide (19), the desired 6-fluoro-1,7-dichloro-isoquinoline was prepared by the method, described for 6-bromo-1-chloro-isoquinoline (5). R_t = 2.34 min (Method B). Detected mass: 216.0 ($M+H^+$).

6-Fluoro-7-chloro-2H-isoquinolin-1-one (21)



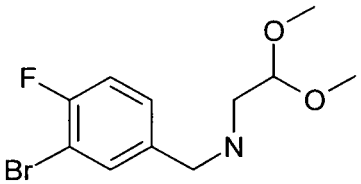
The title compound was prepared by the method, described for 6-bromo-2H-isoquinolin-1-one (6), starting from 6-fluoro-1,7-dichloro-isoquinoline (20). R_t = 1.31 min (Method B). Detected mass: 239.1 ($M+H^+$+ACN).

6-Fluoro-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (22)



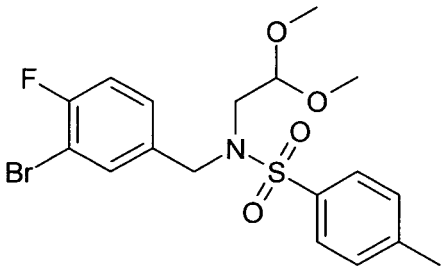
Starting from 6-fluoro-7-chloro-2H-isoquinolin-1-one (21), the title compound was prepared by the method described for 6-bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (13). R_t = 1.94 min (Method B). Detected mass: 318.1 ($M+H^+$).

(4-Fluoro-3-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (23)



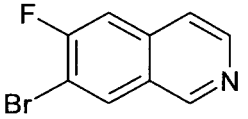
Starting from 4-fluoro-3-bromo-benzaldehyde, the title compound was prepared by the methode described for (4-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1). R_t = 1.01 min (Method B). Detected mass: 292.1 ($M+H^+$).

N-(4-Fluoro-3-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (24)



The title compound was prepared by the protocol described for N-(4-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2), starting from (4-fluoro-3-bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (23). R_t = 2.16 min (Method B). Detected mass: 414.1 ($M\text{-}OMe^-$).

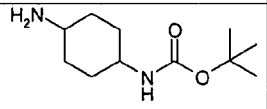
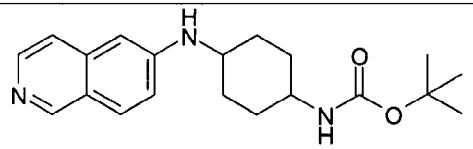
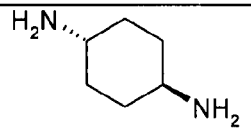
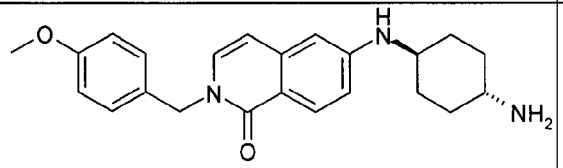
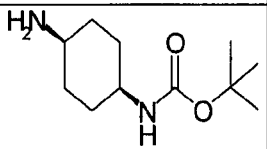
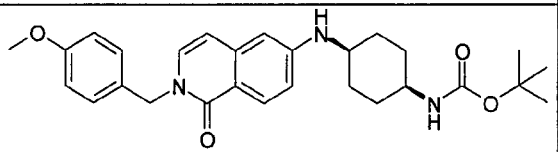
6-Fluoro-7-bromo-isoquinoline (25)

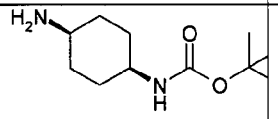
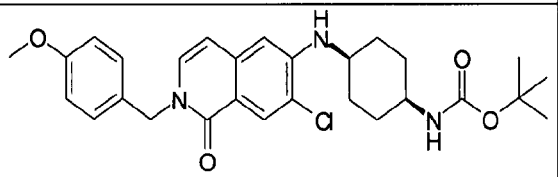
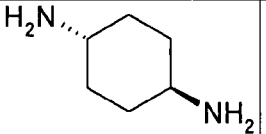
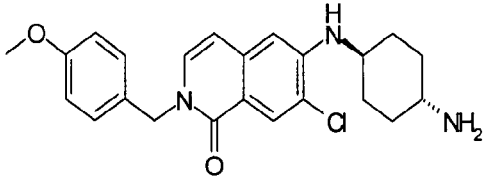
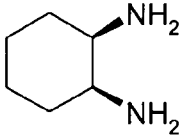
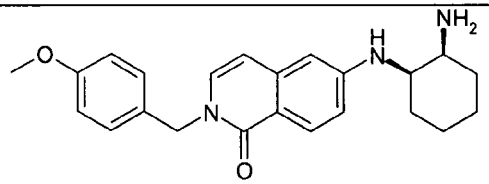
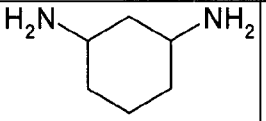
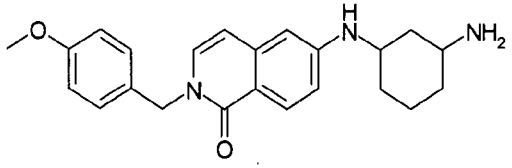


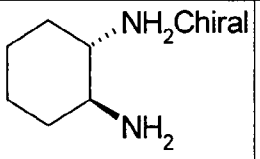
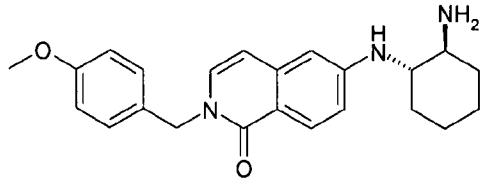
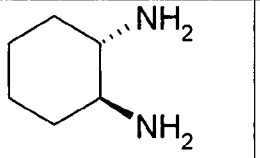
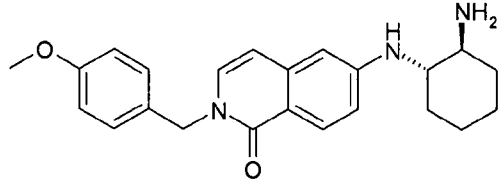
Starting from N-(4-fluoro-3-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (24), the title compound was synthesized by the protocol described for 6-bromo-isoquinoline (3). R_t = 0.80 min (Method B). Detected mass: 226.0 ($M+H^+$).

