SUBSTITUTED ISOQUINOLINE AND ISOQUINOLINONE DERIVATIVES

The present invention relates to novel isoquinoline and isoquinolinone derivatives as described in the claims, their preparation and their use in the treatment and/or 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.

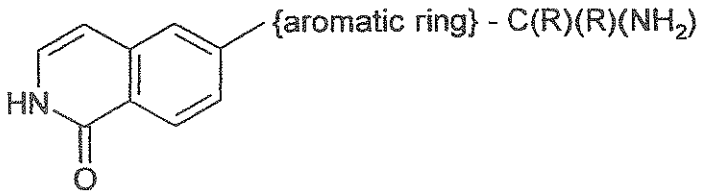
US 5,480,883 generically discloses as EGF and/or PDGF receptor inhibitors useful for inhibiting cell proliferation compounds of the formula "Ar I – X – Ar II" wherein X may be $(CHR_1)_m$-Z-$(CHR_1)_n$, e.g. Z-CH_2, wherein Z may be O, R_1 is hydrogen or alkyl, Ar I may be among others an optionally 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.

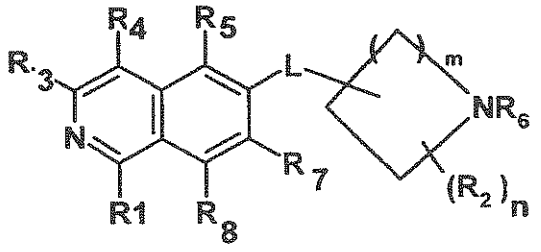
WO 03/053330 (Ube) generically describes isoquinolone derivatives of the formula



as Rho-kinase inhibitors.

Summary

According to a first aspect there is provided, a compound of the formula (I)



(I)

wherein

R_1 is H, OH or NH_2;

R_2 is hydrogen, 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,
$(C_2$-$C_6)$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 is
H,
R',
(C_1-C_8)alkyl,
(C_1-C_6)alkylene-R',
(C_1-C_6)alkylene-O-(C_1-C_6)alkyl,
(C_1-C_6)alkylene-O-R',
(C_1-C_6)alkylene-CH[R']$_2$,
(C_1-C_6)alkylene-C(O)-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', or

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

R_7 is

H,

halogen,

CN,

NO_2,

(C_1-C_6)alkyl,

O-(C_1-C_6)alkyl,

(C_2-C_6)alkenyl,

R',

(C_2-C_6)alkenylene-(C_6-C_{10})aryl,

(C_1-C_6)alkylene-R',

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',

SO_2-NH_2,

SO_2-NHR',

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

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[$(C_1\text{-}C_6)$alkyl]$_2$,
$(C_1\text{-}C_4)$alkylene-N[$(C_6\text{-}C_{10})$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_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)-$(C_6\text{-}C_{10})$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, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$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[$(C_1\text{-}C_6)$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, 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-C_6)alkyl, (C_1-C_6)alkyl, NH_2, NH(C_1-C_6)alkyl, N[(C_1-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;

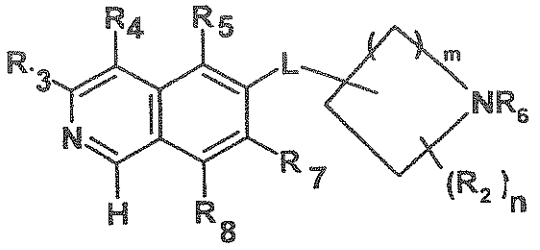
or their stereoisomeric forms and/or their tautomeric forms and/or their pharmaceutically acceptable salts.

According to a second aspect there is provided the use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as defined above for producing a medicament.

According to a third aspect there is provided the use of at least one compounds of the formula (I) and/or their pharmaceutically acceptable salt as defined above 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.

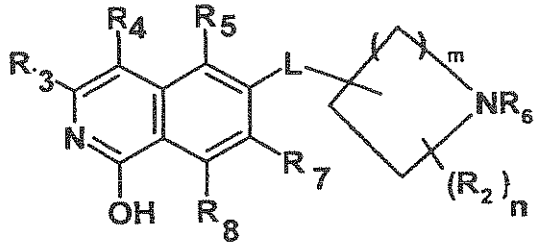
According to a fourth aspect, there is provided a medicament comprising an effective amount of at least one compound as defined above and/or a pharmacologically acceptable salt thereof, physiologically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.

In one embodiment of the present disclosure R_1 is H, the compound is thus characterized by the formula (II)



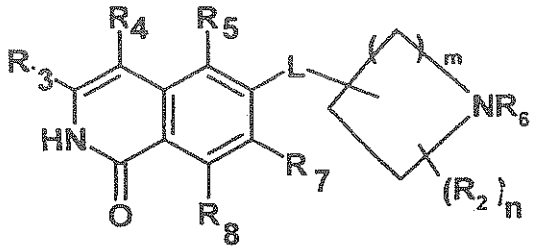
(II)

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



(III)

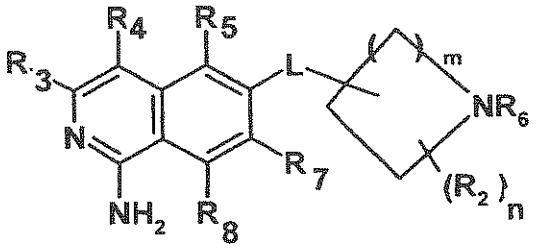
The compound of formula (III) has a tautomeric form of the formula (III`)



(III`)

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

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

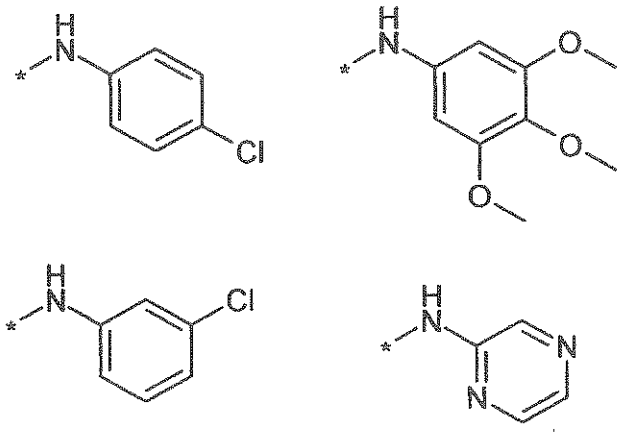


(IV)

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 $(C_1$-$C_6)$alkyl. More preferred, R_4 is H, halogen or $(C_1$-$C_4)$alkyl. Most preferred, R_4 is H.

Preferably, 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'. More preferably, 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'. Most preferably, 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. Especially preferred, R_5 is H, halogen, phenyl, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_6$-$C_{10})$aryl or $(C_5$-$C_6)$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 is H, $(C_1$-$C_6)$alkyl, R', $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$aryl, $(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_6)$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'.

In a further preferred embodiment R_6 is 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_5-$C_{10})$heterocyclyl, C(O)$(C_3$-$C_8)$cycloalkyl, C(O)NH-$(C_1$-$C_6)$alkyl, C(O)N$[(C_1$-$C_6)$alkyl$]_2$, C(O) $(C_1$-$C_6)$alkylene-$(C_3$-$C_8)$cycloalkyl, C(O) $(C_1$-$C_6)$alkylene- C_5-$C_{10})$heterocyclyl, or C(O)$(C_1$-$C_6)$alkylene--$(C_6$-$C_{10})$aryl:

In a further more preferred embodiment 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(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, or C(O)$(C_1$-$C_6)$alkylene--$(C_6$-$C_{10})$aryl.

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

In an even more preferred embodiment R_6 is

H,

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

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

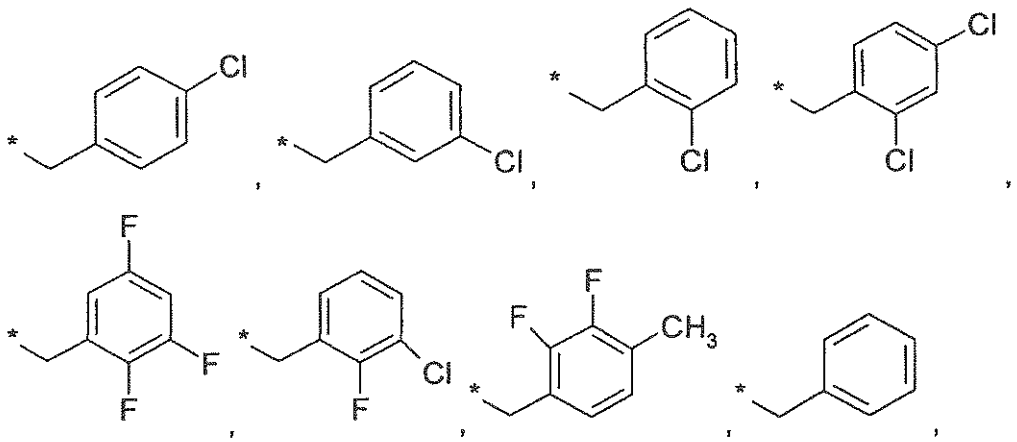
$(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_8)$cycloalkyl;

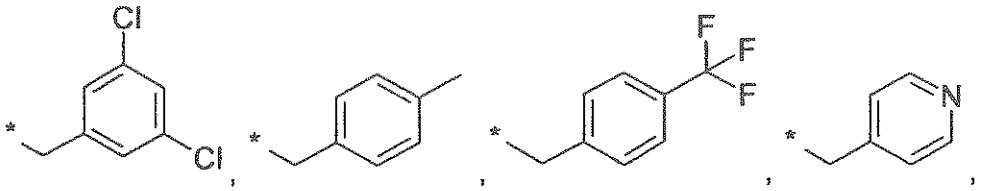
$(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl wherein heterocyclyl is unsubstituted or substituted one or more times, preferably one or two times, by $(C_1\text{-}C_4)$alkyl;

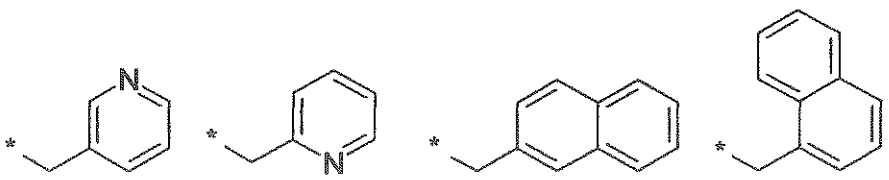
$(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl wherein aryl is unsubstituted or substituted one or more times, preferably one to three times, by halogen, $(C_1\text{-}C_4)$alkyl especially CH_3 or CF_3, O-$(C_1\text{-}C_4)$alkyl especially OCH_3, SO_2-$(C_1\text{-}C_4)$alkyl especially $S(O)_2CH_3$ or SO_2CF_3, or SO_2-N =CH-N[$(C_1\text{-}C_6)$alkyl]$_2$ especially SO_2-N=CH-N$(CH_3)_2$.

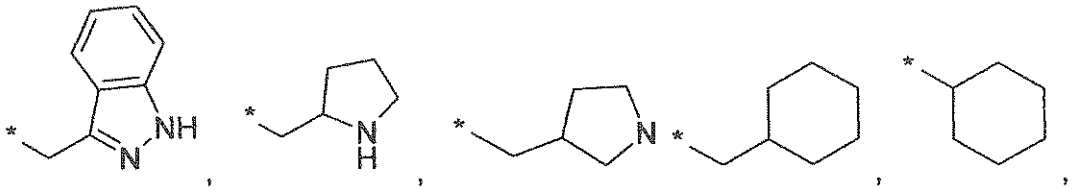
Especially preferred R_6 is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_8)$cycloalkyl. In an even more especially preferred embodiment R_6 is H, preferably unsubstituted $(C_1\text{-}C_6)$alkyl or preferably unsubstituted $(C_3\text{-}C_8)$cycloalkyl. Most preferred R_6 is H.

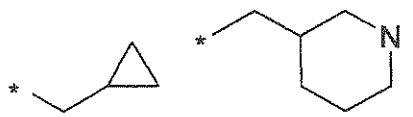
As examples for these embodiments, R6 is hydrogen, methyl, ethyl, propyl, isopropyl, 3-methyl-butyl, 2-methyl-propyl, 1-ethyl-propyl, butyl, pentyl, 3,3,3-trifuoropropyl, 4,4,4-trifluorobutyl or a substituent selected from the group consisting of

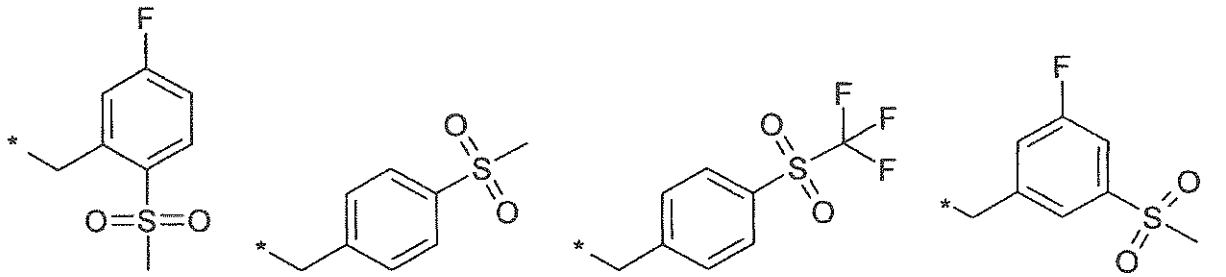


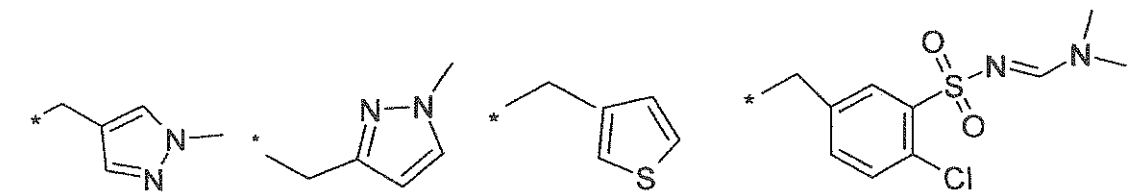


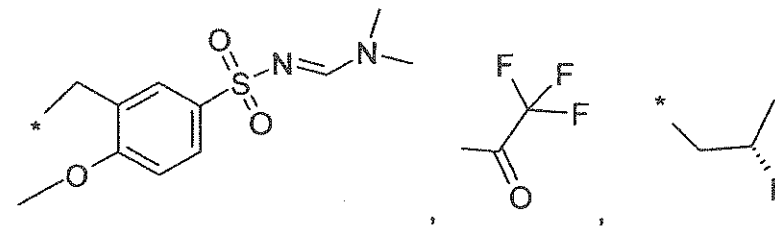




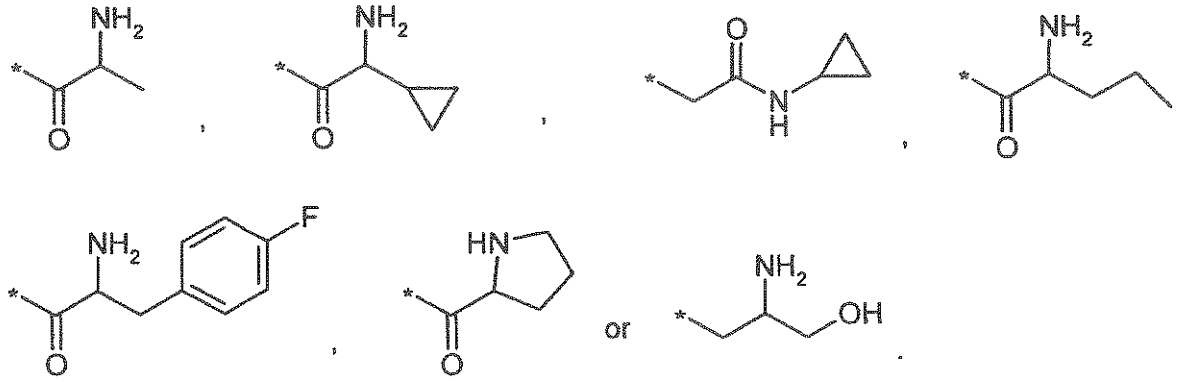








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The asterisk (*) denotes where the bond is connected to the N-atom of the ring.

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, propyl, phenyl, nitrile, cyclopropyl, thienyl or vinyl, most especially preferred R_7 is H, fluoro, chloro, bromo, methyl, propyl or methoxy. Most preferred R_7 is H.

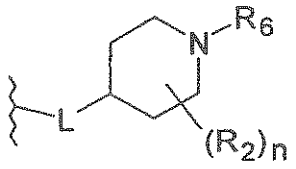
R_8 is preferably H, halogen or $(C_1\text{-}C_4)$alkyl. More preferred, R_8 is H, Cl, F, methyl or ethyl. Most preferred R_8 is H.

Preferably, R_2 is H, halogen or $(C_1\text{-}C_4)$alkyl. Preferably, R_2 is H or $(C_1\text{-}C_2)$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.

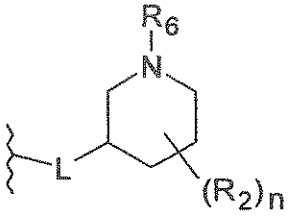
Preferably, n is 1, 2 or 3. More preferred, n is 1 or 2. Most preferred n is 1.

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

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



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



in all their stereochemical forms.

In an especially preferred embodiment, L is attached to the 4-position of the piperidine 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-$(C_5\text{-}C_6)$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 NCH_3 or NCH_2CH_3 with NCH_3 being more preferred. Even more preferred L is $S(CH_2)p$ or $NH(CH_2)p$. 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 piperidine ring.

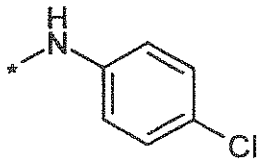
In residues R_2 to R_8 an alkyl or alkylene can optionally be substituted one or more times by halogen. Preferably alkyl or alkylene is substituted one to three times by halogen selected from chloro or bromo but may be substituted by fluoro once or more,

e.g. being perfluorinated. Preferably halogen is Fluor. More preferred an alkyl or alkylene is not halogenated.

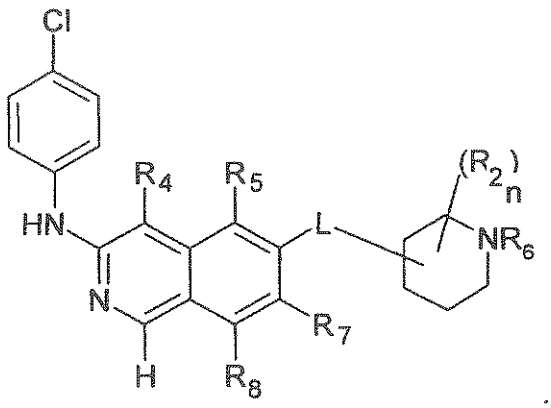
In residues R_4, R_5, R_6, R_7 and R_8 alkyl, alkylene or cycloalkyl can optionally be substituted one or more times by a group selected independently from OH, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$. If substituted, the number of substituents is preferably 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 in R_4, R_5, R_7 and R_8 an alkyl, alkylene or cycloalkyl is not substituted. More preferred, in R_4, R_5, R_6, R_7 and R_8 an alkyl, alkylene or cycloalkyl is not substituted.

In preferred embodiments of the present disclosure 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 disclosure. Also with respect to all preferred embodiments the disclosure 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 and R1 is H a compound of the formula



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

R_1 is H, OH or NH_2;

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 is 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(O)$(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_6)$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)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 or C(O)$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$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 $S(CH_2)p$, $NH(CH_2)p$ or $N(C_1$-$C_6)$alkyl-$(CH_2)p$, and

p is 0, 1 or 2;

or 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 $(C_1$-$C_4)$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 is 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)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$]_2$,

$C(O)(C_1-C_3)$alkylene-(C_3-C_8)cycloalkyl, $C(O)(C_1-C_3)$alkylene-(C_5-C_{10})heterocyclyl, or $C(O)(C_1-C_3)$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;

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-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, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_8)$alkyl, $(C_1$-$C_3)$alkylene-R'; $C(O)(C_1$-$C_6)$alkyl, $C(O)(C_3$-$C_8)$cycloalkyl, $C(O)$-$(C_5$-$C_{10})$heterocyclyl, $C(O)(C_1$-$C_3)$alkylene-$(C_5$-$C_{10})$heterocyclyl, or $C(O)(C_1$-$C_3)$alkylene--$(C_6$-$C_{10})$aryl.