General Procedure A for the Hartwig-Buchwald amination reaction:
1.0 eq of the arylbromide, 1.5 eq Cs_2CO_3 and 1.2 eq of the amine were dissolved in toluene. If the amine was taken as a salt another equivalent of Cs_2CO_3 was used; if additionally the arylbromide was used as a salt (HCl- or TFA-salt of the isoquinolines), again, 1 additional equivalent of Cs_2CO_3 was used. The solution was degassed and flushed with argon. Then, 0.03 eq $Pd(OAc)_2$ and 0.045 eq BINAP were added and the solution was heated at 100 °C until the reaction was complete or no further improvement could be achieved. For product isolation, the solution was cooled to room temperature, filtered and the filtrate was evaporated. The residue was taken up in H_2O and extracted ethyl acetate. The organic layer was separated, dried with $MgSO_4$ and the solvent was removed i. vac. The crude product was purified by preparative HPLC. The following compounds were synthesized following General Procedure A (Table 1):

Table 1:

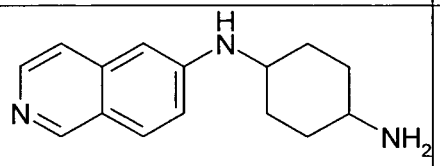
Example	Aryl-bromide	Amine	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LCMS Method
26	3			[4-(Isoquinolin-6-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester	1.07	342.2	C
27	13			6-trans-(4-Amino-cyclohexylamino)-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one	1.01	378.3	C
28	13			cis-{4-[2-(4-Methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylamino]-cyclohexyl}-carbamic acid tert-butyl ester	1.65	478.6	C
29	14			cis-{4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-	1.86	512.4	C

Example	Aryl-bromide	Amine	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LCMS Method
				isoquinolin-6-yl-amino]-cyclohexyl}-carbamic acid tert -butyl ester			
30	14			trans-6-(4-Amino-cyclohexylamino)-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one	1.08	412.5	C
31	13			6-cis-(2-Amino-cyclo-hexylamino)-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one	1.04	378.5	C
32	13			6-(3-Amino-cyclo-hexylamino)-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one	1.01	378.5	C

Example	Aryl-bromide	Amine	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LCMS Method
33	13			6-((1S,2S)-2-Amino-cyclohexylamino) -2-(4-methoxy-benz-yl)-2H-isoquinolin-1-one	1.04	378.5	C
34	13			6-trans-(2-Amino-cyclohexylamino) -2-(4-methoxy-benz-yl)-2H-isoquinolin-1-one	1.01	378.5	C

General procedure B for the deprotection of the Boc-group:
The Boc-protected compounds were dissolved in methanol and the same volume of 2 N HCl was added. The solutions were stirred at room temperature until complete conversion was detected. The solvent was removed i. vac. and the residues were dissolved in H_2O. Final lyophilisation gave the desired product as hydrochlorides. The following compounds were synthesized as hydrochlorides following General Procedure B (Table 2):

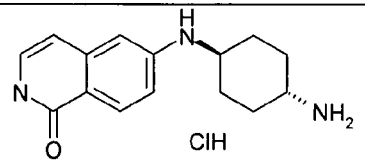
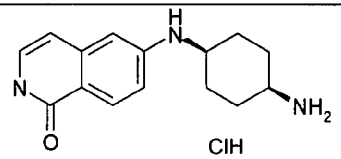
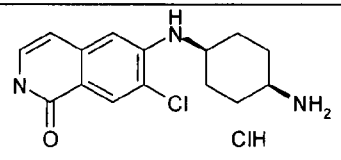
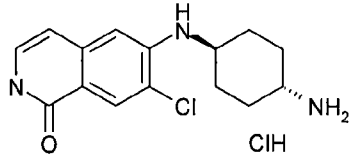
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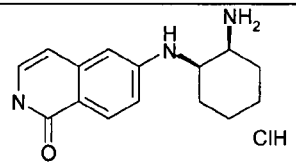
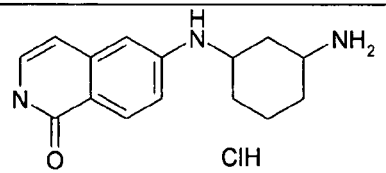
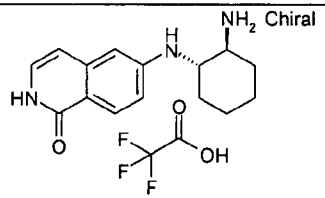
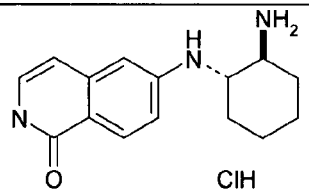
Example	Prot. comp.	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LCMS Method
35	26		N-Isoquinolin-6-yl-cyclo-hexane-1,4-diamine	0.81	242.2	B

General procedure C for the deprotection of PMB-protected compounds:
In the case of PMB- and Boc-protected compounds, the starting materials were dissolved in trifluoro acetic acid and stirred at room temperature for 1 h, followed by 3 h at 140 °C in a microwave. For isolation, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC. The product fractions were combined and evaporated, which gave the desired product as trifluoro acetates, which, in some cases, were dissolved in 2 N HCl and evaporated. After final lyophilisation of the aqueous solutions, the desired products were isolated as hydrochlorides.

The following compounds were synthesized following General Procedure C (Table 3):