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 of the present disclosure relates to a compound independently from the group of

38. 6-(Piperidin-4-ylamino)-2H-isoquinolin-1-one,
39. 7-Chloro-6-(piperidin-4-ylamino)-2H-isoquinolin-1-one,
40. 6-(Methyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one,
41 6-(Ethyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one,
42 6-(Propyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one,
46 6-(Azepan-4-ylamino)-2H-isoquinolin-1-one,
48 [(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
49 6-((S)-1-Benzyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,
50 6-(1-Ethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,
51 6-[(Piperidin-3-ylmethyl)-amino]-2H-isoquinolin-1-one,

52 6-(Azetidin-3-ylamino)-2H-isoquinolin-1-one,

53 6-[(Pyrrolidin-2-ylmethyl)-amino]-2H-isoquinolin-1-one,

54 6-(1-Benzyl-piperidin-4-ylamino)-2H-isoquinolin-1-one,

55 6-((R)-1-Benzyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

61 Isoquinolin-6-yl-(S)-pyrrolidin-3-yl-amine

192 6-[(R)-1-(2,3,5-Trifluoro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

193 6-[(R)-1-(3-Chloro-2-fluoro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

194 6-[(R)-1-(2,3-Difluoro-4-methyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

195 6-((R)-1-Propyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

196 6-((R)-1-Butyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

197 6-((R)-1-Isobutyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

198 6-((R)-1-Cyclopropylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

199 6-[(R)-1-(3-Methyl-butyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

200 6-[(R)-1-(3,3,3-Trifluoro-propyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

201 6-((R)-1-Cyclohexylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

202 6-((R)-1-Cyclohexyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

203 6-[(R)-1-(4-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

204 6-[(R)-1-(3-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

205 6-[(R)-1-(2-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

206 6-[(R)-1-(2,4-Dichloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

207 6-((R)-1-Benzyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

208 6-[(R)-1-(3,5-Dichloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

209 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide,

210 N-[1-Dimethylamino-meth-(E)-ylidene]-4-methoxy-3-[(R)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide,

211 6-[(R)-1-(4-Methyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

212 6-[(R)-1-(4-Trifluoromethyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

213 6-((R)-1-Pyridin-4-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

214 6-((R)-1-Pyridin-3-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

215 6-((R)-1-Pyridin-2-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

216 6-[(R)-1-(4-Methanesulfonyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

217 6-[(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one,

218 6-((R)-1-Naphthalen-2-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one,

219 6-[(S)-1-(2,3,5-Trifluoro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

220 6-[(S)-1-(3-Chloro-2-fluoro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

221 6-[(S)-1-(2,3-Difluoro-4-methyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

222 6-((S)-1-Butyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

223 6-((S)-1-Isopropyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

224 6-[(S)-1-(1-Ethyl-propyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

225 6-((S)-1-Isobutyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

226 6-((S)-1-Cyclopropylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

227 6-[(S)-1-(3-Methyl-butyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

228 6-((S)-1-Cyclohexylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

229 6-((S)-1-Cyclohexyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

230 6-[(S)-1-(4-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

231 6-[(S)-1-(3-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

232 6-[(S)-1-(2-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

233 6-[(S)-1-(2,4-Dichloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

234 6-[(S)-1-(3,5-Dichloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

235 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(S)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-benzenesulfonamide,

236 6-[(S)-1-(4-Methyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

237 6-[(S)-1-(4-Trifluoromethyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

238 6-((S)-1-Pyridin-4-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

239 6-((S)-1-Pyridin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

240 6-((S)-1-Pyridin-2-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

241 6-[(S)-1-(4-Methanesulfonyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

242 6-[(S)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

243 6-((S)-1-Naphthalen-2-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

244 6-((S)-1-Naphthalen-1-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

245 6-((S)-1-Pyrrolidin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

246 6-[(S)-1-(1-Methyl-1H-pyrazol-4-ylmethyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one,

247 6-((S)-1-Thiophen-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

248 6-((S)-1-Piperidin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one,

249 6-[1-(3-Chloro-2-fluoro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

250 6-[1-(2,3-Difluoro-4-methyl-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

251 6-(1-Isopropyl-azetidin-3-ylamino)-2H-isoquinolin-1-one,

252 6-[1-(1-Ethyl-propyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

253 6-(1-Cyclopropylmethyl-azetidin-3-ylamino)-2H-isoquinolin-1-one,

254 6-[1-(3-Methyl-butyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

255 6-(1-Cyclohexylmethyl-azetidin-3-ylamino)-2H-isoquinolin-1-one,

256 6-(1-Cyclohexyl-azetidin-3-ylamino)-2H-isoquinolin-1-one,

257 6-[1-(4-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

258 6-[1-(3-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

259 6-[1-(2-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

260 6-(1-Benzyl-azetidin-3-ylamino)-2H-isoquinolin-1-one,

261 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-benzenesulfonamide, or

262 6-[1-(4-Methyl-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one,

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

In a further embodiment, the present disclosure relates to a compound independently selected from the group of

286 7-Chloro-6-(piperidin-4-ylsulfanyl)-2H-isoquinolin-1-one,

288 7-Chloro-6-(piperidine-4-sulfonyl)-2H-isoquinolin-1-one, or

290 7-Chloro-6-(piperidine-4-sulfinyl)-2H-isoquinolin-1-one,

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

In a further embodiment, the present disclosure relates to a compound independently selected from the group of

18 4-(Isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester,

19 4-(Isoquinolin-6-yl-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester,

20 Isoquinolin-6-yl-(1-methyl-piperidin-4-yl)-amine,

21 2-(Isoquinolin-6-ylaminomethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester,

22 3-(Isoquinolin-6-ylaminomethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester,

23 Isoquinolin-6-yl-methyl-(1-methyl-piperidin-4-yl)-amine,

25 (7-Chloro-isoquinolin-6-yl)-(1-methyl-piperidin-4-yl)-amine,

26 4-(7-Chloro-isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester,

33 Isoquinolin-6-yl-piperidin-4-yl-amine,

34 Isoquinolin-6-yl-methyl-piperidin-4-yl-amine,

35 Isoquinolin-6-yl-pyrrolidin-2-ylmethyl-amine,

36 Isoquinolin-6-yl-pyrrolidin-3-ylmethyl-amine,

37 (7-Chloro-isoquinolin-6-yl)-piperidin-4-yl-amine,

43 (1-Isopropyl-piperidin-4-yl)-isoquinolin-6-yl-amine,

44 Isoquinolin-6-yl-(S)-pyrrolidin-3-yl-amine,

45 Isoquinolin-6-yl-(R)-piperidin-3-yl-amine,

47 Azetidin-3-yl-isoquinolin-6-yl-amine,

56 (1-Butyl-piperidin-4-ylmethyl)-isoquinolin-6-yl-amine,

58 ((S)-1-Benzyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,

61. Isoquinolin-6-yl-(S)-pyrrolidin-3-yl-amine

60 (1-Ethyl-piperidin-3-yl)-isoquinolin-6-yl-amine,

62 Isoquinolin-6-yl-piperidin-3-ylmethyl-amine,

63 Azetidin-3-yl-isoquinolin-6-yl-amine,

64 Isoquinolin-6-yl-piperidin-4-yl-pyridin-3-ylmethyl-amine,

65 Benzyl-isoquinolin-6-yl-piperidin-4-yl-amine,

66 Isoquinolin-6-yl-piperidin-4-yl-pyridin-4-ylmethyl-amine,

67 Isoquinolin-6-yl-(R)-pyrrolidin-3-yl-amine,

68 (1-Ethyl-piperidin-4-yl)-isoquinolin-6-yl-amine,

69 Isoquinolin-6-yl-(1-propyl-piperidin-4-yl)-amine,

70 (1-Butyl-piperidin-4-yl)-isoquinolin-6-yl-amine,

71 (1-Isobutyl-piperidin-4-yl)-isoquinolin-6-yl-amine,
72 (1-Cyclopropylmethyl-piperidin-4-yl)-isoquinolin-6-yl-amine,
73 Isoquinolin-6-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-amine,
74 Isoquinolin-6-yl-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine,
75 (1-Cyclohexylmethyl-piperidin-4-yl)-isoquinolin-6-yl-amine,
76 (1-Cyclohexyl-piperidin-4-yl)-isoquinolin-6-yl-amine,
77 [1-(4-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine,
78 [1-(3-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine,
79 [1-(2-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine,
80 [1-(2,4-Dichloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine,
81 (1-Benzyl-piperidin-4-yl)-isoquinolin-6-yl-amine,
82 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[4-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide,
83 N-[1-Dimethylamino-meth-(E)-ylidene]-3-[4-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-4-methoxy-benzenesulfonamide,
84 Isoquinolin-6-yl-[1-(4-methyl-benzyl)-piperidin-4-yl]-amine,
85 Isoquinolin-6-yl-[1-(4-trifluoromethyl-benzyl)-piperidin-4-yl]-amine,
86 Isoquinolin-6-yl-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amine,
87 Isoquinolin-6-yl-(1-pyridin-3-ylmethyl-piperidin-4-yl)-amine,
88 Isoquinolin-6-yl-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine,
89 Isoquinolin-6-yl-[1-(4-methanesulfonyl-benzyl)-piperidin-4-yl]-amine,
90 [1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine,
91 Isoquinolin-6-yl-[1-(4-trifluoromethanesulfonyl-benzyl)-piperidin-4-yl]-amine,
92 Isoquinolin-6-yl-(1-naphthalen-2-ylmethyl-piperidin-4-yl)-amine,
93 Isoquinolin-6-yl-(1-naphthalen-1-ylmethyl-piperidin-4-yl)-amine,
94 Isoquinolin-6-yl-methyl-(1-propyl-piperidin-4-yl)-amine,
95 (1-Butyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine,
96 (1-Isobutyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine,
97 (1-Cyclopropylmethyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine,
98 Isoquinolin-6-yl-methyl-[1-(3-methyl-butyl)-piperidin-4-yl]-amine,
99 Isoquinolin-6-yl-methyl-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine,
100 [1-(4-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-methyl-amine,

101 Isoquinolin-6-yl-[1-(2,3,5-trifluoro-benzyl)-azetidin-3-yl]-amine,

102 [1-(3-Chloro-2-fluoro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

103 [1-(2,3-Difluoro-4-methyl-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

104 (1-Ethyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

105 Isoquinolin-6-yl-(1-propyl-azetidin-3-yl)-amine,

106 (1-Butyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

107 (1-Isopropyl-azetidin-3-yl)-isoquinolin-6-yl-amin,

108 [1-(1-Ethyl-propyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

109 (1-Isobutyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

110 (1-Cyclopropylmethyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

111 Isoquinolin-6-yl-[1-(3-methyl-butyl)-azetidin-3-yl]-amine,

112 Isoquinolin-6-yl-[1-(3,3,3-trifluoro-propyl)-azetidin-3-yl]-amine,

113 (1-Cyclohexylmethyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

114 (1-Cyclohexyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

115 [1-(4-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

116 [1-(3-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

117 [1-(2-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

118 [1-(2,4-Dichloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

119 (1-Benzyl-azetidin-3-yl)-isoquinolin-6-yl-amine,

120 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[3-(isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-benzenesulfonamide,

121 N-[1-Dimethylamino-meth-(E)-ylidene]-3-[3-(isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-4-methoxy-benzenesulfonamide,

122 Isoquinolin-6-yl-[1-(4-methyl-benzyl)-azetidin-3-yl]-amine,

123 Isoquinolin-6-yl-[1-(4-trifluoromethyl-benzyl)-azetidin-3-yl]-amine,

124 Isoquinolin-6-yl-(1-pyridin-4-ylmethyl-azetidin-3-yl)-amine,

125 Isoquinolin-6-yl-(1-pyridin-3-ylmethyl-azetidin-3-yl)-amine,

126 Isoquinolin-6-yl-(1-pyridin-2-ylmethyl-azetidin-3-yl)-amine,

127 Isoquinolin-6-yl-[1-(4-methanesulfonyl-benzyl)-azetidin-3-yl]-amine,

128 [1-(5-Fluoro-2-methanesulfonyl-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,

129 Isoquinolin-6-yl-(1-naphthalen-2-ylmethyl-azetidin-3-yl)-amine,

130 Isoquinolin-6-yl-(1-naphthalen-1-ylmethyl-azetidin-3-yl)-amine,

131 [1-((S)-2-Amino-propyl)-azetidin-3-yl]-isoquinolin-6-yl-amine,
132 Isoquinolin-6-yl-(1-pyrrolidin-3-ylmethyl-azetidin-3-yl)-amine,
133 Isoquinolin-6-yl-(1-(R)-1-pyrrolidin-2-ylmethyl-azetidin-3-yl)-amine,
134 Isoquinolin-6-yl-[1-(1-methyl-1H-pyrazol-4-ylmethyl)-azetidin-3-yl]-amine,
135 Isoquinolin-6-yl-(1-thiophen-3-ylmethyl-azetidin-3-yl)-amine,
136 Isoquinolin-6-yl-[(R)-1-(2,3,5-trifluoro-benzyl)-pyrrolidin-3-yl]-amine,
137 ((R)-1-Butyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
138 ((R)-1-Isopropyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
139 [(R)-1-(1-Ethyl-propyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine,
140 ((R)-1-Isobutyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
141 ((R)-1-Cyclopropylmethyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
142 Isoquinolin-6-yl-[(R)-1-(3-methyl-butyl)-pyrrolidin-3-yl]-amine,
143 Isoquinolin-6-yl-[(R)-1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-yl]-amine,
144 ((R)-1-Cyclohexylmethyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
145 [(R)-1-(4-Chloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine,
146 [(R)-1-(3-Chloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine,
147 ((R)-1-Benzyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine,
148 [(R)-1-(3,5-Dichloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine,
149 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-benzenesulfonamide,
150 N-[1-Dimethylamino-meth-(E)-ylidene]-3-[(R)-3-(isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-4-methoxy-benzenesulfonamide,
151 Isoquinolin-6-yl-[(R)-1-(4-methyl-benzyl)-pyrrolidin-3-yl]-amine,
152 Isoquinolin-6-yl-[(R)-1-(4-trifluoromethyl-benzyl)-pyrrolidin-3-yl]-amine,
153 Isoquinolin-6-yl-((R)-1-pyridin-4-ylmethyl-pyrrolidin-3-yl)-amine,
154 Isoquinolin-6-yl-((R)-1-pyridin-3-ylmethyl-pyrrolidin-3-yl)-amine,
155 Isoquinolin-6-yl-((R)-1-pyridin-2-ylmethyl-pyrrolidin-3-yl)-amine,
156 Isoquinolin-6-yl-[(R)-1-(4-methanesulfonyl-benzyl)-pyrrolidin-3-yl]-amine,
157 [(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine,
158 Isoquinolin-6-yl-((R)-1-naphthalen-2-ylmethyl-pyrrolidin-3-yl)-amine,
159 Isoquinolin-6-yl-[(R)-1-(2,3,5-trifluoro-benzyl)-piperidin-3-yl]-amine,

160 [(R)-1-(3-Chloro-2-fluoro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
161 [(R)-1-(2,3-Difluoro-4-methyl-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
162 ((R)-1-Ethyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
163 Isoquinolin-6-yl-((R)-1-propyl-piperidin-3-yl)-amine,
164 ((R)-1-Butyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
165 ((R)-1-Isobutyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
166 ((R)-1-Cyclopropylmethyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
167 Isoquinolin-6-yl-[(R)-1-(3-methyl-butyl)-piperidin-3-yl]-amine,
168 Isoquinolin-6-yl-[(R)-1-(3,3,3-trifluoro-propyl)-piperidin-3-yl]-amine,
169 ((R)-1-Cyclohexylmethyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
170 [(R)-1-(4-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
171 [(R)-1-(3-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
172 [(R)-1-(2-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
173 [(R)-1-(2,4-Dichloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
174 ((R)-1-Benzyl-piperidin-3-yl)-isoquinolin-6-yl-amine,
175 [(R)-1-(3,5-Dichloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
176 2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide,
177 N-[1-Dimethylamino-meth-(E)-ylidene]-3-[(R)-3-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-4-methoxy-benzenesulfonamide,
178 Isoquinolin-6-yl-[(R)-1-(4-methyl-benzyl)-piperidin-3-yl]-amine,
179 Isoquinolin-6-yl-[(R)-1-(4-trifluoromethyl-benzyl)-piperidin-3-yl]-amine,
180 Isoquinolin-6-yl-((R)-1-pyridin-4-ylmethyl-piperidin-3-yl)-amine,
181 Isoquinolin-6-yl-((R)-1-pyridin-3-ylmethyl-piperidin-3-yl)-amine,
182 Isoquinolin-6-yl-((R)-1-pyridin-2-ylmethyl-piperidin-3-yl)-amin,
183 Isoquinolin-6-yl-[(R)-1-(4-methanesulfonyl-benzyl)-piperidin-3-yl]-amine,
184 Isoquinolin-6-yl-((R)-1-naphthalen-2-ylmethyl-piperidin-3-yl)-amine,
185 Isoquinolin-6-yl-((R)-1-naphthalen-1-ylmethyl-piperidin-3-yl)-amine,
186 [(R)-1-((S)-2-Amino-propyl)-piperidin-3-yl]-isoquinolin-6-yl-amine,
187 Isoquinolin-6-yl-((R)-1-pyrrolidin-3-ylmethyl-piperidin-3-yl)-amine, or
188 Isoquinolin-6-yl-((R)-1-(R)-1-pyrrolidin-2-ylmethyl-piperidin-3-yl)-amine,

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

In a further embodiment, the present disclosure relates to a compound independently selected from the group of

267 (S)-3-(7-Chloro-isoquinolin-6-ylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester,

268 7-Chloro-6-((S)-pyrrolidin-3-ylsulfanyl)-isoquinoline,

269 (Rac)-7-Chloro-6-(piperidin-3-ylsulfanyl)-isoquinoline,

270 (Rac)-6-(Azepan-4-ylsulfanyl)-7-chloro-isoquinoline,

271 (Rac)-6-(Azepan-4-ylsulfanyl)-7-bromo-isoquinoline,

274 4-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester,

275 7-Chloro-6-(piperidin-4-ylsulfanyl)-isoquinoline,

276 4-(7-Propyl-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester,

277 6-(Piperidin-4-ylsulfanyl)-7-propyl-isoquinoline,

278 7-Bromo-6-(piperidin-4-ylsulfanyl)-isoquinoline,

279 7-Chloro-6-(piperidin-4-ylmethylsulfanyl)-isoquinoline,

280 7-Chloro-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline,

281 7-Bromo-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline,

282 7-Chloro-6-(pyrrolidin-2-ylmethylsulfanyl)-isoquinoline,

283 7-Chloro-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline,

284 7-Bromo-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline,

291 7-Chloro-6-((S)-1-ethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

292 7-Chloro-6-((S)-1-propyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

293 6-((S)-1-Butyl-pyrrolidin-3-ylsulfanyl)-7-chloro-isoquinoline,

294 7-Chloro-6-((S)-1-isopropyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

295 7-Chloro-6-((S)-1-isobutyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

296 7-Chloro-6-((S)-1-cyclopropyl-methyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

297 7-Chloro-6-[(S)-1-(3-methyl-butyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

298 7-Chloro-6-[(S)-1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

299 7-Chloro-6-((S)-1-cyclohexylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

300 7-Chloro-6-((S)-1-cyclohexyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

301 7-Chloro-6-[(S)-1-(4-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

302 7-Chloro-6-[(S)-1-(3-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

303 7-Chloro-6-[(S)-1-(2-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

304 7-Chloro-6-[(S)-1-(2,4-dichloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

305 6-((S)-1-Benzyl-pyrrolidin-3-ylsulfanyl)-7-chloro-isoquinoline,

306 7-Chloro-6-[(S)-1-(3,5-dichloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

307 2-Chloro-5-[(S)-3-(7-chloro-isoquinolin-6-ylsulfanyl)-pyrrolidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)- ylidene]-benzenesulfonamide,

308 3-[(S)-3-(7-Chloro-isoquinolin-6-ylsulfanyl)-pyrrolidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide,

309 7-Chloro-6-[(S)-1-(4-methyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

310 7-Chloro-6-[(S)-1-(4-trifluoromethyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

311 7-Chloro-6-((S)-1-pyridin-4-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

312 7-Chloro-6-((S)-1-pyridin-3-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

313 7-Chloro-6-((S)-1-pyridin-2-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

314 7-Chloro-6-[(S)-1-(4-methanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

315 7-Chloro-6-[(S)-1-(5-fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

316 7-Chloro-6-[(S)-1-(4-trifluoromethanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline,

317 7-Chloro-6-((S)-1-naphthalen-2-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline,

318 7-Chloro-6-(1-ethyl-piperidin-4-ylsulfanyl)-isoquinoline,

319 7-Chloro-6-(1-propyl-piperidin-4-ylsulfanyl)-isoquinoline,

320 6-(1-Butyl-piperidin-4-ylsulfanyl)-7-chloro-isoquinoline,

321 7-Chloro-6-(1-isopropyl-piperidin-4-ylsulfanyl)-isoquinoline,

322 7-Chloro-6-(1-isobutyl-piperidin-4-ylsulfanyl)-isoquinoline,

323 7-Chloro-6-(1-cyclopropylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,

324 7-Chloro-6-[1-(3-methyl-butyl)-piperidin-4-ylsulfanyl]-isoquinoline,

325 7-Chloro-6-[1-(3,3,3-trifluoro-propyl)-piperidin-4-ylsulfanyl]-isoquinoline,

326 7-Chloro-6-(1-cyclohexylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,

327 7-Chloro-6-(1-cyclohexyl-piperidin-4-ylsulfanyl)-isoquinoline,

328 7-Chloro-6-[1-(4-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
329 7-Chloro-6-[1-(3-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
330 7-Chloro-6-[1-(2-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
331 7-Chloro-6-[1-(2,4-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
332 6-(1-Benzyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline,
333 7-Chloro-6-[1-(3,5-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
334 2-Chloro-5-[3-(7-chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-benzenesulfonamide,
335 3-[3-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide,
336 7-Chloro-6-[1-(4-methyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
337 7-Chloro-6-[1-(4-trifluoromethyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,
338 7-Chloro-6-(1-pyridin-4-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,
339 7-Chloro-6-(1-pyridin-3-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,
340 7-Chloro-6-(1-pyridin-2-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,
341 6-Chloro-7-(pyrrolidin-2-ylmethylsulfanyl)-isoquinoline,
342 7-Bromo-6-(1-ethyl-piperidin-4-ylsulfanyl)-isoquinoline,
343 7-Bromo-6-(1-propyl-piperidin-4-ylsulfanyl)-isoquinoline,
344 7-Bromo-6-(1-butyl-piperidin-4-ylsulfanyl)-isoquinoline,
345 7-Bromo-6-(1-isopropyl-piperidin-4-ylsulfanyl)-isoquinoline,
346 7-Bromo-6-(1-isobutyl-piperidin-4-ylsulfanyl)-isoquinoline,
347 7-Bromo-6-(1-cyclopropylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,
348 7-Bromo-6-[1-(3-methyl-butyl)-piperidin-4-ylsulfanyl]-isoquinoline,
349 7-Bromo-6-[1-(3,3,3-trifluoro-propyl)-piperidin-4-ylsulfanyl]-isoquinoline,
350 7-Bromo-6-(1-cyclohexylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,
351 7-Bromo-6-(1-cyclohexyl-piperidin-4-ylsulfanyl)-isoquinoline,
352 7-Bromo-6-[1-(4-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,
353 7-Bromo-6-[1-(3-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,
354 7-Bromo-6-[1-(2-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,
355 7-Bromo-6-[1-(2,4-dichloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,
356 7-Bromo-6-[1-benzyl-piperidin-4-ylsulfanyl]-isoquinoline,

357 7-Bromo-6-[1-(3,5-dichloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,

358 2-Chloro-5-[4-(7-bromo-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylaminometh-(E)-ylidene]-benzene-sulfonamide,

359 3-[4-(7-Bromo-isoquinolin-6-ylsulfanyl)-pipe-ridin-1-ylmethyl]-N-dimethylaminometh(E)-ylidene-4-methoxy benzene-sulfonamide,

360 7-Bromo-6-[1-(4-trifluormethyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,

361 7-Bromo-6-(1-pyridin-2-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,

362 7-Bromo-6-[1-(5-fluoro-2-methanesulfonyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,

363 7-Bromo-6-[1-(4-trifluoromethanesulfonyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline,

364 7-Bromo-6-(1-naphthalen-2-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,

365 7-Bromo-6-(1-naphthalen-1-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline,

366 7-Bromo-6-[1-(1-methyl-1H-pyrrol-3-ylmethyl)-piperidin-4-ylsulfanyl]-isoquinoline,

367 7-Bromo-6-[1-(1-methyl-1H-pyrazol-4-ylmethyl)-piperidin-4-ylsulfanyl]-isoquinoline,

368 7-Chloro-6-(1-ethyl-piperidin-3-ylsulfanyl)-isoquinoline,

369 7-Chloro-6-(1-propyl-piperidin-3-ylsulfanyl)-isoquinoline,

370 6-(1-Butyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline,

371 7-Chloro-6-(1-isopropyl-piperidin-3-ylsulfanyl)-isoquinoline,

372 7-Chloro-6-(1-isobutyl-piperidin-3-ylsulfanyl)-isoquinoline,

373 7-Chloro-6-(1-cyclopropylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,

374 7-Chloro-6-[1-(3-methyl-butyl)-piperidin-3-ylsulfanyl]-isoquinoline,

375 7-Chloro-6-[1-(3,3,3-trifluoro-propyl)-piperidin-3-ylsulfanyl]-isoquinoline,

376 7-Chloro-6-(1-cyclohexylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,

377 7-Chloro-6-(1-cyclohexyl-piperidin-3-ylsulfanyl)-isoquinoline,

378 7-Chloro-6-[1-(4-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

379 7-Chloro-6-[1-(3-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

380 7-Chloro-6-[1-(2-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

381 6-(1-Benzyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline,

382 7-Chloro-6-[1-(3,5-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

383 2-Chloro-5-[3-(7-chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-benzenesulfonamide,

384 3-[3-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide,

385 7-Chloro-6-[1-(4-methyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

386 7-Chloro-6-[1-(4-trifluoromethyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline,

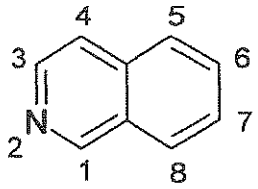
387 7-Chloro-6-(1-pyridin-4-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline, or

388 7-Chloro-6-(1-pyridin-3-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline,

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

As in any embodiment of the disclosure, in the preceding embodiments which contain preferred, more preferred, most preferred or exemplary definitions of compounds according to the disclosure, 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 disclosure 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 disclosure 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 disclosure. These prodrugs may themselves be active or not.

The disclosure relates to compounds of the formula (I), (II), (III), (III ') or (VI) in the form of their stereoisomeric forms, which include racemates, racemic mixtures, pure enantiomers and diastereomers and mixtures thereof.
The compounds of the disclosure may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the disclosure belong within the framework of the disclosure and are a further aspect of the disclosure.

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 atoms can be replaced by one or more heteroatoms such as, for example 1, 2 or 3 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or combinations of different hetero atoms. The heterocyclyl residues can be bound at any positions, for example on the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position. (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 group 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.

(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-C_6)alkenyl, (C_2-C_6)alkynyl, O-(C_1-C_6)alkyl, O-C(O)-(C_1-C_6)alkyl, PO_3H_2, SO_3H, SO_2-NH_2, SO_2NH(C_1-C_6)alkyl, SO_2N[(C_1-C_6)alkyl]$_2$, S-(C_1-C_6)alkyl;SO-(C_1-C_6)alkyl, SO_2-(C_1-C_6)alkyl, SO_2-N=CH-N[(C_1-C_6)alkyl]$_2$,

$C(NH)(NH_2)$, NH_2, NH-$(C_1$-$C_6)$alkyl, N[$(C_1$-$C_6)$alkyl]$_2$, NH-C(O)-$(C_1$-$C_6)$alkyl, NH-C(O)O-$(C_1$-$C_6)$alkyl, NH-SO_2-$(C_1$-$C_6)$alkyl, NH-SO_2-$(C_6$-$C_{10})$aryl, NH-SO_2-$(C_5$-$C_{10})$heterocyclyl, N$(C_1$-$C_6)$alkyl-C(O)-$(C_1$-$C_6)$alkyl, N$(C_1$-$C_6)$alkyl-C(O)O-$(C_1$-$C_6)$alkyl, N$(C_1$-$C_6)$alkyl-C(O)-NH-$(C_1$-$C_6)$alkyl], $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, O-$(C_6$-$C_{10})$aryl, O-$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, $(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, O-$(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, wherein the $(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heterocyclyl may be substituted one to 3 times by a group independently selected from halogen, OH, NO_2, CN, O-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl, NH_2, NH$(C_1$-$C_6)$alkyl, N[$(C_1$-$C_6)$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, 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. 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.

Preferred substituents for $(C_6$-$C_{10})$aryl groups are $(C_1$-$C_4)$alkyl, O-$(C_1$-$C_4)$alkyl, O-phenyl, phenyl, C(O)O-$(C_1$-$C_6)$alkyl, C(O)OH, C(O)-$(C_1$-$C_4)$alkyl, halogen, NO_2, SO_2NH_2, CN, SO_2-$(C_1$-$C_4)$alkyl, SO_2-N=CH-N[$(C_1$-$C_6)$alkyl]$_2$, NH-SO_2-$(C_1$-$C_4)$alkyl, NH_2, NH-C(O)-$(C_1$-$C_4)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_4)$alkyl-OH, C(O)N[$(C_1$-$C_4)$alkyl]$_2$, CONH$(C_1$-$C_6)$alkyl, $C(O)NH_2$, N[$(C_1$-$C_4)$alkyl]$_2$, $(C_1$-$C_4)$alkylene-$(C_6$-$C_{10})$aryl, wherein the $(C_6$-$C_{10})$aryl may be further substituted one to three times, preferably once, by $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylene-O-$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl 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 $(C_6$-$C_{10})$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_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[(CH3)$_2$.

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 (C_1-C_4)alkyl, O-(C_1-C_6)alkyl, halogen, (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, 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_7, R_8, n, m, L and p as described above.

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

The present disclosure 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 disclosure 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.

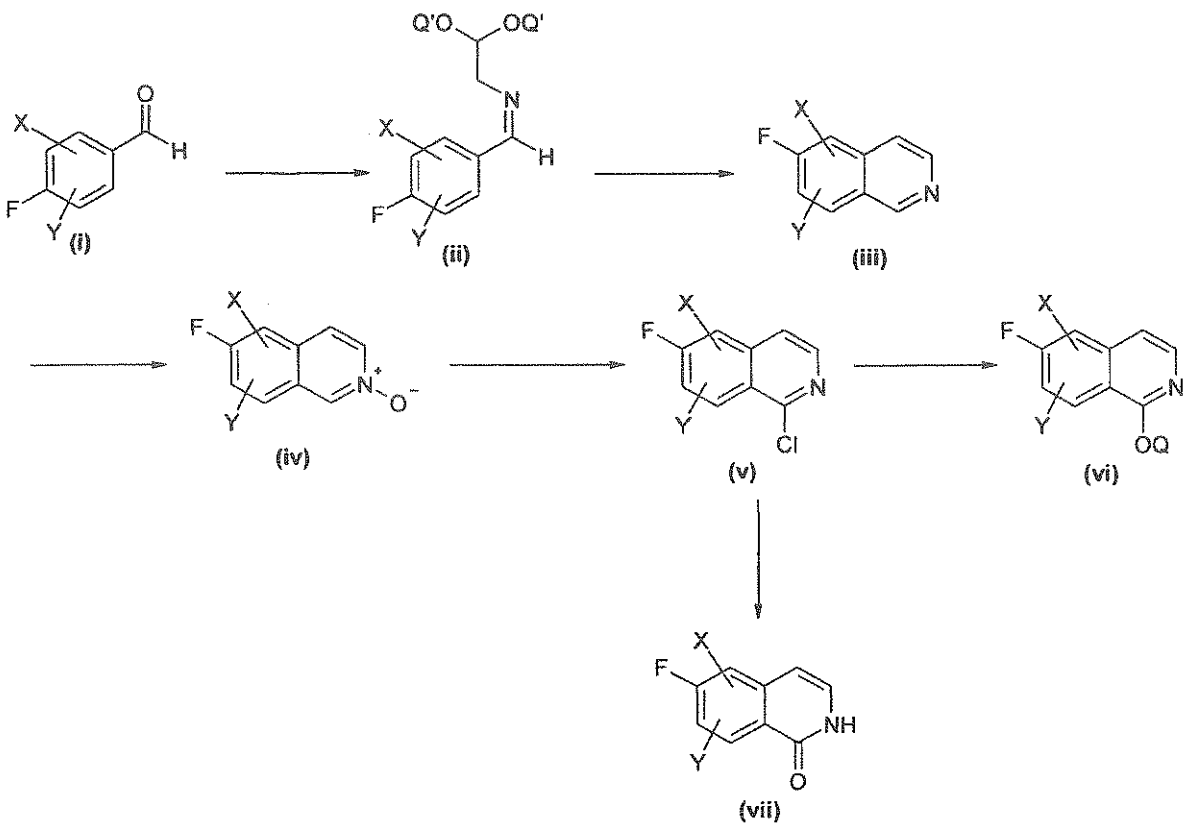
When using the compounds of the formula (I) the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease 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) can then be carried out by known processes.

In general, a reaction mixture containing a final compound of the formula (I) or an intermediate is worked up and, if desired, the product is then purified by customary 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 disclosure.

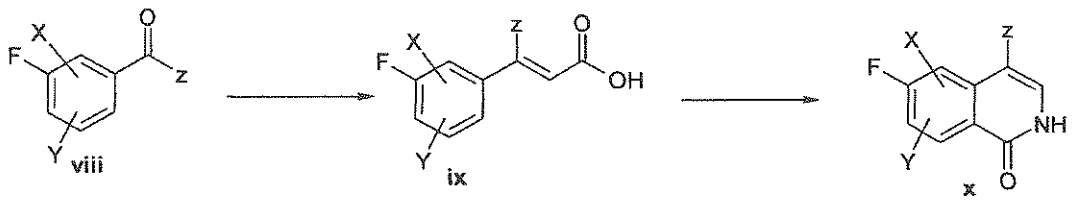


Scheme 1:

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

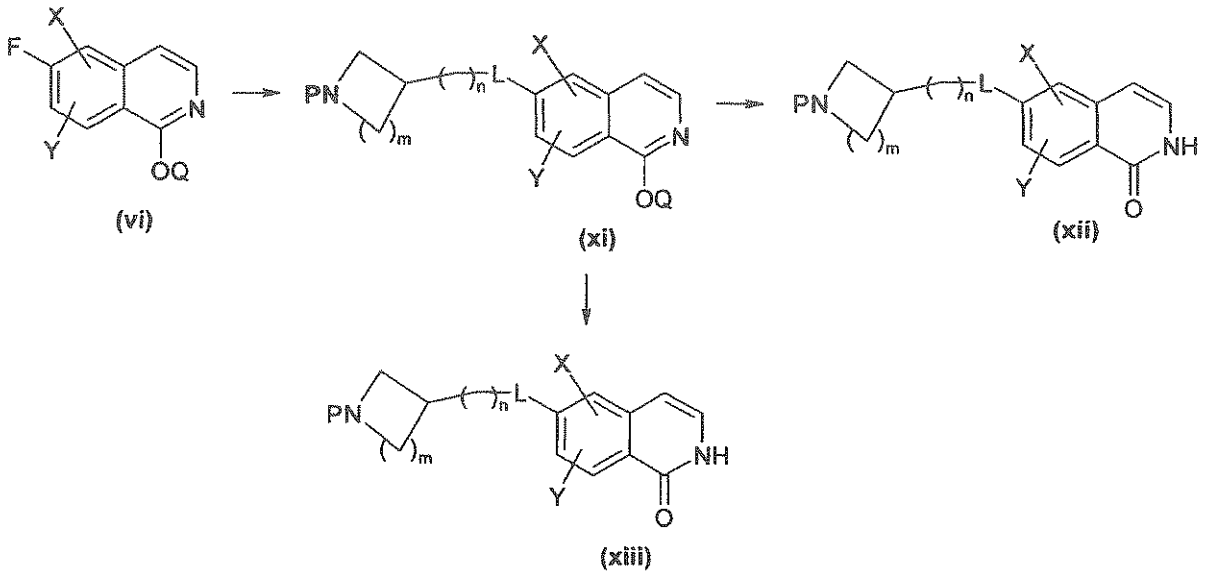
with a reagent like phosphorous oxy chloride in or without presence of phosphorous pentachloride. The derivative (v) can then be turned into suitable 1-alkoxy-derivatives by reacting it with various alcohols Q-OH like methanol, ethanol or benzyl alcohol in the presence of a suitable base like sodium 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 6-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 substituted thiols or amines wherein P is for example hydrogen, alkyl or a protecting group like for example Boc 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 precence of a base like triethyl amine or Hünig's base or by reacting it with a suitable carboxylic acid in the precence of a base like triethylamine ot 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.

Isoquinoline and 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.

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

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

Method A:

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

Method B:

Stationary phase:	Col YMC Jsphere 33 x 2
Gradient:	ACN+0,05% TFA : water + 0.05% TFA

	5:95(0 min) to 95:5(2.5 min) to 95:5(3.0 min)
Flow	1 mL/min

Method C:

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

Method D:

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

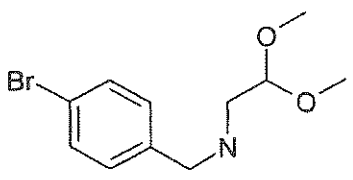
Method E:

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

Method F:

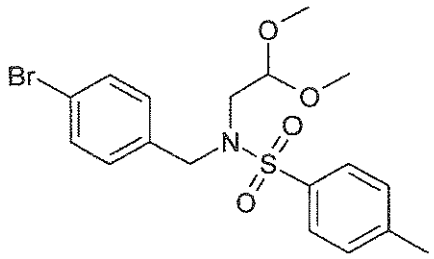
Stationary phase:	Col YMC-Pack Pro C18 RS 33 x 2.1
Gradient:	Grad ACN+0.1% FA : water+0.1%FA (Formic Acid)
	5:95(0min) to 95:5(2.5min) to 95:5(3min)
Flow	1.3 mL/min

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



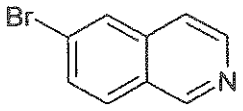
50 g (270.2 mmol) 4-bromobenzaldehyde were dissolved in 200 ml of toluene and 28.4 g (270.2 mmol) aminoacetaldehyde dimethylacetal were added.. After the addition of 5.1 g (27.0 mmol) p-toluenesulfonic acid monohydrate, the reaction mixture was heated under reflux in a Dean Stark apparatus. After 4 h, the reaction was cooled to room temperature and washed with saturated sodium hydrogen carbonate-solution (2x) and water. The combined aqueous layers were extracted with Toluene and the combined organic layers were dried over magnesium sulfate and evaporated. The residue was dissolved in 200 ml of ethanol and 5.11 g (135.1 mmol) of 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 water. After drying over magnesium sulfate 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 ($M+H^+$).

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



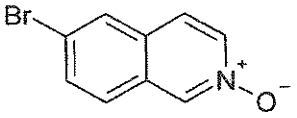
60.5 g (4-Bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1, crude product) were dissolved in 270 ml of dichloromethane/pyridine (8:1). At 0 °C a solution of 76.0 g (386.4 mmol) p-toluenesulfonylchloride in 100 ml of dichloromethane was added and the solution was stirred at room temperature. After 3 h, the reaction mixture was washed twice with 2 N HCl and saturated sodium hydrogen carbonate-solution. The organic layer was dried over magnesium sulfate and evaporated. Final silica gel 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 ($M-OMe^-$).