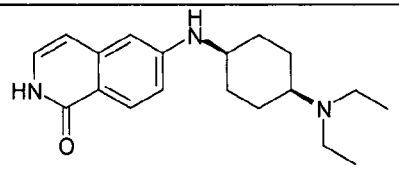
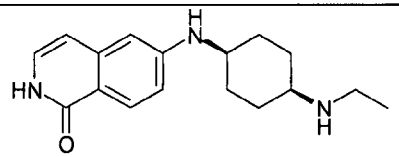
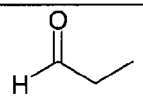
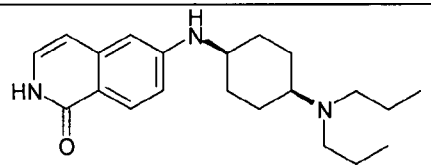
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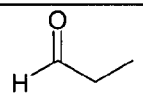
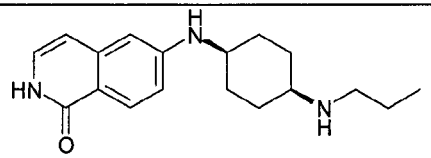
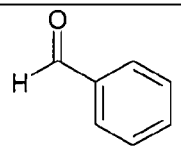
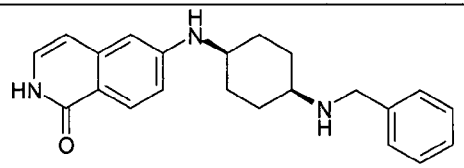
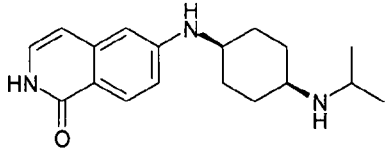
Example	Protected compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/MS-Method
36	27		6-trans-(4-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one	0.85	258.2	B
37	28		6-cis-(4-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one	0.90	258.2	B
38	29		6-cis-(4-Amino-cyclohexyl-amino)-7-chloro-2H-isoquinolin-1-one	0.88	292.1	B
39	30		6-trans-(4-Amino-cyclohexyl-amino)-7-chloro-2H-isoquinolin-1-one	0.86	292.2	B

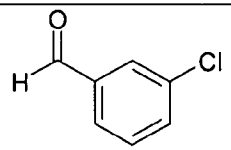
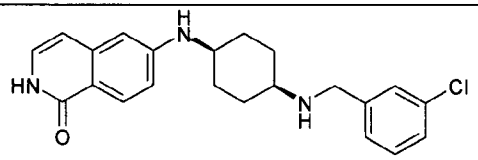
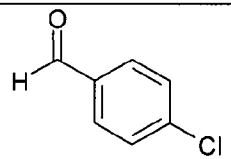
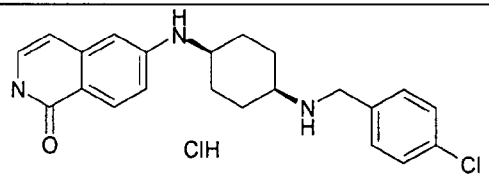
Example	Protected compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/MS-Method
40	31		6-cis-(2-Amino-cyclohexyl-amino)-2H-isoquinolin-1-one	0.87	258.2	B
41	32		6-(3-Amino-cyclohexylamino)-2H-isoquinolin-1-one	0.80	258.2	B
42	33		6-((1S,2S)-2-Amino-cyclo-hexylamino)-2H-isoquinolin-1-one	0.87	258.2	B
43	34		6-trans-(2-Amino-cyclo-hexylamino)-2H-isoquinolin-1-one	0.83	258.2	B

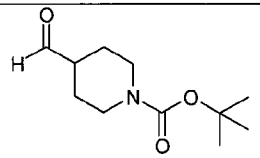
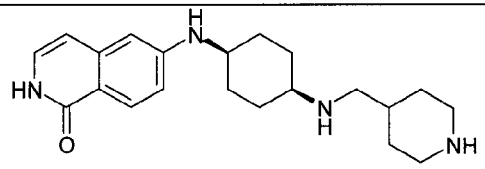
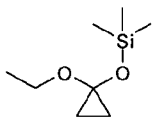
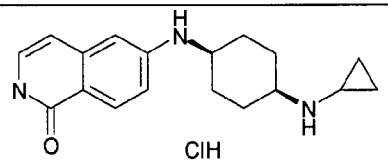
General procedure D for the reductive amination:
The starting material (1.0 eq) was dissolved in dry methanol. After adding freshly dried molecular sieves (4Å), triethylamine (2.0 eq), acetic acid (10.0 eq), the carbonyl compounds (3.0 – 6.0 eq) and sodium cyanoborohydride (3.0 eq), the mixture was stirred at room temperature. To achieve complete conversion, in some cases the reaction was heated to 70 °C (bath temperature) or further equivalents of the carbonyl compound and sodium cyanoborohydride were added. For product isolation, the solution was filtered and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with 1 N NaOH. The aqueous layer was separated and extracted twice with etyl acetate. The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude products were purified by preparative HPLC. The product fractions were combined and evaporated, which gave the desired product as trifluoro acetates, which were dissolved in 2 N HCl and evaporated. After final lyophilisation of the aqueous solutions, the desired products were isolated as hydrochlorides. The following compounds were synthesized as hydrochlorides following General Procedure D (Table 4):

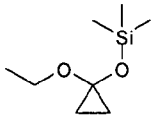
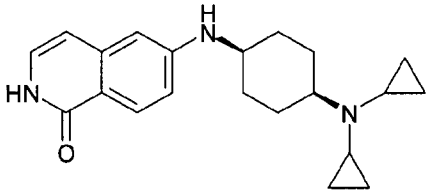
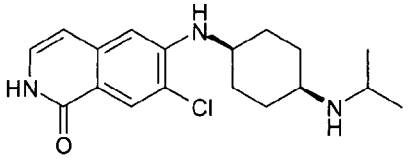
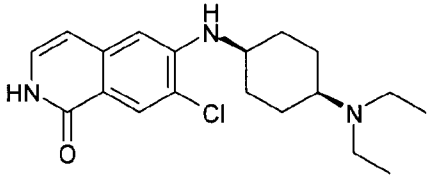
Table 4:

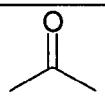
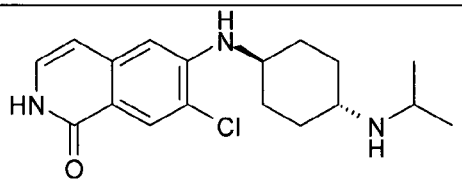
Exam -ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
44	37			6-cis-(4-Diethyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one	0.97	314.2	B	6.0 eq acet-aldehyde were used
45	37			6-cis-(4-ethylamino-cyclohexylamino)-2H-isoquinolin-1-one	0.78	286.1	B	3.0 eq acet-aldehyde were used
46	37			6-cis-(4-Dipropyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one	1.07	342.2	B	5.0 eq propion-aldehyde were used

Exam -ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
47	37			6-cis-(4-Propyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one	0.90	300.3	A	3.0 eq propion-aldehyde were used
48	37			6-cis-(4-Benzyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one	1.11	348.3	B	1.0 eq benz-aldehyde was used
49	37			6-cis-(4-Isopropyl-amino-cyclohexyl-amino)-2H-iso-quinolin-1-one	0.88	300.3	B	1.0 + 5.0 eq acetone were used

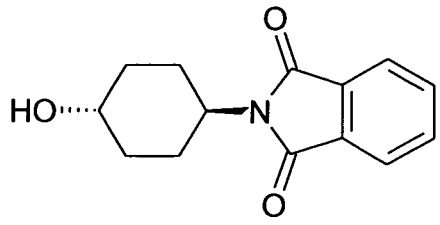
Exam -ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
50	37			6-cis-[4-(3-Chloro-benzylamino)-cyclohexyl-amino]-2H-isoquinolin-1-one	1.27	382.4	B	1.0 + 3.0 eq 3-chloro-benz-aldehyde was used
51	37			6-cis-[4-(4-Chloro-benzylamino)-cyclohexyl-amino]-2H-isoquinolin-1-one	1.27	382.4	B	1.0 + 3.0 eq 4-chloro-benz-aldehyde was used

Exam -ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
52	37			6-cis-{4-[(Piperidin-4-ylmethyl)-amino]-cyclohexyl-amino}-2H-isoquinolin-1-one	0.72	355.3	B	1.0 eq aldehyde was used. Boc-de-protection was achieved by stirring in 2 HCl before final lyophilisation.
53	37			6-cis-(4-Cyclopropyl-amino-cyclo-hexylamino)-2H-isoquinolin-1-one	0.97	298.2	B	1.0+1.0+0.5 eq "carbonyl compound" was used.

Exam-ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
54	37			6-cis-(4-Dicyclopropyl-amino-cyclohexyl-amino)-2H-isoquinolin-1-one	0.94	338.2	B	1.0+1.0+0.5 eq "carbonyl compound" was used. Side product from Ex. 53.
55	38			7-Chloro-6-cis-(4-isopropyl-amino-cyclohexylamino)-2H-isoquinolin-1-one	0.97	334.1	B	1.25 + 1.25 eq acetone were used.
56	38			7-Chloro-6-cis-(4-diethylamino-cyclohexyl-amino)-2H-iso-quinolin-1-one	1.00	348.2	B	12.0 eq acetalde-hyde were used.

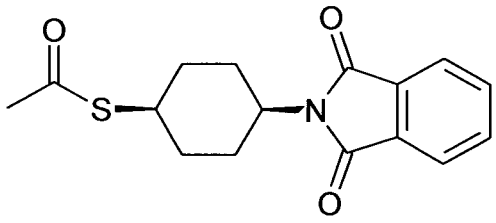
Exam -ple	Starting material	Carbonyl compound	Product	Chemical Name	R_t [min]	Mass [M+H$^+$]	LC/ MS-Met.	Remark
57	39			7-Chloro-6-trans-(4-isopropyl-amino-cyclohexyl-amino)-2H-isoquinolin-1-one	0.98	334.2	B	2.5 + 1.25 eq acetone were used.

trans-2-(4-Hydroxy-cyclohexyl)-isoindole-1,3-dione (58)



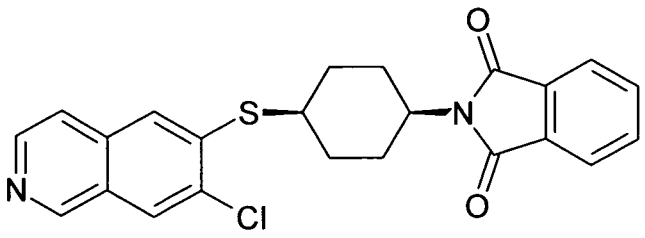
5 g (33 mmol) trans-4-aminocyclohexanol, 4.88 g phthalic anhydride and 7.85 ml tributylamin were stirred at 150°C for 10h. The mixture was dissolved in dichloromethane and washed with 1N HCl and saturated sodium hydrogen carbonate solution. The organic phase was dried with Na_2SO_4 and evaporated. Purification over silica gel (50% ethyl acetate in heptane) gave 4.8 g of the expected compound.

cis-Thioacetic acid 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclohexyl ester (59)



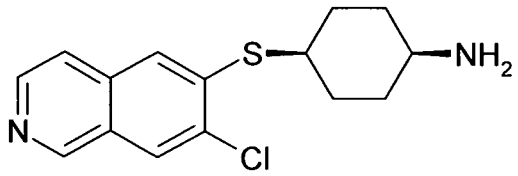
3 g (12.2 mmol) trans-2-(4-Hydroxy-cyclohexyl)-isoindole-1,3-dione (58) and 3.51 g (13.1 mmol) triphenylphosphine were dissolved in 55 ml of dry THF. At 0°C 2 ml (12.2 mmol) diethylazodicarboxylate (15 min) and thereafter 873 µl (12.2 mmol) thioacetic acid were added and stirring was continued over night at RT. After evaporation of all volatiles the residue was purified over silica gel (2% to 10 % ethyl acetate in heptane) to give 2.56 g of the expected compound.

cis-2-[4-(7-Chloro-isoquinolin-6-ylsulfanyl)-cyclohexyl]-isoindole-1,3-dione (60)



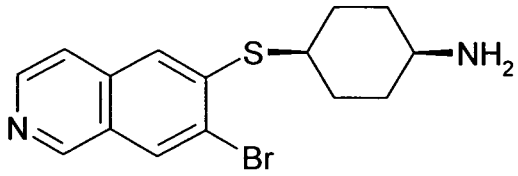
454 mg (1.5 mmol) cis-thioacetic acid 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclohexyl ester (59) and 273 mg (1.5 mmol) 6-fluoro-7-chloro-isoquinoline (18) were dissolved in 5 ml degassed DMF. After addition of 675 µl (3 mmol) DBU the mixture was heated to 78°C for 7 h. The mixture was taken up in ethyl acetate and washed with brine. The organic phases were dried with Na_2SO_4 and evaporated. Purification over silica gel (30% to 50% ethyl acetate in heptane) gave 220 mg of the expected compound.

cis-4-(7-Chloro-isoquinolin-6-ylsulfanyl)-cyclohexylamine (61)