3: 6-Bromo-isoquinoline



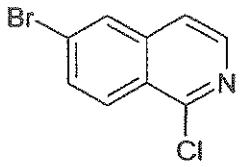
To a mechanically stirred suspension of 95.2 g (699,5 mmol) of $AlCl_3$ in 400 ml of dichloromethane a solution of 59.9 g (139.8 mmol) N-(4-bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2) in 400 ml of dichloromethane was added and the reaction was stirred at room temperature for 4 h. After standing overnight, the reaction mixture was poured onto 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 sodium hydrogen carbonate-solution (2x). After drying with magnesium sulfate and evaporation of the solvent, the crude product was purified by silica gel 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 ($M+H^+$).

4: 6-Bromo-isoquinoline 2-oxide



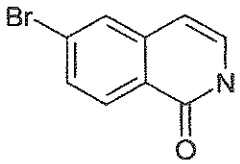
To a solution of 51.0 g (245.1 mmol) of 6-bromo-isoquinoline (3) in 800 ml of dichloromethane were added under mechanical stirring 90.6 g (367.6 mmol) of 3-chloro-benzenecarboperoxoic acid (70%). After stirring for 4 h at room temperature and standing overnight, saturated sodium hydrogen carbonate-solution 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 over magnesium sulfate and evaporated. The obtained crude product (53,0 g) was used without further purification. R_t = 0.89 min (Method C). Detected mass: 226.2 ($M+H^+$).

5: 6-Bromo-1-chloro-isoquinoline



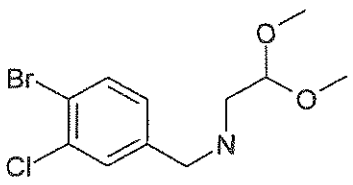
53.0 g (236,. mmol) of 6-bromo-isoquinoline 2-oxide (4) were heated in 400 ml of $POCl_3$ under reflux conditions in two portions. After 4 h, the reaction was cooled to room temperature and poured carefully on ice with mechanical stirring. The aqueous solution was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate 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: 6-Bromo-2H-isoquinolin-1-one



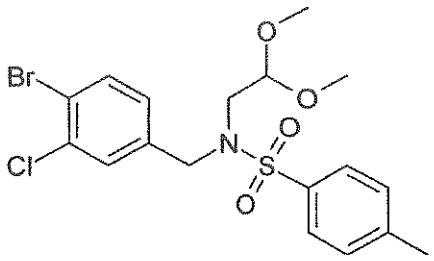
To a solution of 42.8 g (173.5 mmol) of 6-Bromo-1-chloro-isoquinoline (5) in 700 ml of acetic acid were added 133.6 g (1.74 mol) ammonium acetate. After stirring at 100 °C for 3 h, the solution was cooled to room temperature and the solvent was removed i. vac. to a small volume. The residue was poured on water 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 ($M+H^+$).

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



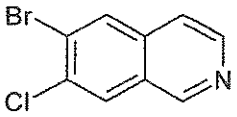
Starting from 4-Bromo-3-chloro-benzaldehyde, the title compound was prepared by the method described for (4-Bromo-benzyl)-(2,2-dimethoxy-ethyl)-amine (1). R_t = 0.94 min (Method C). Detected mass: 308.3/310.3 ($M+H^+$).

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



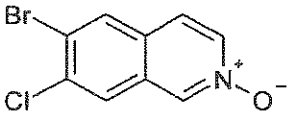
The title compound was prepared by the protocol described for N-(4-Bromo-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzenesulfonamide (2), starting from (4-Bromo-3-chloro-benzyl)-(2,2-dimethoxy-ethyl)-amine (7). R_t = 1.93 min (Method C). Detected mass: 430.3/432.3 ($M-OMe^-$).

9: 6-Bromo-7-chloro-isoquinoline



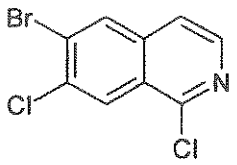
Starting from N-(4-Bromo-3-chloro-benzyl)-N-(2,2-dimethoxy-ethyl)-4-methyl-benzene-sulfonamide (8), the title compound was synthesized by the protocol described for 6-Bromo-isoquinoline (3). R_t = 1.02 min (Method C). Detected mass: 242.2/244.2 ($M+H^+$).

10: 6-Bromo-7-chloro-isoquinoline 2-oxide



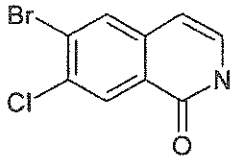
The title compound was prepared by the method, described for 6-Bromo-isoquinoline 2-oxide (4), starting with 6-Bromo-7-chloro-isoquinoline (9). R_t = 1.05 min (Method C). Detected mass: 258.1/260.2 ($M+H^+$).

11: 6-Bromo-1,7-dichloro-isoquinoline



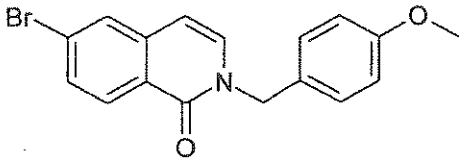
Starting with 6-Bromo-7-chloro-isoquinoline 2-oxide (10), the desired 6-Bromo-1,7-dichloro-isoquinoline was prepared by the method, described for 6-Bromo-1-chloro-isoquinoline (5). R_t = 1.85 min (Method C). Detected mass: 276.1/278.2 ($M+H^+$).

12: 6-Bromo-7-chloro-2H-isoquinolin-1-one



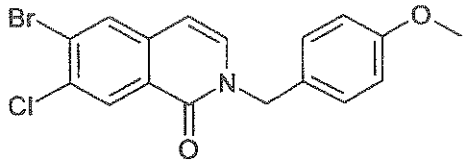
The title compound was prepared by the method, described for 6-Bromo-2H-isoquinolin-1-one (6), starting from 6-Bromo-1,7-dichloro-isoquinoline (11). R_t = 1.26 min (Method C). Detected mass: 258.2/260.2 ($M+H^+$).

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



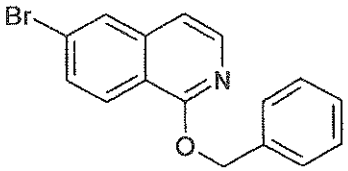
28.18 g (125.8 mmol) 6-Bromo-2H-isoquinolin-1-one (6) were dissolved in 200 ml Dimethylacetamide and 7.55 g (188.7 mmol) sodium hydride (60%) were added at room temperature. After stirring for 30 minutes, 29.94 g (188.7 mmol) 4-Methoxy-benzylchloride were added and stirring was continued at room temperature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

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



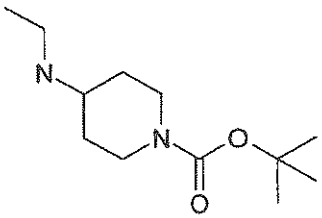
Starting from 6-Bromo-7-chloro-2H-isoquinolin-1-one (12), the title compound was prepared by the method described for 6-Bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (compound 13). R_t = 2.12 min (Method B). Detected mass: 378.1/380.1 ($M+H^+$).

15: 1-Benzyloxy-6-bromo-isoquinoline



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) silver carbonate and 3.60 g (21.1 mmol) of benzyl bromide. The reaction mixture was refluxed for 1.5 h and then cooled to room temperature. The solution was filtered. The filtrate was washed with water and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and evaporated. Final purification was achieved by preparative HPLC. R_t = 2.47 min (Method B). Detected mass: 314.1/316.5 ($M+H^+$).

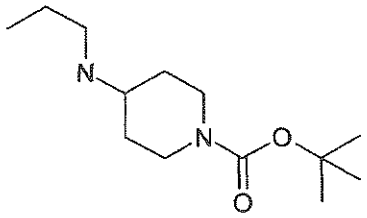
16: 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester



3.0 g (15.0 mmol) 4-Amino-piperidine-1-carboxylic acid tert-butyl ester were dissolved in 40 ml Methanol. After adding molecular sieves, 3.0 g (30.0 mmol) Triethylamine, 9.0 g (149.8 mmol) acetic acid and 659.9 mg (15.0 mmol) acetaldehyde, a solution of 2.82 g (44.9 mmol) sodium cyanoborohydride in 2 ml of methanol was added and the reaction mixture was stirred at room temperature until complete conversion of the

starting material was detected. For working up, the reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate-solution and water. After drying with magnesium sulfate, the solvent was removed under reduced pressure. Purification was achieved by preparative HPLC, which gave the title compound as trifluoroacetate. The product fractions were combined and brought to alkaline pH by adding sodium hydrogen carbonate(s). After evaporation of the solvent i. vac., the residue was dissolved in water and extracted three times with dichloromethane. Drying with magnesium sulfate and evaporation of the solvent gave the title compound as free base. R_t = 0.95 min (Method B). Detected mass: 229.2 ($M+H^+$).

17: 4-Propylamino-piperidine-1-carboxylic acid tert-butyl ester

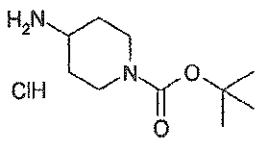
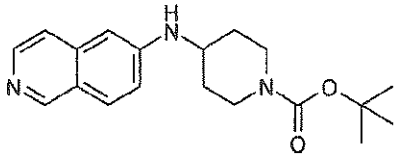
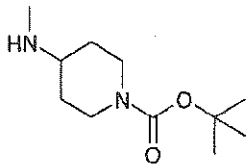
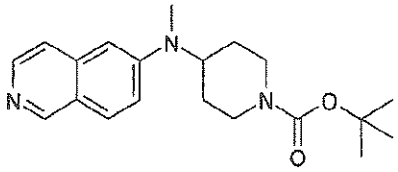
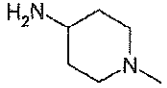
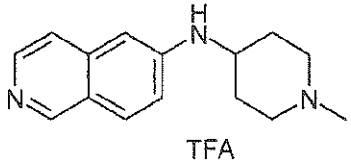


The title compound was synthesized by the method, described for 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester (16), using propionaldehyde instead of acetaldehyde. R_t = 1.43 min (Method B). Detected mass: 243.2 ($M+H^+$).

General Procedure A for the Hartwig-Buchwald amination reaction:
1.0 eq of the arylbromide, 1.5 eq cesium carbonate and 1.2 eq of the amine were dissolved in Toluene. If the amine was taken as a salt another equivalent of cesium carbonate was used; if additionally the arylbromide was used as a salt (HCl- or TFA-salt of the isoquinolines) again, 1 additional equivalent of cesium carbonate 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 water and extracted ethyl acetate. The organic layer was separated, dried over magnesium sulfate and the solvent was removed i. vac. The crude product was purified by preparative HPLC.

General Procedure B for the Hartwig-Buchwald amination reaction:
1.0 eq of the arylbromide, 2.5 eq NaO^tBu and 1.2 eq of the amine were dissolved in dry Dioxane. The solution was degassed and flushed with argon. Then, 0.03 eq $Pd(OAc)_2$ and 0.045 eq 1,1'-Bis(di-tert-butylphophino)ferrocene 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 solvent was removed i. vac. and the residue dissolved in dichloromethane. The organic phase was washed with saturated sodium hydrogen carbonate-solution and water, dried over magnesium sulfate and evaporated. Final purification was achieved by silicagel chromatography (Ttable 1).

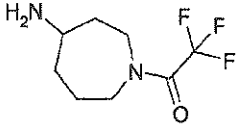
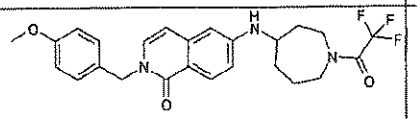
Table 1

Example	Arylbromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Procedure	Chemical Name
18	3			1.05	328.2	C	A	4-(Isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester
19	3			1.10	342.2	C	A	4-(Isoquinolin-6-yl-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester
20	3			0.57	242.2	B	A	Isoquinolin-6-yl-(1-methyl-piperidin-4-yl)-amine

Example	Arylbromide	Amine	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Procedure	Chemical Name
21	3			1.06	328.2	C	A	2-(Isoquinolin-6-ylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester
22	3			1.04	328.2	C	A	3-(Isoquinolin-6-ylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester
23	3			0.16	256.2	A	A	Isoquinolin-6-yl-methyl-(1-methyl-piperidin-4-yl)-amine

Example	Arylbromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Procedure	Chemical Name
25	9			0.75	276.2	B	A; NaO^{t}Bu was used instead of cesium carbonate	(7-Chloro-isoquinolin-6-yl)-(1-methyl-piperidin-4-yl)-amine
26	9			1.11	362.2	C	A: NaO^{t}Bu was used instead of cesium carbonate	4-(7-Chloro-isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester
27	13			1.89	464.4	B	A	

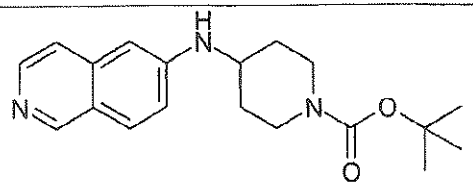
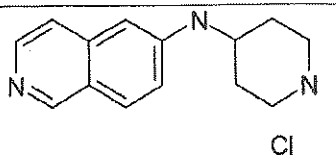
Example	Arylbromide	Amine	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Procedure	Chemical Name
28	14			1.83	498.5	C	A	
29	13			2.00	478.2	B	B	
30	13			1.74	492.6	C	B	
31	13			1.86	506.7	C	B	

Example	Arylbromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Procedure	Chemical Name
32	13			1.81	474.2	B	A	

General procedure C 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 water. Final lyophilisation gave the desired product as hydrochlorides. (Table 2)

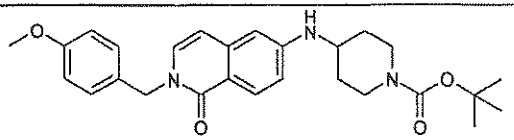
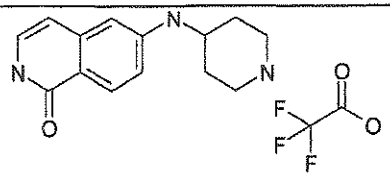
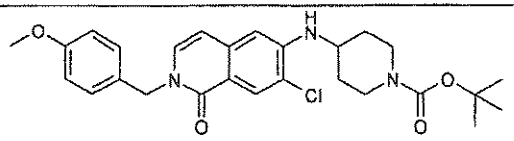
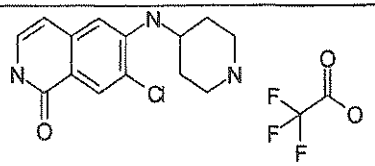
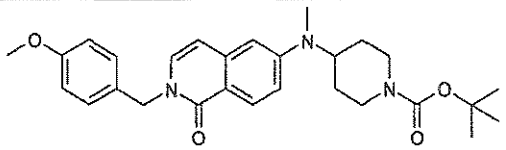
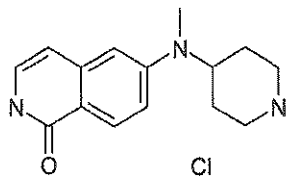
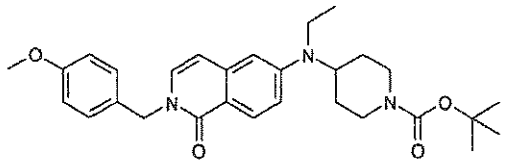
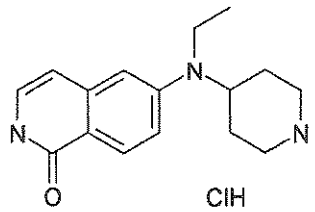
Table 2

Example	Boc-protected compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
33			0.33	228.2	C	Isoquinolin-6-yl-piperidin-4-yl-amine

Example	Boc-protected compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
34			0.50	242.2	C	Isoquinolin-6-yl-methyl-piperidin-4-yl-amine
35			0.68	228.2	B	Isoquinolin-6-yl-pyrrolidin-2-ylmethyl-amine
36			0.68	228.2	B	Isoquinolin-6-yl-pyrrolidin-3-ylmethyl-amine
37			0.63	262.0	B	(7-Chloro-isoquinolin-6-yl)-piperidin-4-yl-amine

General procedure D for the deprotection of PMB-protected compounds;
In the case of PMB- and Boc-protected compounds, the starting materials were dissolved in Trifluoroacetic 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 trifluoroacetates, which, in some cases, were dissolved in 2 N HCl and evaporated. After final lyophilisation of the aqueous solutions, these desired products were isolated as hydrochlorides. By this method, the following compounds were synthesized (Table 3):

Table 3

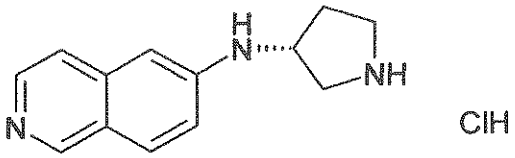
Example	Protected compound	Product	R_t [min]	Mass [M+H$^+$]	Method	Chemical name
38			0.64	244.2	B	6-(Piperidin-4-ylamino)-2H-isoquinolin-1-one
39			0.80	278.1	B	7-Chloro-6-(piperidin-4-ylamino)-2H-isoquinolin-1-one
40			0.75	258.2	B	6-(Methyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one
41			0.76	272.2	B	6-(Ethyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one

Example	Protected compound	Product	R_t [min]	Mass $[M+H^+]$	Method	Chemical name
42			0.90	286.2	B	6-(Propyl-piperidin-4-yl-amino)-2H-isoquinolin-1-one

General procedure E for the reductive amination:
The starting material (1.0 eq) was dissolved in dry Methanol. After adding freshly dried molecular sieves (4A), Triethylamine (2.0 eq), acetic acid (10.0 eq), the carbonyl compounds (3.0 – 6.0 eq) and sodium cyano borohydride (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 cyano borohydride 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 ethyl acetate. The combined organic layers were dried over Sodium sulfate 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.

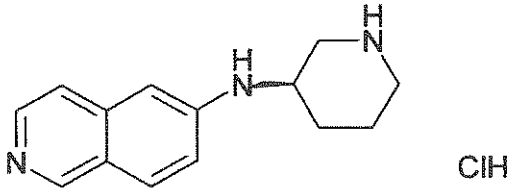
Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemica Name
43				0.84	270.2	B	2.0 + 3.0 eq acetone were used. (1-Isopropyl-piperidin-4-yl)-isoquinolin-6-yl-amine

44: Isoquinolin-6-yl-(R)-pyrrolidin-3-yl-amine hydrochloride



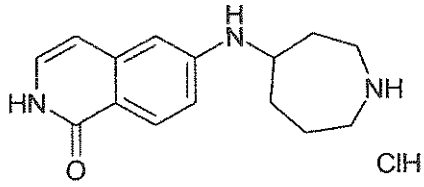
Isoquinolin-6-yl-(R)-pyrrolidin-3-yl-amine was prepared in analogous fashion as described for 33 starting from (R)-3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester.

45: Isoquinolin-6-yl-(R)-piperidin-3-yl-amine hydrochloride



Isoquinolin-6-yl-(R)-piperidin-3-yl-amine was prepared in analogous fashion as described for 47 starting from (R)-3-Amino-piperidine-1-carboxylic acid tert-butyl ester.

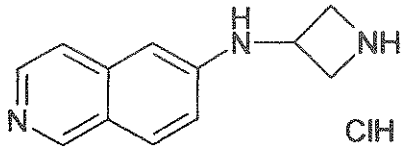
46: 6-(Azepan-4-ylamino)-2H-isoquinolin-1-one



450 mg (0.95 mmol) 2-(4-Methoxy-benzyl)-6-[1-(2,2,2-trifluoro-acetyl)-azepan-4-ylamino]-2H-isoquinolin-1-one (compound 42) were heated in a microwave at 140°C for 3.5 h. After evaporation of the solvent, the residue was dissolved in 15 ml Ethanol and 2 ml 2 N NaOH were added. The solution was stirred for 1 h at room temperature and the solvent was removed under reduced pressure. The residue was taken up in water and washed with dichloromethane. The aqueous layer was separated and filtered. After lyophilisation, the crude product was stirred in Ethanol, filtered and the solvent evaporated. Final purification by preparative HPLC gave the title compound as

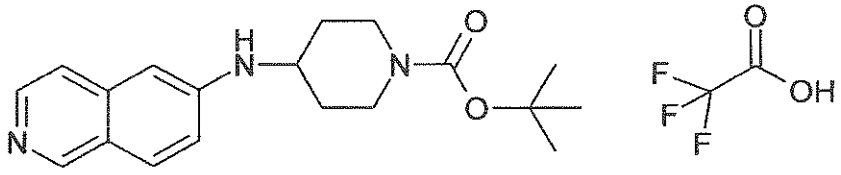
trilfuoroacetate, which was dissolved in 1 N HCl. The solvent was removed and the residue was dissolved in water. Final lyophylisation gave the desired compound as hydrochloride. R_t = 0.76 min (Method B). Detected mass: 258.2 ($M+H^+$).

47: Azetidin-3-yl-isoquinolin-6-yl-amine hydrochloride



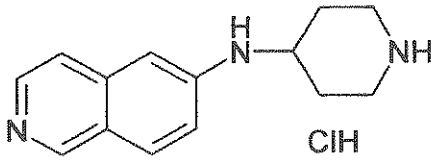
Azetidin-3-yl-isoquinolin-6-yl-amine was prepared in analogous fashion as described for 33 starting from (3-Amino-azetidine-1-carboxylic acid tert-butyl ester.

18: 4-(Isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester trifluoroacetate



To 187 mg (0.9 mmol) 6-Bromoisoquinoline (3) in 5 ml Dioxan were added 733 mg (2.25 mmol) Cesiumcarbonate, 216 mg (1.08 mmol) 4-Amino-1-BOC-piperidine and the mixture was degassed. 56 mg (0.09 mmol) BINAP and 17.5 mg (78.3 µmol) Palladium acetate were added and the mixture was heated to 100°C for 16 h. After filtration from solids the volatiles were evaporated and the residue was purified by preparative HPLC (Method A). 258 mg 4-(Isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester trifluoroacetate could be obtained.

33: Isoquinolin-6-yl-piperidin-4-yl-amine Hydrochloride



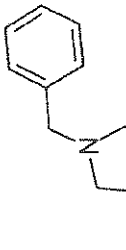
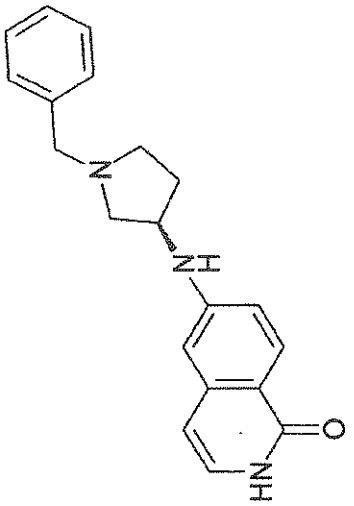
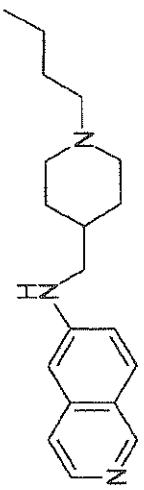
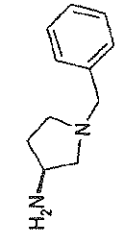
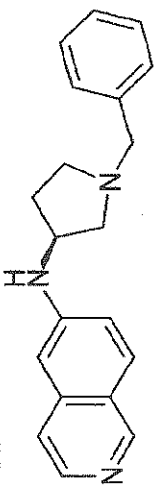
258 mg (0.79 mmol) 4-(Isoquinolin-6-ylamino)-piperidine-1-carboxylic acid tert-butyl ester were stirred in 6N HCl in isopropanol for 2 h. After evaporation the residue was taken up in water and lyophilized. 206 mg of Isoquinolin-6-yl-piperidin-4-yl-amine as the hydrochloride could be obtained.

The compounds described in the following table were synthesized in a similar fashion as described for 18 / 33 (Table 4).

Table 4

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
49	13			1.06	320.3	B	6-((S)-1-Benzyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
50	13			0.77	272.2	B	6-(1-Ethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
51	13			0.99	258.3	B	6-[(Piperidin-3-ylmethyl)-amino]-2H-isoquinolin-1-one

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
52	13			0.59	216.2	B	6-(Azetidin-3-ylamino)-2H-isoquinolin-1-one
53	13			0.69	244.3	B	6-[(Pyrrolidin-2-ylmethyl)-amino]-2H-isoquinolin-1-one
54	13			1.04	334.1	B	6-(1-Benzyl-piperidin-4-ylamino)-2H-isoquinolin-1-one

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
55	13			0.95	320.1	B	6-((R)-1-Benzyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
56	3			1.01	298.2	B	(1-Butyl-piperidin-4-ylmethyl)-isoquinolin-6-yl-amine
58	3			0.89	304.2	B	((S)-1-Benzyl-pyrroidin-3-yl)-isoquinolin-6-yl-amine

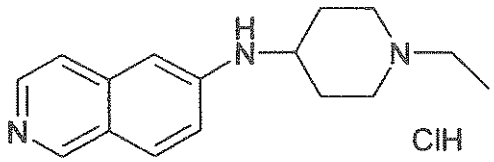
Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
60	3			0.87	256.2	B	(1-Ethyl-piperidin-3-yl)-isoquinolin-6-yl-amine
61	3			0.60	214.2	B	Isoquinolin-6-yl-(S)-pyrrolidin-3-yl-amine

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
62	3			0.70	242.3	B	Isoquinolin-6-yl-piperidin-3-ylmethyl-amine
63	3			0.85	200.2	B	Azetidin-3-yl-isoquinolin-6-yl-amine
64	3			0.32	319.4	B	Isoquinolin-6-yl-piperidin-4-yl-pyridin-3-ylmethyl-amine

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
65	3			1.09	318.3	B	Benzyl-isoquinolin-6-yl-piperidin-4-yl-amine
66	3			0.69	319.3	B	Isoquinolin-6-yl-piperidin-4-yl-pyridin-4-ylmethyl-amine

Example	Aryl-bromide	Amine	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
67	3			0.19	214.2	B	Isoquinolin-6-yl-(R)-pyrrolidin-3-yl-amine

68: (1-Ethyl-piperidin-4-yl)-isoquinolin-6-yl-amine hydrochloride



To 32 mg (0.12 mmol) Isoquinolin-6-yl-piperidin-4-yl-amine Hydrochloride (48) in 4 ml THF was added (0.12 mmol) acetaldehyde and 104 mg MP-Cyano borohydride resin (2.3 mmol/g) and stirred over night. After filtration from the resin and evaporation the residue was purified by preparative HPLC (Method A) to obtain (1-Ethyl-piperidin-4-yl)-isoquinolin-6-yl-amine as the trifluoroacetate. The obtained trifluoroacetate was dissolved in 6 N HCl in Isopropanol and evaporated. Final lyophilization gave 2 mg of the title compound R_t = 0.63 min (Method B). Detected mass: 256.2 ($M+H^+$).

The compounds described in the following table were synthesized in an analogous fashion as described for 68 (Table 5):

Table 5

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
69				0.68	270.2	B	Isoquinolin-6-yl-(1-propyl-piperidin-4-yl)-amine
70				0.82	284.2	B	(1-Butyl-piperidin-4-yl)-isoquinolin-6-yl-amine
71				0.82	284.2	B	(1-Isobutyl-piperidin-4-yl)-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
72				0.72	282.2	B	(1-Cyclopropylmethyl-piperidin-4-yl)-isoquinolin-6-yl-amine
73				0.97	298.2	B	Isoquinolin-6-yl-[1-(3-methyl-butyl)-piperidin-4-yl]-amine
74				0.79	324.2	B	Isoquinolin-6-yl-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
75				1.00	324.3	B	(1-Cyclohexylmethyl-piperidin-4-yl)-isoquinolin-6-yl-amine
76				0.82	310.3	B	(1-Cyclohexyl-piperidin-4-yl)-isoquinolin-6-yl-amine
77				0.99	352.2	B	[1-(4-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
78				0.99	352.2	B	[1-(3-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine
79				0.91	352.2	B	[1-(2-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine
80				1.06	386.2	B	[1-(2,4-Dichloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
81				0.82	318.2	B	(1-Benzyl-piperidin-4-yl)-isoquinolin-6-yl-amine
82				1.00	486.2	B	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[4-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide
83				0.87	482.3	B	N-[1-Dimethylamino-meth-(E)-ylidene]-3-[4-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-4-methoxy-benzenesulfonamide

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
84				0.92	332.2	B	Isoquinolin-6-yl-[1-(4-methyl-benzyl)-piperidin-4-yl]-amine
85				1.04	386.2	B	Isoquinolin-6-yl-[1-(4-trifluoromethyl-benzyl)-piperidin-4-yl]-amine
86				0.77	319.2	B	Isoquinolin-6-yl-(1-pyridin-4-ylmethyl-piperidin-4-yl)-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
87				0.50	319.2	B	Isoquinolin-6-yl-(1-pyridin-3-ylmethyl-piperidin-4-yl)-amine
88				0.73	319.2	B	Isoquinolin-6-yl-(1-pyridin-2-ylmethyl-piperidin-4-yl)-amine
89				0.78	396.2	B	Isoquinolin-6-yl-[1-(4-methanesulfonyl-benzyl)-piperidin-4-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
90				0.82	414.2	B	[1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-amine
91				1.15	450.1	B	Isoquinolin-6-yl-[1-(4-trifluoromethanesulfonyl-benzyl)-piperidin-4-yl]-amine
92				1.13	368.2	B	Isoquinolin-6-yl-(1-naphthalen-2-ylmethyl-piperidin-4-yl)-amine

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
93				1.05	368.2	B	Isoquinolin-6-yl-(1-naphthalen-1-ylmethyl-piperidin-4-yl)-amine
94				0.82	284.3	B	Isoquinolin-6-yl-methyl-(1-propyl-piperidin-4-yl)-amine
95				0.79	298.3	B	(1-Butyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
96				0.82	298.2	B	(1-Isobutyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine
97				0.79	296.2	B	(1-Cyclopropylmethyl-piperidin-4-yl)-isoquinolin-6-yl-methyl-amine
98				0.95	312.3	B	Isoquinolin-6-yl-methyl-[1-(3-methyl-butyl)-piperidin-4-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
99				0.74	338.2	B	Isoquinolin-6-yl-methyl-[1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amine
100				1.02	366.2	B	[1-(4-Chloro-benzyl)-piperidin-4-yl]-isoquinolin-6-yl-methyl-amine
101				0.78	344.2	A	Isoquinolin-6-yl-[1-(2,3,5-trifluoro-benzyl)-azetidin-3-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
102				0.86	342.2/344.2	A	[1-(3-Chloro-2-fluoro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
103				0.87	340.2	A	[1-(2,3-Difluoro-4-methyl-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
104				0.14	228.2	A	(1-Ethyl-azetidin-3-yl)-isoquinolin-6-yl-amine
105				0.18	242.2	A	Isoquinolin-6-yl-(1-propyl-azetidin-3-yl)-amine

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
106				0.12	256.3	A	(1-Butyl-azetidin-3-yl)-isoquinolin-6-yl-amine
107				0.4$	242.2	A	(1-Isopropyl-azetidin-3-yl)-isoquinolin-6-yl-amin
108				0.68	270.3	A	[1-(1-Ethyl-propyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
109				0.66	256.3	A	(1-Isobutyl-azetidin-3-yl)-isoquinolin-6-yl-amine
110				0.5$	254.3	A	(1-Cyclopropylmethyl-azetidin-3-yl)-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
111				0.77	270.2	A	Isoquinolin-6-yl-[1-(3-methyl-butyl)-azetidin-3-yl]-amine
112				0.54	296.2	A	Isoquinolin-6-yl-[1-(3,3,3-trifluoro-propyl)-azetidin-3-yl]-amine
113				0.81	296.3	A	(1-Cyclohexylmethyl-azetidin-3-yl)-isoquinolin-6-yl-amine
114				0.79	282.3	A	(1-Cyclohexyl-azetidin-3-yl)-isoquinolin-6-yl-amine
115				0.76	324.2/326.2	A	[1-(4-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
116				0.84	324.2/3 26.2	A	[1-(3-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
117				0.79	324.2/3 26.2	A	[1-(2-Chloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
118				0.93	358.2	A	[1-(2,4-Dichloro-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
119				0.72	290.2	A	(1-Benzyl-azetidin-3-yl)-isoquinolin-6-yl-amine

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
120				0.75	458.3/460.3	A	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[3-(isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-benzenesulfonamide
121				0.73	454.3	A	N-[1-Dimethylamino-meth-(E)-ylidene]-3-[3-(isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-4-methoxy-benzenesulfonamide
122				0.84	304.3	A	Isoquinolin-6-yl-[1-(4-methyl-benzyl)-azetidin-3-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
123				0.92	358.2	A	Isoquinolin-6-yl-[1-(4-trifluoromethyl-benzyl)-azetidin-3-yl]-amine
124				0.18	291.2	A	Isoquinolin-6-yl-(1-pyridin-4-ylmethyl-azetidin-3-yl)-amine
125				0.21	291.2	A	Isoquinolin-6-yl-(1-pyridin-3-ylmethyl-azetidin-3-yl)-amine
126				0.23	291.3	A	Isoquinolin-6-yl-(1-pyridin-2-ylmethyl-azetidin-3-yl)-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
127				0.61	368.3	A	Isoquinolin-6-yl-[1-(4-methanesulfonyl-benzyl)-azetidin-3-yl]-amine
128				0.74	386.2	A	[1-(5-Fluoro-2-methanesulfonyl-benzyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
129				1.03	340.3	A	Isoquinolin-6-yl-(1-naphthalen-2-ylmethyl-azetidin-3-yl)-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
130				0.96	340.3	A	Isoquinolin-6-yl-(1-naphthalen-1-ylmethyl-azetidin-3-yl)-amine
131				0.14	257.3	A	[1-((S)-2-Amino-propyl)-azetidin-3-yl]-isoquinolin-6-yl-amine
132				0.14	283.3	A	Isoquinolin-6-yl-(1-pyrrolidin-3-ylmethyl-azetidin-3-yl)-amine

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
133				0.12	283.3	A	Isoquinolin-6-yl-(1-(R)-1-pyrrolidin-2-ylmethyl-azetidin-3-yl)-amine
134				0.46	294.3	A	Isoquinolin-6-yl-[1-(1-methyl-1H-pyrazol-4-ylmethyl)-azetidin-3-yl]-amine
135				0.70	296.2	A	Isoquinolin-6-yl-(1-thiophen-3-ylmethyl-azetidin-3-yl)-amine
136				0.82	358.2	B	Isoquinolin-6-yl-[(R)-1-(2,3,5-trifluoro-benzyl)-pyrrolidin-3-yl]-amine

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
137				0.70	270.2	B	((R)-1-Butyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine
138				0.49	256.2	B	((R)-1-Isopropyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine
139				0.74	284.2	B	[(R)-1-(1-Ethyl-propyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine
140				0.65	270.2	B	((R)-1-Isobutyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine
141				0.64	268.2	B	((R)-1-Cyclopropylmethyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
142				0.80	284.2	B	Isoquinolin-6-yl-[(R)-1-(3-methyl-butyl)-pyrrolidin-3-yl]-amine
143				0.62	310.2	B	Isoquinolin-6-yl-[(R)-1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-yl]-amine
144				0.87	310.2	B	((R)-1-Cyclohexylmethyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine
145				0.58	338.4/340.4	B	[(R)-1-(4-Chloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
146				0.60	338.5/340.4	B	[(R)-1-(3-Chloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine
147				0.79	304.1	B	((R)-1-Benzyl-pyrrolidin-3-yl)-isoquinolin-6-yl-amine
148				1.02	372..0/374.0	B	[(R)-1-(3,5-Dichloro-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine
149				0.86	472.0	B	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
							benzenesulfonamide
150				0.82	468.3	A	N-[1-Dimethylamino-meth-(E)-ylidene]-3-[(R)-3-(isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-4-methoxy-benzenesulfonamide
151				0.81	318.3	A	Isoquinolin-6-yl-[(R)-1-(4-methyl-benzyl)-pyrrolidin-3-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
152				1.03	372.2	A	Isoquinolin-6-yl-[(R)-1-(4-trifluoromethyl-benzyl)-pyrrolidin-3-yl]-amine
153				0.16	305.3	A	Isoquinolin-6-yl-((R)-1-pyridin-4-ylmethyl-pyrrolidin-3-yl)-amine
154				0.14	305.3	A	Isoquinolin-6-yl-((R)-1-pyridin-3-ylmethyl-pyrrolidin-3-yl)-amine
155				0.16	305.3	A	Isoquinolin-6-yl-((R)-1-pyridin-2-ylmethyl-pyrrolidin-3-yl)-amine

Exam -ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
156				0.60	382.3	A	Isoquinolin-6-yl-[(R)-1-(4-methanesulfonyl-benzyl)-pyrrolidin-3-yl]-amine
157				0.64	400.2	A	[(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-yl]-isoquinolin-6-yl-amine
158				0.97	354.3	A	Isoquinolin-6-yl-((R)-1-naphthalen-2-ylmethyl-pyrrolidin-3-yl)-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
159				0.81	372.3	A	Isoquinolin-6-yl-[(R)-1-(2,3,5-trifluoro-benzyl)-piperidin-3-yl]-amine
160				0.93	370.3	A	[(R)-1-(3-Chloro-2-fluoro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
161				0.91	368.2	A	[(R)-1-(2,3-Difluoro-4-methyl-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
162				0.77	256.2	A	((R)-1-Ethyl-piperidin-3-yl)-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
163				0.21	270.3	A	Isoquinolin-6-yl-((R)-1-propyl-piperidin-3-yl)-amine
164				0.69	284.3	A	((R)-1-Butyl-piperidin-3-yl)-isoquinolin-6-yl-amine
165				0.65	284.3	A	((R)-1-Isobutyl-piperidin-3-yl)-isoquinolin-6-yl-amine
166				0.59	282.3	A	((R)-1-Cyclopropylmethyl-piperidin-3-yl)-isoquinolin-6-yl-amine
167				0.80	298.3	A	Isoquinolin-6-yl-[(R)-1-(3-methyl-butyl)-piperidin-3-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
168				0.62	324.3	A	Isoquinolin-6-yl-[(R)-1-(3,3,3-trifluoro-propyl)-piperidin-3-yl]-amine
169				0.75	324.3	A	((R)-1-Cyclohexylmethyl-piperidin-3-yl)-isoquinolin-6-yl-amine
170				0.91	352.3/354.3	A	[(R)-1-(4-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
171				0.73	352.3/354.3	A	[(R)-1-(3-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
172				0.85	352.3/354.3	A	[(R)-1-(2-Chloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
173				1.00	386.2/388.2	A	[(R)-1-(2,4-Dichloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
174				0.77	318.4	A	((R)-1-Benzyl-piperidin-3-yl)-isoquinolin-6-yl-amine
175				1.00	386.2/388.2	A	[(R)-1-(3,5-Dichloro-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine

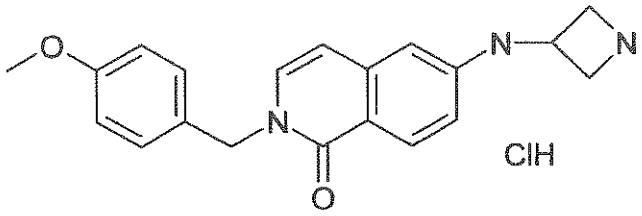
Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
176				0.64	486.3	A	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide
177				0.80	482.4	A	N-[1-Dimethyl-amino-meth-(E)-ylidene]-3-[(R)-3-(isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-4-methoxy-benzenesulfonamide
178				0.90	332.3	A	Isoquinolin-6-yl-[(R)-1-(4-methyl-benzyl)-piperidin-3-yl]-amine

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
179				0.96	386.3	A	Isoquinolin-6-yl-[(R)-1-(4-trifluoromethyl-benzyl)-piperidin-3-yl]-amine
180				0.12	319.3	A	Isoquinolin-6-yl-((R)-1-pyridin-4-ylmethyl-piperidin-3-yl)-amine
181				0.16	319.3	A	Isoquinolin-6-yl-((R)-1-pyridin-3-ylmethyl-piperidin-3-yl)-amine
182				0.18	319.3	A	Isoquinolin-6-yl-((R)-1-pyridin-2-ylmethyl-piperidin-3-yl)-amin

Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
183				0.67	396.3	A	Isoquinolin-6-yl-[(R)-1-(4-methanesulfonyl-benzyl)-piperidin-3-yl]-amine
48				0.70	414.3	A	[(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
184				1.06	368.3	A	Isoquinolin-6-yl-((R)-1-naphthalen-2-ylmethyl-piperidin-3-yl)-amine

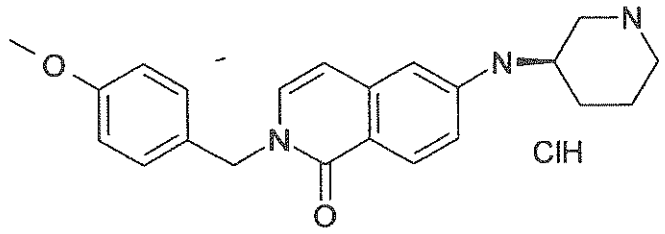
Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
185				0.97	368.3	A	Isoquinolin-6-yl-((R)-1-naphthalen-1-ylmethyl-piperidin-3-yl)-amine
186				0.18	285.3	A	[(R)-1-((S)-2-Amino-propyl)-piperidin-3-yl]-isoquinolin-6-yl-amine
187				0.14	311.3	A	Isoquinolin-6-yl-((R)-1-pyrrolidin-3-ylmethyl-piperidin-3-yl)-amine
188				0.21	311.3	A	Isoquinolin-6-yl-((R)-1-(R)-1-pyrrolidin-2-ylmethyl-piperidin-3-yl)-amine

189: 6-(Azetidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride



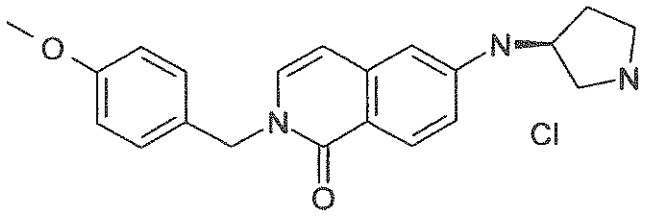
6-(Azetidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride was prepared by Buchwald Reaction starting from 6-Bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (13) and 3-Amino-azetidine-1-carboxylic acid tert-butyl ester. BOC deprotection was performed as described for Isoquinolin-6-yl-piperidin-4-yl-amine (48).