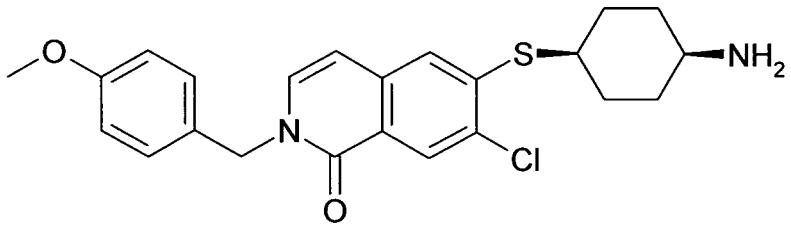
220 mg (0.52 mmol) cis-2-[4-(7-chloro-isoquinolin-6-ylsulfanyl)-cyclohexyl]-isoindole-1,3-dione (60) in 5 ml methanol were treated with 250 µl hydrazine hydrate at RT until complete conversion was achieved. After evaporation, the residue was purified by HPLC. 131 mg of cis-4-(7-chloro-isoquinolin-6-ylsulfanyl)-cyclohexylamine could be obtained as the trifluoroacetate. The obtained trifluoroacetate was dissolved in 2 N HCl. Final lyophilization gave 95 mg of the title compound as hydrochloride. R_t = 0.82 min (Method B). Detected mass: 293.1/295.1 ($M+H^+$).

cis-4-(7-Bromo-isoquinolin-6-ylsulfanyl)-cyclohexylamine hydrochloride (62)



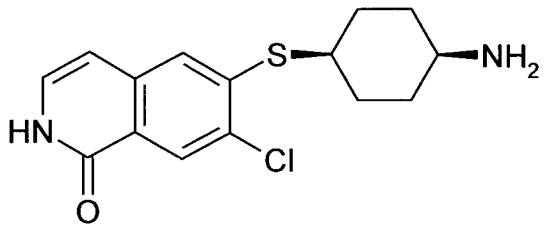
Starting from 6-fluoro-7-bromoisoquinoline (25) the title compound could be obtained as hydrochloride by the same reaction sequence as described for cis-4-(7-chloro-isoquinolin-6-ylsulfanyl)-cyclohexylamine (61) via its phthaloyl protected intermediate. R_t = 0.81 min (Method B). Detected mass: 337.1 ($M+H^+$).

6-cis-(4-Amino-cyclohexylsulfanyl)-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (63)



Starting from 7-chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (22) the title compound could be obtained as trifluoroacetate by the same reaction sequence as described for cis-4-(7-chloro-isoquinolin-6-ylsulfanyl)-cyclohexylamine (61) via its phthaloyl protected intermediate.

6-cis-(4-Amino-cyclohexylsulfanyl)-7-chloro-2H-isoquinolin-1-one (64)



34 mg (0.08 mmol) 6-cis-(4-Amino-cyclohexylsulfanyl)-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (63) were dissolved in 2 ml TFA and stirred in the microwave at 150°C for 1.5 h. After evaporation the residue was taken up in 1N HCl and extracted with dicloromethan and lyophilized. 11 mg of the desired product could be obtained as hydrochloride. R_t = 0.97 min (Method B). Detected mass: 309.1/311.1 ($M+H^+$).

LC/MS-Methods:

Method A:

Stationary phase:	Col YMC Jsphere 33 x 2
Gradient:	ACN+0.05% TFA : H_2O+0.05% TFA
	5:95(0 min) to 95:5(3.4 min) to 95:5(4.4 min)
Flow	1 ml/min

Method B:

Stationary phase:	Col YMC Jsphere 33 x 2
Gradient:	ACN+0.05% TFA : H_2O+0.05% TFA
	5:95(0 min) to 95:5(2.5 min) to 95:5(3.0 min)
Flow:	1 ml/min

Method C:

Stationary phase:	Col YMC Jsphere ODS H80 20 x 2
Gradient:	ACN : H_2O+0.05% TFA
	4:96(0 min) to 95:5(2.0 min) to 95:5(2.4 min)
Flow	1 ml/min

Determination of Rho kinase inhibition

To measure Rho-kinase inhibition, IC_{50} values were determined according to the following protocol:

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.

Test compounds were diluted to the appropriate concentrations in buffer 1 (25 mM Tris-HCl, pH 7.4, 5 mM $MgCl_2$, 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 $MgCl_2$, 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.

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.	pIC50
53	+++++
54	+++++
52	+++++
51	++++
50	++++
48	++++
47	+++++
49	++++
45	+++++
44	++++
46	++++
40	+++++
41	+++++
36	+++++
61	+++++
62	+++++
64	+++++

The given activity is denoted as the negative decadal logarithm of the IC_{50} (pIC_{50}) as follows:

+: pIC50 ≤ 3.0

++: $3.0 \leq pIC_{50} < 4.0$

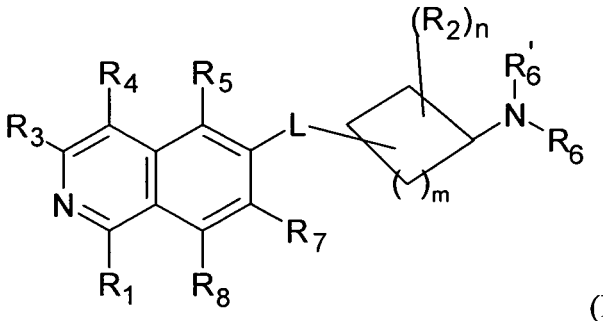
+++ $4.0 \leq pIC_{50} < 5.0$

++++: $5.0 \leq pIC_{50} < 6.0$

+++++ $6.0 \leq pIC_{50}$

Claims

1. A compound of the formula (I)



(I)

wherein

R_1 is H, OH or NH_2;

R_2 is H, halogen or $(C_1\text{-}C_6)$alkyl;

R_3 is
H,
halogen,
$(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$alkylene-R',
OH,
O-R'',
NH_2,
NHR'',
NR''R'' or
NH-C(O)-R'';

R_4 is
H,
halogen,

hydroxy,
CN,
(C_1-C_6)alkyl,
R',
(C_1-C_6)alkylene-R';