190: 2-(4-Methoxy-benzyl)-6-((R)-piperidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride



2-(4-Methoxy-benzyl)-6-((R)-piperidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride was prepared in analogy to 189.

191: 2-(4-Methoxy-benzyl)-6-((S)-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride



2-(4-Methoxy-benzyl)-6-((S)-Pyrrolidin-3-ylamino)-2H-isoquinolin-1-one hydrochloride was prepared in analogy to 189.

Reductive aminations were carried out in analogy to (1-Ethyl-piperidin-4-yl)-isoquinolin-6-yl-amine (68). PMB deprotection was carried out as described in general procedure D with a reaction time of 1.5 h to give the products listed in table below as hydrochloride salts.

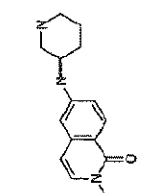
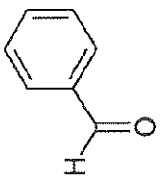
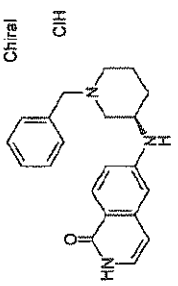
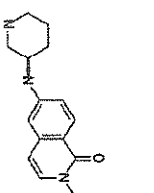
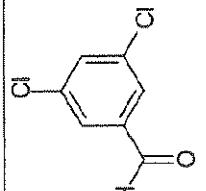
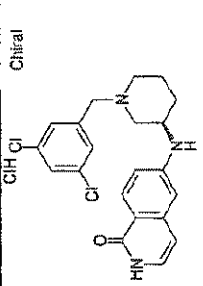
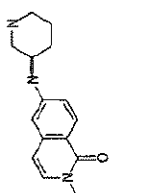
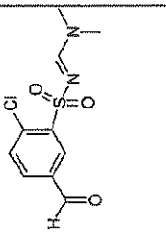
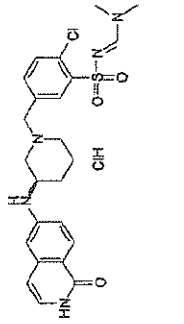
Table 6

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
192				1.07	388.1	B	6-[(R)-1-(2,3,5-Trifluoro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
193				1.04	386.1	B	6-[(R)-1-(3-Chloro-2-fluoro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
194				1.12	384.1	B	6-[(R)-1-(2,3-Difluoro-4-methyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one

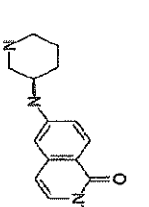
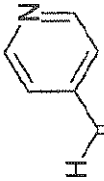
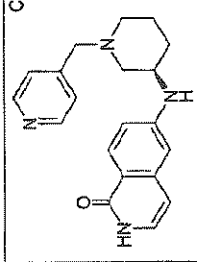
Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
195				0.79	286.2	B	6-((R)-1-Propyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
196				0.83	300.2	B	6-((R)-1-Butyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
197				0.80	300.2	B	6-((R)-1-Isobutyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
198				0.76	298.2	B	6-((R)-1-Cyclopropylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one

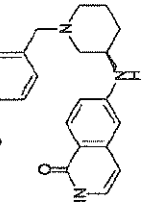
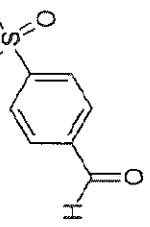
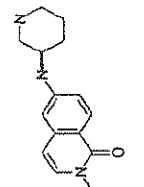
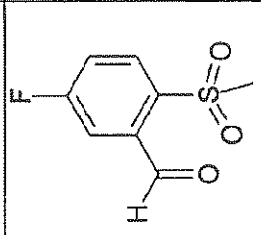
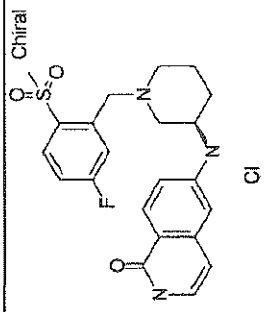
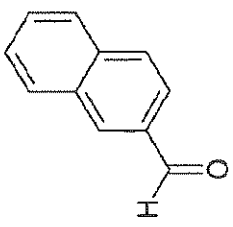
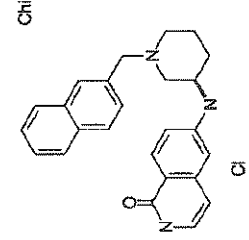
Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
199				0.95	314.2	B	6-[(R)-1-(3-Methyl-butyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
200				0.81	340.1	B	6-[(R)-1-(3,3,3-Trifluoro-propyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
201				1.02	340.2	B	6-((R)-1-Cyclohexylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
202				0.98	326.2	B	6-((R)-1-Cyclohexyl-piperidin-3-ylamino)-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
203				1.05	368.1	B	6-[(R)-1-(4-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
204				1.05	368.1	B	6-[(R)-1-(3-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
205				0.98	368.1	B	6-[(R)-1-(2-Chloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
206				1.17	402.1/404.1	B	6-[(R)-1-(2,4-Dichloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
207				0.92	334.2	B	6-((R)-1-Benzyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
208				1.18	402.1/404.1	B	6-[(R)-1-(3,5-Dichloro-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
209				0.95	502.1	B	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(R)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
210				0.92	498.2	B	N-[1-Dimethylamino-meth-(E)-ylidene]-4-methoxy-3-[(R)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-piperidin-1-ylmethyl]-benzenesulfonamide
211				1.06	348.2	B	6-[(R)-1-(4-Methyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
212				1.13	402.1	B	6-[(R)-1-(4-Trifluoromethyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
213				0.77	355.2	B	6-((R)-1-Pyridin-4-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
214				0.69	355.2	B	6-((R)-1-Pyridin-3-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one
215				0.78	355.2	B	6-((R)-1-Pyridin-2-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
216				0.80	412.1	B	6-[(R)-1-(4-Methanesulfonyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
217				0.92	430.1	B	6-[(R)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-piperidin-3-ylamino]-2H-isoquinolin-1-one
218				1.12	384.2	B	6-((R)-1-Naphthalen-2-ylmethyl-piperidin-3-ylamino)-2H-isoquinolin-1-one

Exam-ple	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
219				0.97	374.1	B	6-[(S)-1-(2,3,5-Trifluoro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
220				1.00	372.1	B	6-[(S)-1-(3-Chloro-2-fluoro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
221				1.06	370.1	B	6-[(S)-1-(2,3-Difluoro-4-methyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
222				0.87	286.2	D	6-((S)-1-Butyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
223				1.32	272.2	D	6-((S)-1-Isopropyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
224				0.94	300.2	D	6-[(S)-1-(1-Ethyl-propyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
225				0.76	286.2	B	6-((S)-1-Isobutyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
226				0.69	284.2	B	6-((S)-1-Cyclopropylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
227				0.89	300.2	B	6-[(S)-1-(3-Methyl-butyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
228				1.04	326.2	B	6-((S)-1-Cyclohexylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
229				0.85	312.2	B	6-((S)-1-Cyclohexyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
230				1.05	354.1/ 356.1	B	6-[(S)-1-(4-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
231				1.03	354.1/ 356.1	B	6-[(S)-1-(3-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
232				0.95	354.1/ 356.1	B	6-[(S)-1-(2-Chloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
233				1.12	388.1	B	6-[(S)-1-(2,4-Dichloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
234				1.16	388.1	B	6-[(S)-1-(3,5-Dichloro-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
235				0.96	488.1	B	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[(S)-3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-pyrrolidin-1-ylmethyl]-benzenesulfonamide
236				1.04	334.2	B	6-[(S)-1-(4-Methyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
237				1.20	388.1	B	6-[(S)-1-(4-Trifluoromethyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
238				0.46	321.2	B	6-((S)-1-Pyridin-4-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
239				0.50	321.2	B	6-((S)-1-Pyridin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
240				0.80	321.2	B	6-((S)-1-Pyridin-2-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
241				0.92	398.1	B	6-[(S)-1-(4-Methanesulfonyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
242				0.78	416.1	B	6-[(S)-1-(5-Fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
243				1.17	370.2	B	6-((S)-1-Naphthalen-2-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
244				1.13	370.2	B	6-((S)-1-Naphthalen-1-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
245				0.43	313.2	A	6-((S)-1-Pyrrolidin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
246				0.69	324.2	A	6-[(S)-1-(1-Methyl-1H-pyrazol-4-ylmethyl)-pyrrolidin-3-ylamino]-2H-isoquinolin-1-one
247				0.83	326.1	A	6-((S)-1-Thiophen-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one
248				0.50	327.2	B	6-((S)-1-Piperidin-3-ylmethyl-pyrrolidin-3-ylamino)-2H-isoquinolin-1-one

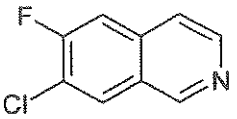
Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
249				1.02	358.1	A	6-[1-(3-Chloro-2-fluoro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
250				1.08	356.2	A	6-[1-(2,3-Difluoro-4-methyl-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
251				0.61	258.2	A	6-(1-Isopropyl-azetidin-3-ylamino)-2H-isoquinolin-1-one
252				0.78	286.2	A	6-[1-(1-Ethyl-propyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
253				0.67	270.2	A	6-(1-Cyclopropylmethyl-azetidin-3-ylamino)-2H-isoquinolin-1-one
254				0.92	286.2	A	6-[1-(3-Methyl-butyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
255				1.06	312.2	A	6-(1-Cyclohexylmethyl-azetidin-3-ylamino)-2H-isoquinolin-1-one
256				0.88	298.2	A	6-(1-Cyclohexyl-azetidin-3-ylamino)-2H-isoquinolin-1-one

Example	Amine	Aldehyde	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
257				1.04	340.2	A	6-[1-(4-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
258				1.08	340.2	A	6-[1-(3-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
259				0.91	340.2	A	6-[1-(2-Chloro-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one
260				0.75	306.2	A	6-(1-Benzyl-azetidin-3-ylamino)-2H-isoquinolin-1-one

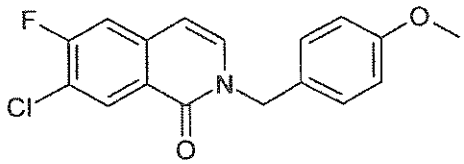
Example	Amine	Aldehyde	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
261				0.92	492.2	A	2-Chloro-N-[1-dimethylamino-meth-(E)-ylidene]-5-[3-(1-oxo-1,2-dihydro-isoquinolin-6-ylamino)-azetidin-1-ylmethyl]-benzenesulfonamide
262				1.03	320.2	A	6-[1-(4-Methyl-benzyl)-azetidin-3-ylamino]-2H-isoquinolin-1-one

263: 6-Fluoro-7-chloro-isoquinoline



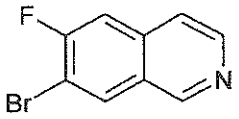
Starting from 4-Fluoro-3-chlorobenzaldehyde, the title compound was synthesized by the protocol described for 6-Bromo-isoquinoline (3). Rt = 0.77 min (Method A). Detected mass: 182.1/184.1 (M+H+).

264: 6-Bromo-7-chloro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one



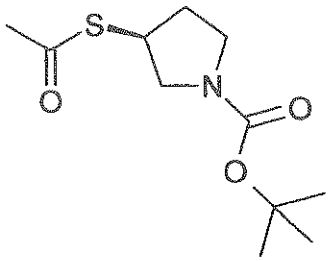
Starting from 6-Bromo-7-chloro-isoquinoline (263), the title compound was prepared by the method described for 6-Bromo-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (13). R_t = 1.66 min (Method C). Detected mass: 318.3 ($M+H^+$).

265: 6-Fluoro-7-bromo-isoquinoline



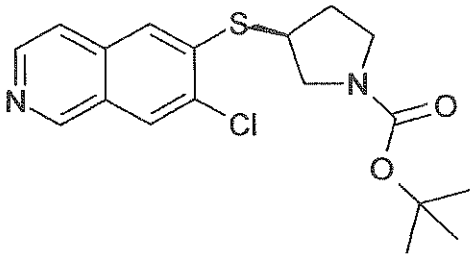
Starting from 4-Fluoro-3-bromobenzaldehyde, the title compound was synthesized by the protocol described for 6-Bromo-isoquinoline (3). R_t = 0.91 min (Method B). Detected mass: 226.0 / 228.0 ($M+H^+$).

266: (S)-3-Acetylsulfanyl-pyrrolidine-1-carboxylic acid tert-butyl ester



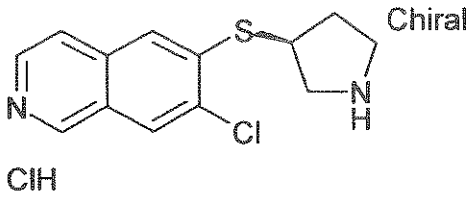
3 g (16 mmol) (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 4.63 g Triphenylphosphine were dissolved in 70 ml THF. Over a period of 10 min 2.8 ml (17.6 mmol) Diethylazodicarboxylate were added at 0°C. After 10 min 1.26 ml (17.6 mmol) Thioacetic acid was added and the mixture was allowed to come to RT and stirring was continued for 18 h. After evaporation the residue was purified over silica gel (heptane to 20% ethyl acetate in heptane) to give 3.5 g of the expected compound.

267: (S)-3-(7-Chloro-isoquinolin-6-ylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



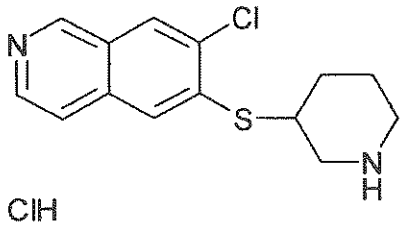
3.5 g (14.2 mmol) (S)-3-Acetylsulfanyl-pyrrolidine-1-carboxylic acid tert-butyl ester (266) were dissolved in 95 ml MeOH and treated with 2.34 g (16.9 mmol) potassium carbonate and stirred over night. After evaporation of all volatiles the residue was taken up in 60 ml of degassed DMF, 1.27 g (15 mmol) 6-Fluoro-7-chloroisoquinoline and 2.25 ml (15 mmol) DBU were added. After 3 h at RRT the mixture was concentrated, taken up in ethyl acetate and washed with brine. The organic phases were dried over Sodium sulfate and evaporated. Purification over silica gel (10% to 40% ethyl acetate in heptane) gave 4.5 g of the expected compound.

268: 7-Chloro-6-((S)-pyrrolidin-3-ylsulfanyl)-isoquinoline hydrochloride



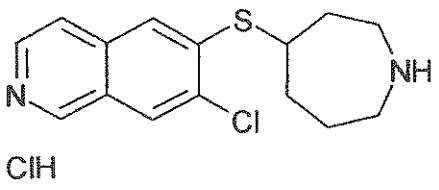
4.5 g (6.1 mmol) (S)-3-(7-Chloro-isoquinolin-6-ylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester in 15 ml dichloromethane and 7.5 ml 6N HCl in isopropanol were stirred over night. After evaporation water was added and lyophilized. 1.98 g of 7-Chloro-6-((S)-pyrrolidin-3-ylsulfanyl)-isoquinoline hydrochloride were obtained. R_t = 0.76 min (Method B). Detected mass: 264.1/266.1 ($M+H^+$).

269: (Rac)-7-Chloro-6-(piperidin-3-ylsulfanyl)-isoquinoline hydrochloride



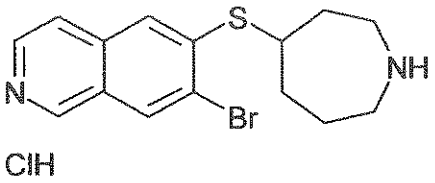
Starting from 6-Fluoro-7-chloroisoquinoline (263) and 3-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester (Rac)-7-Chloro-6-(piperidin-3-ylsulfanyl)-isoquinoline could be obtained as the hydrochloride as described for compound (268). R_t = 0.80 min (Method B). Detected mass: 279.1/281.1 ($M+H^+$).

270: (Rac)-6-(Azepan-4-ylsulfanyl)-7-chloro-isoquinoline hydrochloride



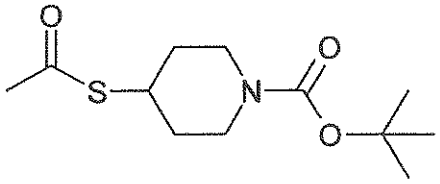
Starting from 6-Fluoro-7-chloroisoquinoline (263) and 4-Hydroxy-azepane-1-carboxylic acid tert-butyl ester (Rac)-6-(Azepan-4-ylsulfanyl)-7-chloro-isoquinoline could be obtained as the hydrochloride as described for compound (268). R_t = 0.83 min (Method B). Detected mass: 293.1/295.1 ($M+H^+$).

271: (Rac)-6-(Azepan-4-ylsulfanyl)-7-bromo-isoquinoline hydrochloride



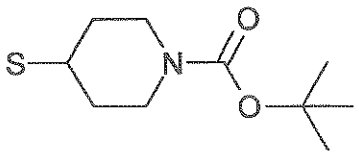
Starting from 6-Fluoro-7-bromoisoquinoline (265) and 4-Hydroxy-azepane-1-carboxylic acid tert-butyl ester (Rac)-6-(Azepan-4-ylsulfanyl)-7-bromo-isoquinoline could be obtained as the hydrochloride as described for compound (268). R_t = 0.83 min (Method B). Detected mass: 337.1 ($M+H^+$).

272: 4-Acetylsulfanyl-piperidine-1-carboxylic acid tert-butyl ester



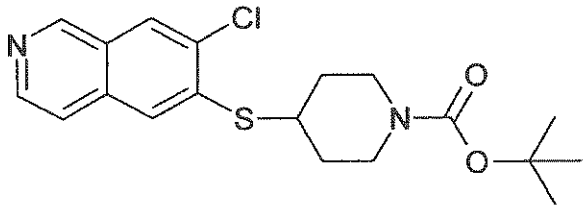
2.2 g (19.3 mmol) Potassium thioacetate and 2.65 g (10 mmol) 4-Bromo-piperidine-1-carboxylic acid tert-butyl ester were dissolved in 50 ml of DMF and stirred at 100°C vor 4 h. The mixture was taken up in ethyl acetate and washed with brine. The organic phases were dried over Sodium sulfate and evaporated. Purification over silica gel (10% to 20% ethyl acetate in heptane) gave 2.15 g of the expected compound.

273: 4-Mercapto-piperidine-1-carboxylic acid tert-butyl ester



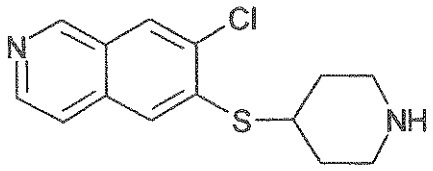
2.15 g 4-Acetylsulfanyl-piperidine-1-carboxylic acid tert-butyl ester (272) were dissolved in 84 ml MeOH and treated with 2.1 g (55.5 mmol) sodium borohydride at 0°C. after stirring for 2 h at RT all volatiles were removed in vacuo and to the residue was added slowly water and 2.3 g (11 mmol) citric acid monohydrate. Extraction with dichloromethane, drying with Sodium sulfate and evaporation gave 1.78 g of crude 4-Mercapto-piperidine-1-carboxylic acid tert-butyl ester

274: 4-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester



To 1.78 g of crude 4-Mercapto-piperidine-1-carboxylic acid tert-butyl ester (273) were dissolved in 20 ml degassed DMF was added 1.3 g (7.1 mmol) 6-Fluoro-7-chloroisoquinoline (263) and 1.23 ml (8.2 mmol) DBU. After stirring for 90 min at 80°C the solvent was evaporated. The residue was taken up in ethyl acetate and washed with brine. The organic phases were dried over Sodium sulfate and evaporated. Purification over silica gel (40% to 60% ethyl acetate in heptane) gave 1.98 g of the expected compound.

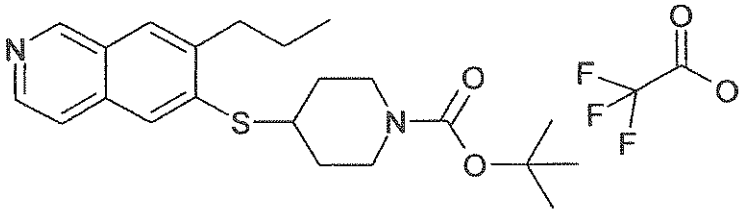
275: 7-Chloro-6-(piperidin-4-ylsulfanyl)-isoquinoline hydrochloride



ClH

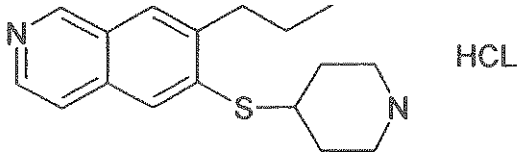
1.98 g of 4-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester (274) were dissolved in7 ml dichloromethane and 5 ml 6N HCl in isopropanol. After 18 h at RT the volatiles were evaporated, water was added and lyophilized. 1.85 g of the expected compound were obtained. R_t = 0.70 min (Method B). Detected mass: 279.1/281.1 ($M+H^+$).

276: 4-(7-Propyl-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester trifluoroacetate



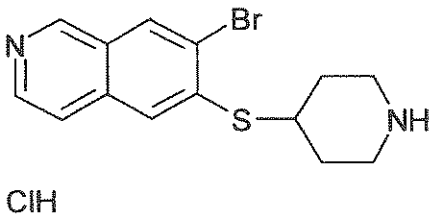
To 200 mg (0.52 mmol) 4-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester (274) dissolved in 5 ml THF and 1ml NMP were added 20 mg (0.055 mmol) Ferric (III) acetylacetonate. To the red solution 0.3 ml of propylmagnesium-chloride (2M in THF) were added and 2 min stirred at RT. 1 ml 1N HCl and 20 ml diethyl ether were added and the organic layer was washed with brine. The organic phases were dried over Sodium sulfate and evaporated. The residue was purified by HPLC. 85 mg of 4-(7-Propyl-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester could be obtained as the trifluoroacetate.

277: 6-(Piperidin-4-ylsulfanyl)-7-propyl-isoquinoline hydrochloride



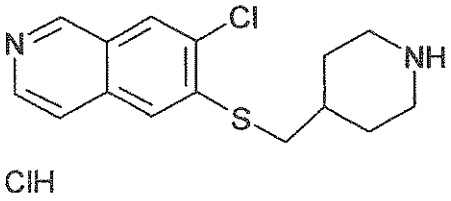
85 mg (107 mmol) 4-(7-Propyl-isoquinolin-6-ylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester trifluoroacetate (276) were stirred in 6N HCl in iPrOH for 1h at RT. After evaporation water was added and lyophilized. 42 mg of 6-(Piperidin-4-ylsulfanyl)-7-propyl-isoquinoline hydrochloride were obtained. R_t = 0.94 min (Method B). Detected mass: 287.1 ($M+H^+$).

278: 7-Bromo-6-(piperidin-4-ylsulfanyl)-isoquinoline hydrochloride



Starting from 6-Fluoro-7-bromoisoquinoline (265) 7-Bromo-6-(piperidin-4-ylsulfanyl)-isoquinoline could be obtained as the hydrochloride as described for compound (275). R_t = 0.26 min (Method B). Detected mass: 325.3 ($M+H^+$).

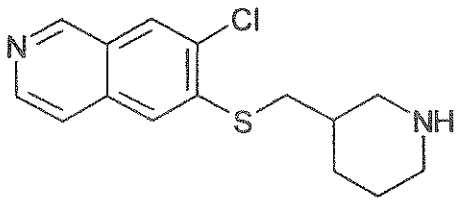
279: 7-Chloro-6-(piperidin-4-ylmethylsulfanyl)-isoquinoline hydrochloride



Starting from 6-Fluoro-7-chloroisoquinoline (263) and 4-Bromomethyl-piperidine-1-carboxylic acid tert-butyl ester 7-Chloro-6-(piperidin-4-ylmethylsulfanyl)-isoquinoline

could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.78 min (Method B). Detected mass: 293.1/295.1 ($M+H^+$).

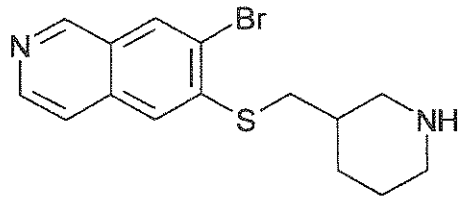
280: 7-Chloro-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline hydrochloride



ClH

Starting from 6-Fluoro-7-chloroisoquinoline (263) and 3-Bromomethyl-piperidine-1-carboxylic acid tert-butyl ester 7-Chloro-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.75 min (Method B). Detected mass: 293.1/295.1 ($M+H^+$).

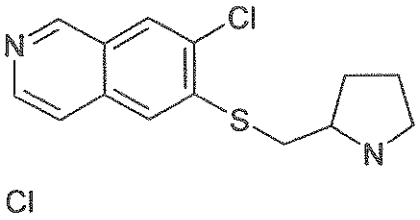
281: 7-Bromo-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline hydrochloride



ClH

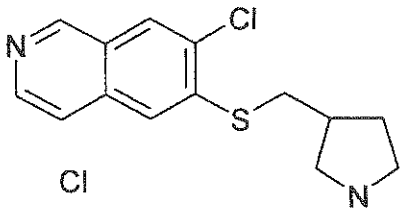
Starting from 7-Bromo-6-chloroisoquinoline (265) and 3-Bromomethyl-piperidine-1-carboxylic acid tert-butyl ester 7-Bromo-6-(piperidin-3-ylmethylsulfanyl)-isoquinoline could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.82 min (Method B). Detected mass: 337.1 ($M+H^+$).

282: 7-Chloro-6-(pyrrolidin-2-ylmethylsulfanyl)-isoquinoline hydrochloride



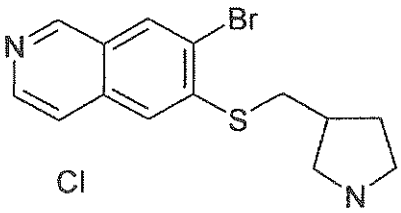
Starting from 6-Chloro-7-chloroisoquinoline (263) and 2-Bromomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester 7-Chloro-6-(pyrrolidin-2-ylmethylsulfanyl)-isoquinoline could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.85 min (Method B). Detected mass: 279.1/281.2 ($M+H^+$).

283: 7-Chloro-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline hydrochloride



Starting from 6-Fluoro-7-chloroisoquinoline (263) and 3-Bromomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester 7-Chloro-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.87 min (Method B). Detected mass: 279.1/281.2 ($M+H^+$).

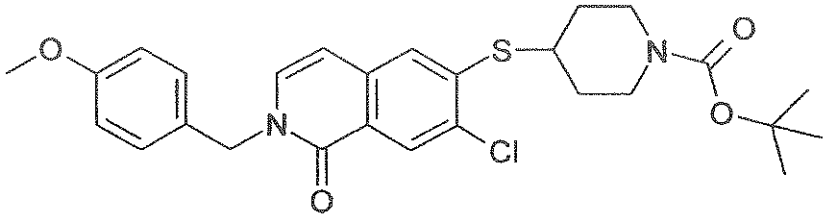
284: 7-Bromo-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline hydrochloride



Starting from 7-Bromo-6-chloroisoquinoline (265) and 3-Bromomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester 7-Bromo-6-(pyrrolidin-3-ylmethylsulfanyl)-isoquinoline

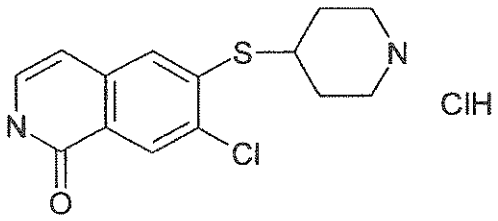
could be obtained according to the procedures described for 272, 267, 268 as the hydrochloride. R_t = 0.72 min (Method B). Detected mass: 323.1/325.2 ($M+H^+$).

285: 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester



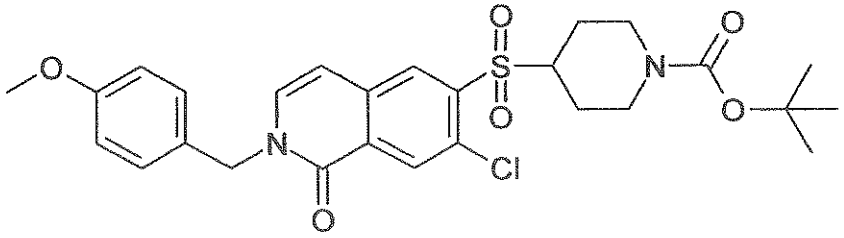
Starting from 7-Chloro-6-fluoro-2-(4-methoxy-benzyl)-2H-isoquinolin-1-one (264) 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester could be obtained as described for compound (274).
7-Chloro-6-(piperidin-4-ylsulfanyl)-2H-isoquinolin-1-one.

286: 7-Chloro-6-(piperidin-4-ylsulfanyl)-2H-isoquinolin-1-one hydrochloride



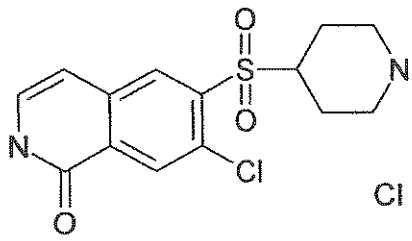
188 mg 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester (285) in 2 ml TFA were heated in the microwave at 150 °C for 1.5 h. After evaporation the residue is taken up in 1N HCl and extracted with dichloromethane and lyophilized. 79 mg of 7-Chloro-6-(piperidin-4-ylsulfanyl)-2H-isoquinolin-1-one could be obtained as the hydrochloride. R_t = 0.93 min (Method B). Detected mass: 295.1/297.1 ($M+H^+$).

287: 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester



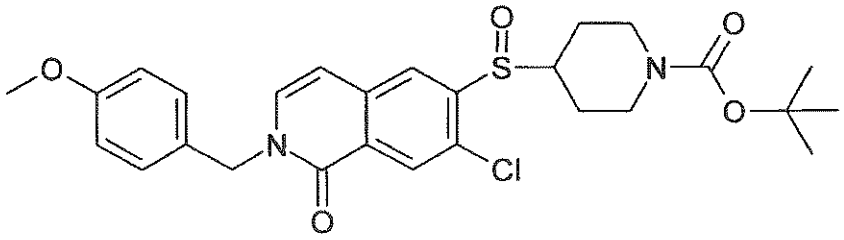
103 mg 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester (285) in 2 ml of dichloromethane were treated with 123 mg *m*-Chloroperbenzoic acid in total over 2 h. The mixture was diluted with dichloromethane and washed with sodium hydrogen carbonate solution and brine. After drying over sodium sulfate all volatiles were evaporated and the crude product purified by chromatography 2:1 (ethyl acetate/Heptane) to obtain 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester as an off white solid.

288: 7-Chloro-6-(piperidine-4-sulfonyl)-2H-isoquinolin-1-one hydrochloride



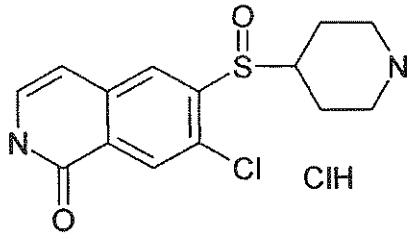
190 mg 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfonyl]-piperidine-1-carboxylic acid tert-butyl ester (287) were dissolved in 2 ml of TFA and heated in a microwave at 150 °C for 50 min in total. After evaporation the mixture was dissolved in 1 N HCl und extracted with dichloromethane and lyophilized. 58 mg of 7-Chloro-6-(piperidine-4-sulfonyl)-2H-isoquinolin-1-one could be obtained as the hydrochloride. R_t = 0.81 min (Method B). Detected mass: 327.1/329.1 ($M+H^+$).

289: 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester



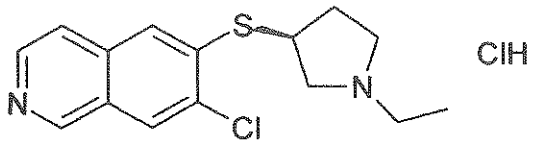
206 mg 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinolin-6-ylsulfanyl]-piperidine-1-carboxylic acid tert-butyl ester (285) in 6 ml of dichloromethane were treated with 83 mg *m*-Chloroperbenzoic acid over 2 h. The mixture was diluted with dichloromethane and washed with sodium hydrogen carbonate solution and brine. After drying over sodium sulfate all volatiles were evaporated and the crude product purified by chromatography 2:1 (ethyl acetate/Heptane) to obtain 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester as an off white solid.

290: 7-Chloro-6-(piperidine-4-sulfinyl)-2H-isoquinolin-1-one hydrochloride



180 mg 4-[7-Chloro-2-(4-methoxy-benzyl)-1-oxo-1,2-dihydro-isoquinoline-6-sulfinyl]-piperidine-1-carboxylic acid tert-butyl ester (289) were dissolved in 2 ml of TFA and heated in a microwave at 150 °C for 40 min in total. After evaporation the mixture was dissolved in 1 N HCl und extracted with dichloromethane and lyophilized. 58 mg of 7-Chloro-6-(piperidine-4-sulfinyl)-2H-isoquinolin-1-one could be obtained as the hydrochloride. R_t = 0.78 min (Method B). Detected mass: 311.1/313.1 ($M+H^+$).

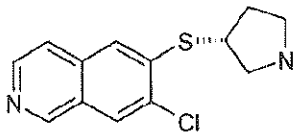
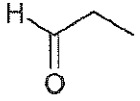
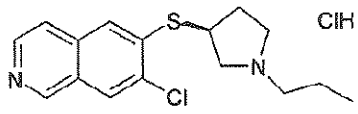
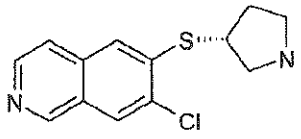
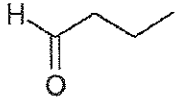
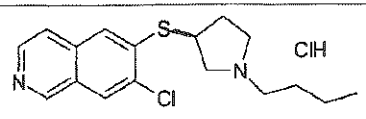
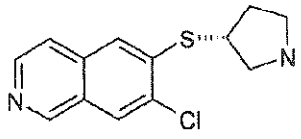
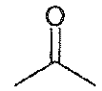
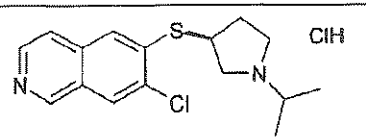
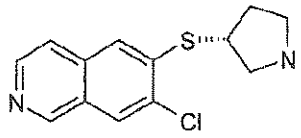
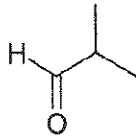
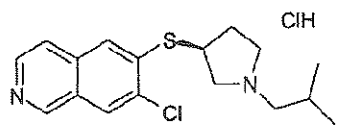
291: 7-Chloro-6-((S)-1-ethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline hydrochloride



To 36 mg (0.12 mmol) 7-Chloro-6-((S)-pyrrolidin-3-ylsulfanyl)-isoquinoline hydrochloride (268) in 4 ml THF was added (0.12 mmol) acetaldehyde and 104 mg MP-Cyano borohydride resin (2.3 mmol/g) and stirred over night. After filtration from the resin and evaporation the residue was purified by preparative HPLC (Method A) to obtain 7-Chloro-6-((S)-1-ethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline as the trifluoroacetate. The obtained trifluoroacetate was dissolved in 6 N HCl in isopropanol and evaporated. Final lyophilization gave 12 mg of the title compound as the hydrochloride R_t = 0.71 min (Method B). Detected mass: 293.1/295.1 ($M+H^+$).

The compounds described in the following table were obtained in an analogous fashion as described for 291 (Table 7).