R_5 is
H,
halogen,
CN,
NO_2,
(C_1-C_6)alkyl,
(C_2-C_6)alkenyl,
R',
(C_1-C_6)alkylene-(C_6-C_{10})aryl,
(C_1-C_6)alkenylene-(C_6-C_{10})aryl,
(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl,
CH(OH)-(C_1-C_6)alkyl,
NH_2,
NH-R',
NH-SO_2H,
NH-SO_2-(C_1-C_6)alkyl,
NH-SO_2-R',
NH-C(O)-(C_1-C_6)alkyl,
NH-C(O)-R',
C(O)N[(C_1-C_6)alkyl]$_2$,
C(O)OH, or
C(O)O-(C_1-C_6)alkyl;

R_6 and R_6' are independently of each other

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)-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]$_2$,

$(C_1$-$C_6)$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,

C(O)R',

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

C(O)NHR',

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_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$ heterocyclyl group;

R_7 is

H,

halogen,
CN,
NO_2,
$(C_1\text{-}C_6)$alkyl,
$O\text{-}(C_1\text{-}C_6)$alkyl,
$(C_2\text{-}C_6)$alkenyl,
R',
$(C_1\text{-}C_6)$alkenylene-$(C_6\text{-}C_{10})$aryl,
$(C_1\text{-}C_6)$alkylene-R',
$CH(OH)\text{-}(C_1\text{-}C_6)$alkyl,
NH_2,
NH-R',
$NH\text{-}SO_2H$,
$NH\text{-}SO_2\text{-}(C_1\text{-}C_6)$alkyl,
$NH\text{-}SO_2\text{-}R'$,
$SO_2\text{-}NH_2$,
$SO_2\text{-}NHR'$,
$NH\text{-}C(O)\text{-}(C_1\text{-}C_6)$alkyl,
NH-C(O)-R',
$C(O)N[(C_1\text{-}C_6)alkyl]_2$,
C(O)OH, or
$C(O)O\text{-}(C_1\text{-}C_6)$alkyl;

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

n is 1, 2, 3 or 4;

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

L is $S(CH_2)p$, $S(O)(CH_2)p$, $SO_2(CH_2)p$, $NH(CH_2)p$, $N(C_1\text{-}C_6)$alkyl-$(CH_2)p$; $N(C_3\text{-}C_6)$cycloalkyl-$(CH_2)p$; $N[CO(C_1\text{-}C_6)$alkyl$]\text{-}(CH_2)p$ or $N[(C_1\text{-}C_3)$alkylene-R´$]\text{-}(CH_2)p$;

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

wherein

R' is

$(C_3\text{-}C_8)$cycloalkyl,

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

$(C_6\text{-}C_{10})$aryl; and

R" is

$(C_3\text{-}C_8)$cycloalkyl,

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

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

$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-R',

$(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-O-R', or

$(C_1\text{-}C_6)$alkylene-NR_xR_y; and

wherein R_x and R_y are independently of each other

$(C_1\text{-}C_6)$alkyl,

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

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

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

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

$(C_1\text{-}C_4)$alkylene-NH$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_4)$alkylene-N$[(C_1\text{-}C_6)\text{alkyl}]_2$,

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

$(C_1\text{-}C_4)$alkylene-N[$(C_5\text{-}C_{10})$heterocyclyl]$_2$;

wherein in residues R_4, R_5, R_6, R_6', R_7 and R_8 alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by OH, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, ,$CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

wherein in residues R_2 to R_8 alkyl or alkylene can optionally be substituted one or more times by halogen;

wherein in residues R_3 to R_8 $(C_6\text{-}C_{10})$aryl and $(C_5\text{-}C_{10})$heterocyclyl are unsubstituted or substituted one or more times by suitable groups independently selected from halogen, OH, NO_2, N_3, CN, C(O)-$(C_1\text{-}C_6)$alkyl, C(O)-$(C_1\text{-}C_6)$aryl, COOH, COO$(C_1\text{-}C_6)$alkyl, $CONH_2$, CONH$(C_1\text{-}C_6)$alkyl, CON[$(C_1\text{-}C_6)$alkyl]$_2$, $(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-OH, $(C_1\text{-}C_6)$alkylene-NH_2, $(C_1\text{-}C_6)$alkylene-NH$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylene-N[$(C_1\text{-}C_6)$alkyl]$_2$, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, O-$(C_1\text{-}C_6)$alkyl, O-C(O)-$(C_1\text{-}C_6)$alkyl, PO_3H_2, SO_3H, SO_2-NH_2, $SO_2NH(C_1\text{-}C_6)$alkyl, $SO_2N[(C_1\text{-}C_6)\text{alkyl}]_2$, S-$(C_1\text{-}C_6)$alkyl; SO-$(C_1\text{-}C_6)$alkyl, SO_2-$(C_1\text{-}C_6)$alkyl, SO_2-N=CH-N[$(C_1\text{-}C_6)$alkyl]$_2$, C(NH)(NH_2), NH_2, NH-$(C_1\text{-}C_6)$alkyl, N[$(C_1\text{-}C_6)$alkyl]$_2$, NH-C(O)-$(C_1\text{-}C_6)$alkyl, NH-C(O)O-$(C_1\text{-}C_6)$alkyl, NH-SO_2-$(C_1\text{-}C_6)$alkyl, NH-SO_2-$(C_6\text{-}C_{10})$aryl, NH-SO_2-$(C_5\text{-}C_{10})$heterocyclyl, N$(C_1\text{-}C_6)$alkyl-C(O)-$(C_1\text{-}C_6)$alkyl, N$(C_1\text{-}C_6)$alkyl-C(O)O-$(C_1\text{-}C_6)$alkyl, N$(C_1\text{-}C_6)$alkyl-C(O)-NH-$(C_1\text{-}C_6)$alkyl], $(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, O-$(C_6\text{-}C_{10})$aryl, O-$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, O-$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, wherein the $(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heterocyclyl may be substituted one to three times by a group independently selected from halogen, OH, NO_2, CN, O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, NH_2, NH$(C_1\text{-}C_6)$alkyl, N[$(C_1\text{-}C_6)$alkyl]$_2$, SO_2CH_3, COOH, C(O)O-$(C_1$-

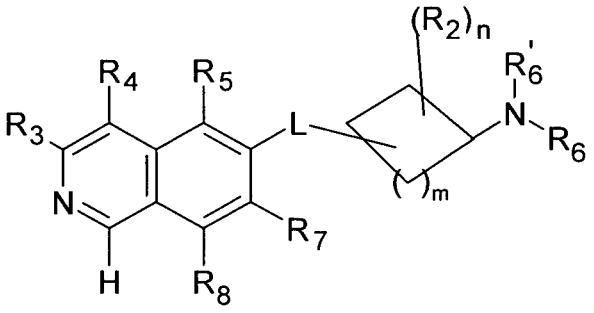
C_6)alkyl, $CONH_2$, (C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_1-C_6)alkylene-O-(C_6-C_{10})aryl, or O-(C_1-C_6)alkylene-(C_6-C_{10})aryl;

or wherein (C_6-C_{10})aryl is vicinally substituted by a O-(C_1-C_4)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 (C_6-C_{10})aryl and (C_5-C_{10})heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group;

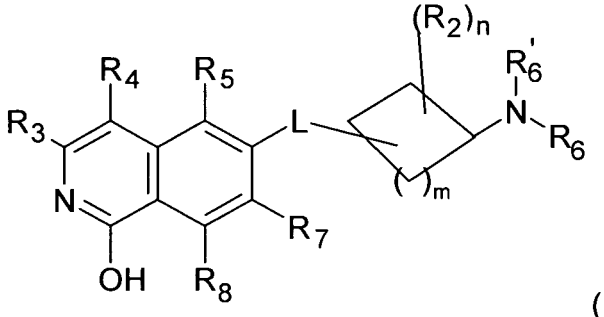
or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

2. A compound of formula (I) according to claim 1, wherein R_1 is H and is characterized by the formula (II)



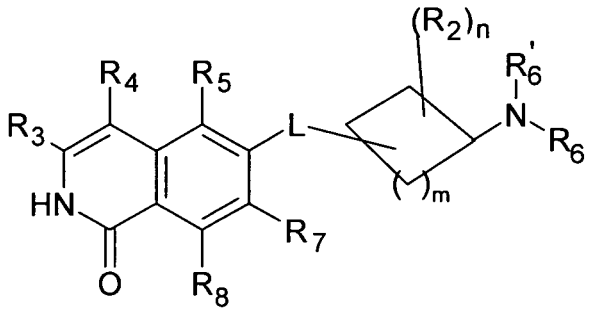
(II)

3. A compound of formula (I) according to claim 1, wherein R_1 is OH and is characterized by the formula (III)



(III)

4. A compound of formula (I) according to claim 1 or claim 3, wherein R_1 is OH and is characterized by the formula (III')



(III')

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

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

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

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

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

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

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

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.

14. A compound according to one of claims 1 to 13, wherein R_4 is H, halogen or $(C_1$-$C_4)$alkyl.

15. A compound according to one of claims 1 to 14, wherein R_4 is H.

16. A compound according to one of claims 1 to 15, wherein R_5 is H, halogen, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'.

17. A compound according to one of claims 1 to 16, wherein R_5 is H, halogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'.

18. A compound according to one of claims 1 to 17, wherein R_5 is H, halogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_6$-$C_{10})$aryl, NH-$(C_6$-$C_{10})$aryl, $(C_1$-$C_2)$alkyl-$(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heteroaryl.

19. A compound according to one of claims 1 to 18, wherein R_5 is H, halogen, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_6$-$C_{10})$aryl, or $(C_5$-$C_{10})$heteroaryl.

20. A compound according to one of claims 1 to 19, wherein R_5 is H, halogen, methyl, ethyl, vinyl, phenyl, thienyl, or pyridyl.

21. A compound according to one of claims 1 to 20, wherein R_5 is H, halogen, methyl, or ethyl.

22. A compound according to one of claims 1 to 21, wherein R_5 is H.

23. A compound according to one of claims 1 to 22, wherein R_7 is H, halogen, CN, $(C_1$-$C_6)$alkyl, O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, R' or $(C_1$-$C_6)$alkylene-$(C_3$-$C_8)$cycloalkyl.

24. A compound according to one of claims 1 to 23, wherein R_7 is H, halogen, CN, $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, phenyl, cyclopropyl or $(C_5$-$C_6)$heteroaryl.

25. A compound according to one of claims 1 to 24, wherein R_7 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 R_7 is H, fluoro, chloro, bromo, methyl or methoxy.

27. A compound according to one of claims 1 to 26, wherein R_7 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.

30. A compound according to one of claims 1 to 29, wherein R_2 is H, halogen or $(C_1$-$C_4)$alkyl.

31. A compound according to one of claims 1 to 30, wherein R_2 is H or $(C_1$-$C_2)$alkyl

32. A compound according to one of claims 1 to 31, wherein R_2 is H, methyl or ethyl.

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.

36. A compound according to one of claims 1 to 35, wherein
R_6 and R_6' are independently of each other
H,
$(C_1$-$C_6)$alkyl,
R',
$(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl,
$(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl,
C_1-$C_4)$alkylene-$(C_6$-$C_{10})$aryl,
$(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl,
$(C_1$-$C_4)$alkylene-C(O)-$(C_5$-$C_{10})$heterocyclyl,
$(C_1$-$C_4)$alkylene-C(O)-$(C_6$-$C_{10})$aryl,
$(C_1$-$C_6)$alkylene-C(O)N$[(C_1$-$C_6)$alkyl$]_2$,
$(C_1$-$C_6)$alkylene-C(O)NH-$(C_1$-$C_6)$alkyl,
$(C_1$-$C_6)$alkylene-C(O)O-$(C_1$-$C_6)$alkyl,
C(O)O-$(C_1$-$C_6)$alkyl,
C(O)$(C_1$-$C_6)$alkyl,
C(O)R'
C(O)NH-$(C_1$-$C_6)$alkyl,
C(O)N$[(C_1$-$C_6)$alkyl$]_2$, or
C(O)$(C_1$-$C_6)$alkylene-R',
or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$heterocyclyl group.

37. A compound according to any of claims 1 to 36, wherein R_6 and R_6' are independently of each other
H,

$(C_1\text{-}C_6)$alkyl,

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

$(C_3\text{-}C_8)$cycloalkyl,

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

$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_8)$cycloalkyl,

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

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

$(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$,

$(C_1\text{-}C_6)$alkylene-C(O)NH-$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-C(O)O-$(C_1\text{-}C_6)$alkyl,

C(O)O-$(C_1\text{-}C_6)$alkyl,

C(O)$(C_1\text{-}C_6)$alkyl,

C(O)$(C_3\text{-}C_8)$cycloalkyl,

C(O)NH-$(C_1\text{-}C_6)$alkyl,

C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$,

C(O) $(C_1\text{-}C_6)$alkylene-$(C_3\text{-}C_8)$cycloalkyl,

C(O) $(C_1\text{-}C_6)$alkylene- $(C_5\text{-}C_{10})$heterocyclyl,

C(O) $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl,

or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5\text{-}C_{10})$heterocyclyl group.

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

R_6 is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl or $(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_6)$cycloalkyl, and

R_6' is H,

$(C_1\text{-}C_6)$alkyl,

$(C_3\text{-}C_8)$cycloalkyl,

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

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

$(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl,

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

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

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

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

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,

C(O)$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, or

R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$heterocyclyl group.

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

R_6 is H, $(C_1$-$C_6)$alkyl and

R_6' is H,

$(C_1$-$C_6)$alkyl,

$(C_3$-$C_8)$cycloalkyl,

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

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

$(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl,

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

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

$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl,

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

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

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

$C(O)(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, or

R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_{10})$heterocyclyl group.

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

R_6 is H, $(C_1$-$C_6)$alkyl and

R_6' is

H,

$(C_1$-$C_6)$alkyl;

$(C_3$-$C_8)$cycloalkyl;

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

$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl;

$(C_1$-$C_4)$alkylene-C(O)N$[(C_1$-$C_4)$alkyl$]_2$;

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

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

$C(O)(C_1$-$C_4)$alkyl;

$C(O)(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl;

or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_6)$heterocyclyl group.

41. A compound according to any of claims 1 to 40, wherein R_6 is H, $(C_1$-$C_6)$alkyl and R_6' is H, $(C_1$-$C_6)$alkyl or $(C_3$-$C_8)$cycloalkyl.

42. A compound according to any of claims 1 to 41, wherein R_6 is H and R_6' is H, (C_1-C_6)alkyl or (C_3-C_8)cycloalkyl.

43. A compound according to any of claims 1 to 42, wherein R_6 and R_6' are 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 amino cyclohexane 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 amino cyclohexane 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 $NH(CH_2)p$, $N(C_1$-$C_6)$alkyl)-$(CH_2)p$.

48. A compound according to one of claims 1 to 47, wherein p is 0.

49. A compound according to claim 1, wherein

R_1 is H or OH;

R_2 is hydrogen, halogen, or (C_1-C_6)alkyl;

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

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;

R_6 and R_6' are independently of each other 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]$_2$, $(C_1$-$C_6)$alkylene-C(O)N[R']$_2$, C(O)O-$(C_1$-$C_6)$alkyl, C(O)$(C_1$-$C_6)$alkyl, C(O)$(C_3$-$C_8)$cycloalkyl, C(O)$(C_5$-$C_{10})$heterocyclyl, 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, C(O)$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, or R_6 and R_6', together with the N-atom to which they are attached, form a $(C_5$-$C_6)$heterocyclyl group;

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

R_8 is H, halogen or $(C_1$-$C_6)$alkyl;

m is 2, 3 or 4

n is 1, 2 or 3,

L is S(CH_2)p, NH(CH_2)p or N$(C_1$-$C_2)$alkyl-(CH_2)p, and

p is 0, 1 or 2;

50. A compound according to claim 1, wherein

R_1 is H or OH;

R_2 is H or $(C_1$-$C_4)$alkyl;

R_3 is H, halogen or NHR'', wherein R'' is defined as above;

R_4 is H, halogen or $(C_1$-$C_4)$alkyl;

R_5 is H, $(C_1$-$C_6)$alkyl, halogen, $(C_2$-$C_4)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heterocyclyl;

R_6 and R_6' are independently of each other H, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkyl, $(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl, $(C_1$-$C_3)$alkylene-R', C(O)$(C_1$-$C_6)$alkyl, C(O)$(C_3$-$C_8)$cycloalkyl, C(O)$(C_5$-$C_6)$heterocyclyl, C(O)$(C_1$-$C_6)$alkylene-$(C_3$-$C_8)$cycloalkyl, C(O)$(C_1$-$C_6)$alkylene-$(C_5$-$C_6)$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';

R_8 is H, halogen or $(C_1$-$C_6)$alkyl;

m is 2, 3 or 4;

n is 1, 2 or 3;

L is S(CH_2)p or NH(CH_2)p; and

p is 0 or 1;

51. A compound according to claim 1, wherein

R_1 is H or OH;

R_2 is H, $(C_1$-$C_4)$alkyl;

R_3 is H, NH-$(C_5$-$C_6)$heteroaryl or NH-phenyl;

R_4 is H, halogen or $(C_1$-$C_4)$alkyl;

R_5 is H, $(C_1$-$C_4)$alkyl, halogen, $(C_1$-$C_4)$alkenyl, $(C_6$-$C_{10})$aryl, $(C_1$-$C_2)$alkyl-$(C_6$-$C_{10})$aryl or $(C_5$-$C_6)$heteroaryl;

R_6 is H, $(C_3$-$C_6)$cycloalkyl or $(C_1$-$C_4)$alkyl;

R_6' is H, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkyl, $(C_1$-$C_3)$alkylene-R'; C(O)O-$(C_1$-$C_6)$alkyl, C(O)$(C_1$-$C_6)$alkyl, C(O)$(C_3$-$C_6)$cycloalkyl, C(O)$(C_5$-$C_6)$heterocyclyl, C(O)$(C_1$-$C_3)$alkylene-$(C_3$-$C_6)$cycloalkyl, C(O)$(C_1$-$C_3)$alkylene-$(C_5$-$C_6)$heterocyclyl, or C(O)$(C_1$-$C_3)$alkylene-phenyl;

R_7 is H, halogen, CN, $(C_1$-$C_4)$alkyl, O$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, phenyl, cyclopropyl, $(C_5$-$C_6)$heteroaryl;

R_8 is H, halogen or $(C_1$-$C_4)$alkyl;

m is 3

n is 1; and

L is S or NH;

52. Use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as claimed in one of claims 1 to 51 for producing a medicament.

53. Use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as claimed in one of claims 1 to 51 for producing a medicament for the treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, retinopathy, glaucoma, peripheral circulatory disorder, peripheral arterial occlusive 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.

54. A medicament comprising an effective amount of at least one compound as claimed in any of claims 1 to 51 and/or a pharmacologically acceptable salt thereof, pharmaceutically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.