Table 7

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
292				0.80	307.1/ 309.1	B	7-Chloro-6-((S)-1-propyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
293				0.95	321.1.2/ 323.1	B	6-((S)-1-Butyl-pyrrolidin-3-ylsulfanyl)-7-chloro-isoquinoline
294				0.82	307.1/ 309.1	B	7-Chloro-6-((S)-1-isopropyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
295				0.89	321.1.2/ 323.1	B	7-Chloro-6-((S)-1-isobutyl-pyrrolidin-3-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
296			Chiral ClH	0.81	319.1/ 321.1	B	7-Chloro-6-((S)-1-cyclopropyl-methyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
298			ClHChiral	1.01	335.1/ 337.1	B	7-Chloro-6-[(S)-1-(3-methyl-butyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
299			Chiral ClH	0.92	361.0	B	7-Chloro-6-[(S)-1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline

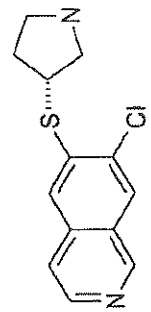
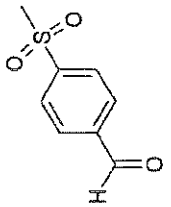
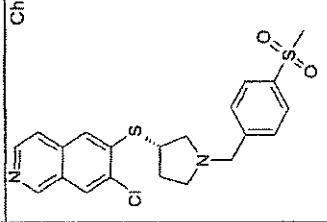
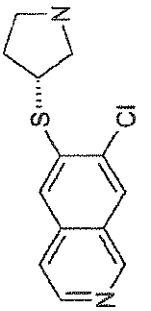
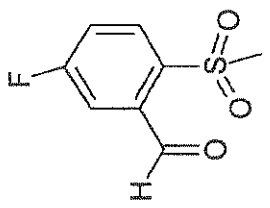
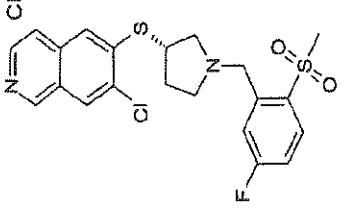
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
300				1.07	361.2/ 363.2	B	7-Chloro-6-((S)-1-cyclohexylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
301				0.95	347.1/ 349.1	B	7-Chloro-6-((S)-1-cyclohexyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
302				1.12	389.2/ 391.2	B	7-Chloro-6-[(S)-1-(4-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
303				1.15	389.0	B	7-Chloro-6-[(S)-1-(3-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
304				1.06	389.1	B	7-Chloro-6-[(S)-1-(2-chloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
305				1.15	423.0	B	7-Chloro-6-[(S)-1-(2,4-dichloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
306				1.01	355.1/3 57.1	B	6-((S)-1-Benzyl-pyrrolidin-3-ylsulfanyl)-7-chloro-isoquinoline
307				1.15	423.1/4 27.1	B	7-Chloro-6-[(S)-1-(3,5-dichloro-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
308				0.99	523.1/5 25.1	B	2-Chloro-5-[(S)-3-(7-chloro-isoquinolin-6-ylsulfanyl)-pyrroiidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)- ylidene]-benzenesulfonamide

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
309				0.95	519.1/5 21.2	B	3-[(S)-3-(7-Chloro-isoquinolin-6-ylsulfanyl)-pyrrolidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide
310				1.06	369.1/3 71.1	B	7-Chloro-6-[(S)-1-(4-methyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
311				1.13	423.1/4 25.1	B	7-Chloro-6-[(S)-1-(4-trifluoromethyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
312				0.72	356.1/3 58.1	B	7-Chloro-6-((S)-1-pyridin-4-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
313				0.75	356.1/3 58.1	B	7-Chloro-6-((S)-1-pyridin-3-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
314				0.82	356.1/3 58.1	B	7-Chloro-6-((S)-1-pyridin-2-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
315				0.87	433.1/4 35.1	B	7-Chloro-6-[(S)-1-(4-methanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
316				0.95	451.1/4 53.1	B	7-Chloro-6-[(S)-1-(5-fluoro-2-methanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
317				1.16	487.1/489.1	B	7-Chloro-6-[(S)-1-(4-trifluoromethanesulfonyl-benzyl)-pyrrolidin-3-ylsulfanyl]-isoquinoline
317				1.14	405.1/407.1	BB	7-Chloro-6-((S)-1-naphthalen-2-ylmethyl-pyrrolidin-3-ylsulfanyl)-isoquinoline
318				0.77	307.1/309.1	B	7-Chloro-6-(1-ethyl-piperidin-4-ylsulfanyl)-isoquinoline

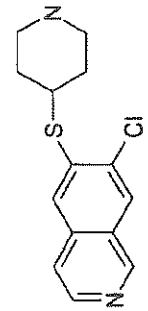
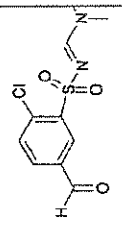
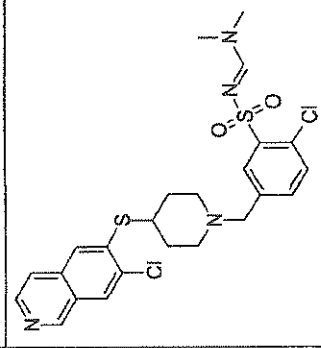
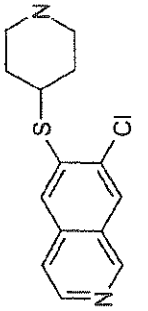
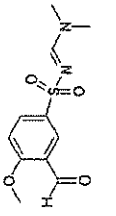
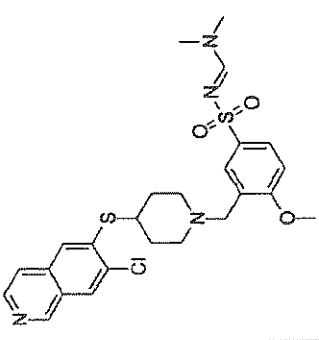
Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
319				0.85	321.1/3 23.1		7-Chloro-6-(1-propyl-piperidin-4-ylsulfanyl)-isoquinoline
320				0.92	335.1/3 37.1	B	6-(1-Butyl-piperidin-4-ylsulfanyl)-7-chloro-isoquinoline
321				1.10	321.1/3 23.1	B	7-Chloro-6-(1-isopropyl-piperidin-4-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
322				0.92	335.1/337.1	B	7-Chloro-6-(1-isobutyl-piperidin-4-ylsulfanyl)-isoquinoline
323				0.93	333.1/335.1	B	7-Chloro-6-(1-cyclopropylmethyl-piperidin-4-ylsulfanyl)-isoquinoline
324				1.07	349.1/351.2	B	7-Chloro-6-[1-(3-methyl-butyl)-piperidin-4-ylsulfanyl]-isoquinoline

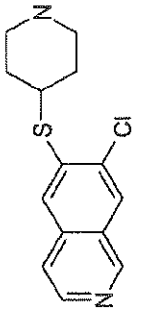
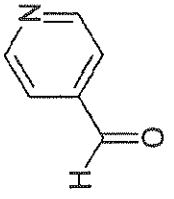
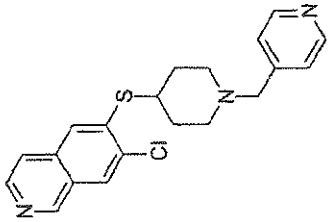
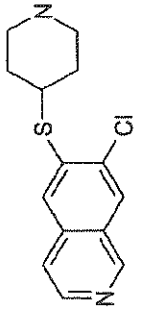
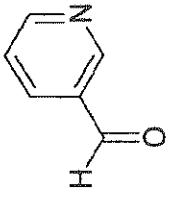
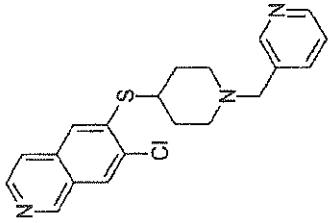
Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
325				0.90	375.1/3 77.1	B	7-Chloro-6-[1-(3,3,3-trifluoro-propyl)-piperidin-4-ylsulfanyl]-isoquinoline
326				1.08	375.2/3 77.2	B	7-Chloro-6-(1-cyclohexylmethyl-piperidin-4-ylsulfanyl)-isoquinoline
327				0.97	361.1/3 63.2	B	7-Chloro-6-(1-cyclohexyl-piperidin-4-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
328				1.10	403.1/405.1	B	7-Chloro-6-[1-(4-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
329				1.09	403.1/405.1	B	7-Chloro-6-[1-(3-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
330				1.05	403.1/405.1	B	7-Chloro-6-[1-(2-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
331				1.15	437.1	B	7-Chloro-6-[1-(2,4-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
332				1.09	369.1/3 71.1	B	6-(1-Benzyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline
333				1.20	437.1	B	7-Chloro-6-[1-(3,5-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

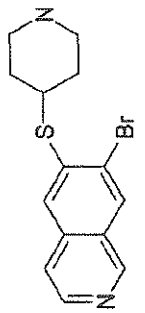
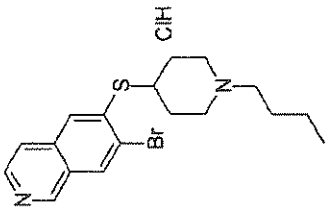
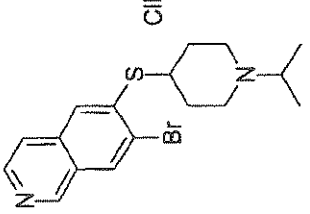
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
334				1.05	537.1/539.1	B	2-Chloro-5-[3-(7-chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-benzenesulfonamide
335				1.00	533.2/535.1	B	3-[3-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide

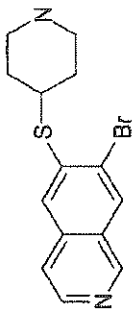
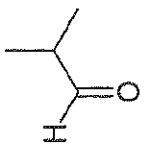
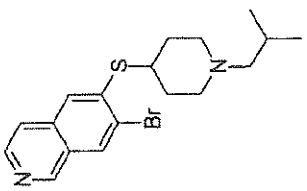
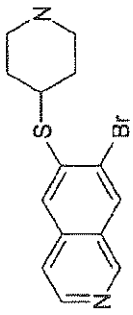
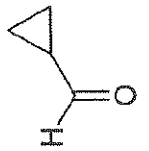
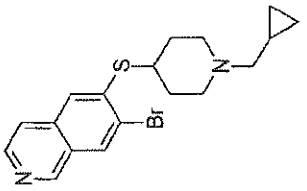
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
336				1.07	383.1/3 85.2	B	7-Chloro-6-[1-(4-methyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
337				1.19	437.1/4 39.1	B	7-Chloro-6-[1-(4-trifluoromethyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
338				0.76	370.1	B	7-Chloro-6-(1-pyridin-4-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline
339				0.75	370.1/372.1	B	7-Chloro-6-(1-pyridin-3-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline

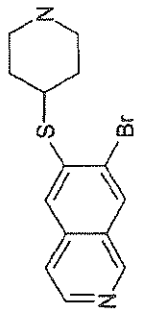
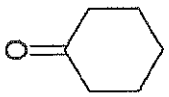
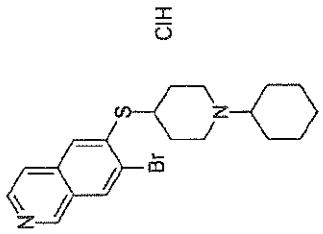
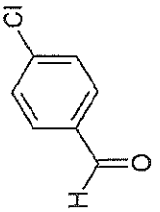
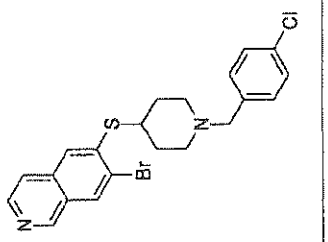
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
340				0.95	370.1/372.1	B	7-Chloro-6-(1-pyridin-2-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline
341				0.93	447.1/449.1	B	6-Chloro-7-(pyrrolidin-2-ylmethylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
342				0.81	351.1	B	7-Bromo-6-(1-ethyl-piperidin-4-ylsulfanyl)-isoquinoline
343				0.87	365.1	B	7-Bromo-6-(1-propyl-piperidin-4-ylsulfanyl)-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
344				0.95	379.1/3 81.1	B	7-Bromo-6-(1-butyl-piperidin-4-ylsulfanyl)-isoquinoline
345				0.85	365.1/3 67.1	B	7-Bromo-6-(1-isopropyl-piperidin-4-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
346				1.00	379.1/3 81.1	B	7-Bromo-6-(1-isobutyl-piperidin-4-ylsulfanyl)-isoquinoline
347				0.95	377.1/3 79.1	B	7-Bromo-6-(1-cyclopropylmethyl-piperidin-4-ylsulfanyl)-isoquinoline

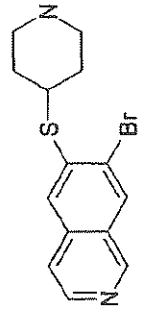
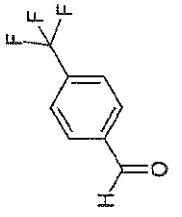
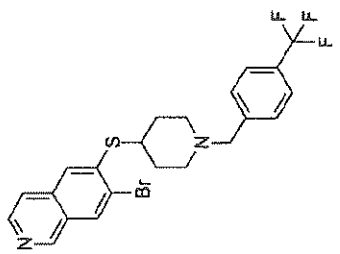
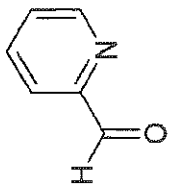
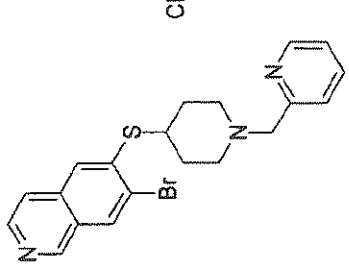
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
348				1.02	393.1	B	7-Bromo-6-[1-(3-methyl-butyl)-piperidin-4-ylsulfanyl]-isoquinoline
349				0.90	419.0	B	7-Bromo-6-[1-(3,3,3-trifluoro-propyl)-piperidin-4-ylsulfanyl]-isoquinoline
350				1.10	419.1	B	7-Bromo-6-(1-cyclohexylmethyl-piperidin-4-ylsulfanyl)-isoquinoline

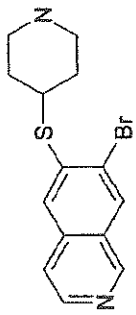
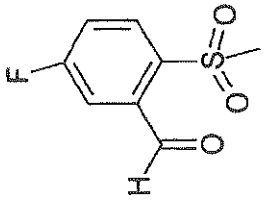
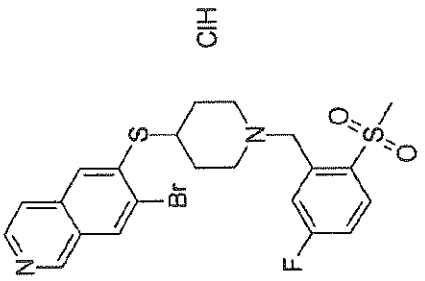
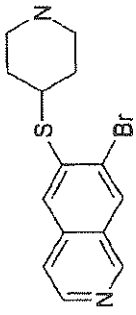
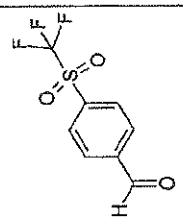
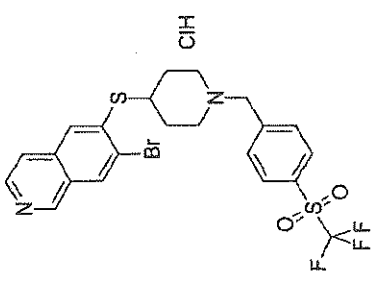
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
351				0.99	405.1	B	7-Bromo-6-(1-cyclohexyl-piperidin-4-ylsulfanyl)-isoquinoline
352				1.13	449.1	B	7-Bromo-6-[1-(4-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline

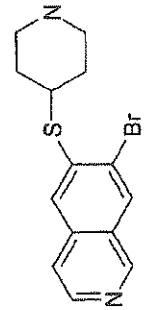
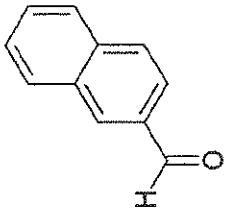
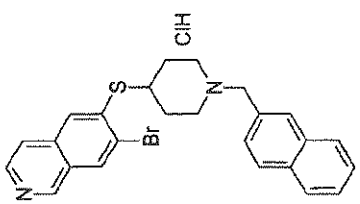
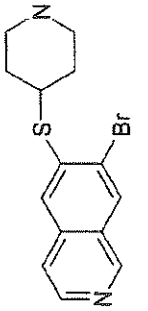
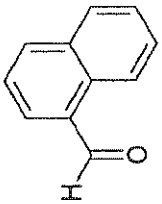
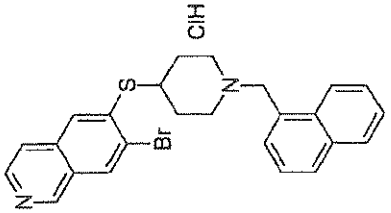
Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
353				1.10	449.0	B	7-Bromo-6-[1-(3-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline
354				1.06	449.0	B	7-Bromo-6-[1-(2-chloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline

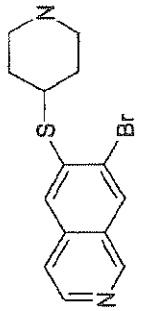
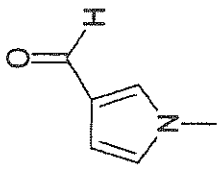
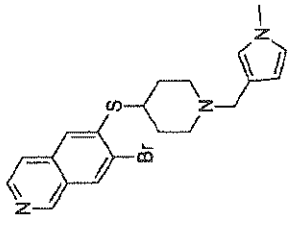
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
355			ClH	1.16	481.1/483.1/485.1	B	7-Bromo-6-[1-(2,4-dichloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline
356			ClH	1.05	413.1	B	7-Bromo-6-[1-benzyl-piperidin-4-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
357				1.20	483.0/485.0	B	7-Bromo-6-[1-(3,5-dichloro-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline
358				1.03	581.1/583.1	B	2-Chloro-5-[4-(7-bromo-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-(dimethylaminomethylene)-(E)-ylidene]-benzene-sulfonamide
359				1.05	579.1	B	3-[4-(7-Bromo-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-dimethylamino-meth(E)-ylidene-4-methoxy benzene-sulfonamide

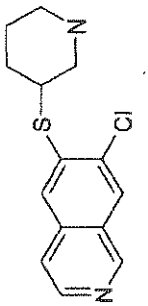
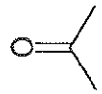
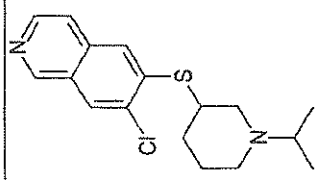
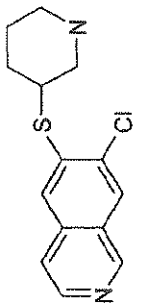
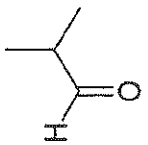
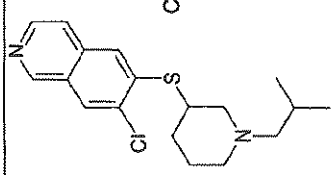
Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
360			 ClH	1.18	481.0	B	7-Bromo-6-[1-(4-trifluormethyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline
361			 ClH	0.89	414.1	B	7-Bromo-6-(1-pyridin-2-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
362				1.00	509.1	B	7-Bromo-6-[1-(5-fluoro-2-methanesulfonyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline
363				1.22	545.0	B	7-Bromo-6-[1-(4-trifluoromethanesulfonyl-benzyl)-piperidin-4-ylsulfanyl]-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H+]	LCMS Method	Chemical name
364				1.18	463.1/465.1	B	7-Bromo-6-(1-naphthalen-2-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline
365				1.16	463.1	B	7-Bromo-6-(1-naphthalen-1-ylmethyl-piperidin-4-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
366				1.00	416.1	B	7-Bromo-6-[1-(1-methyl-1H-pyrrol-3-ylmethyl)-piperidin-4-ylsulfanyl]-isoquinoline
367				0.86	417.1	B	7-Bromo-6-[1-(1-methyl-1H-pyrazol-4-ylmethyl)-piperidin-4-ylsulfanyl]-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
368				0.95	307.1/309.1	B	7-Chloro-6-(1-ethyl-piperidin-3-ylsulfanyl)-isoquinoline
369				0.99	321.1/323.1	B	7-Chloro-6-(1-propyl-piperidin-3-ylsulfanyl)-isoquinoline
370				0.96	335.1/337.2	B	6-(1-Butyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
371				0.84	321.1/323.1	B	7-Chloro-6-(1-isopropyl-piperidin-3-ylsulfanyl)-isoquinoline
372				0.90	335.1	B	7-Chloro-6-(1-isobutyl-piperidin-3-ylsulfanyl)-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
373				0.90	333.1/3 35.2	B	7-Chloro-6-(1-cyclopropylmethyl-piperidin-3-ylsulfanyl)-isoquinoline
374				1.02	349.1	B	7-Chloro-6-[1-(3-methyl-butyl)-piperidin-3-ylsulfanyl]-isoquinoline

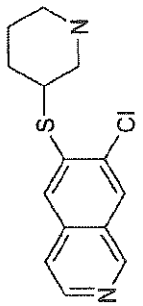
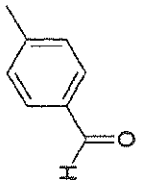
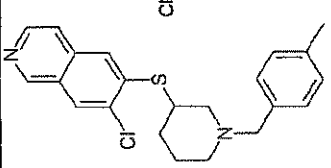
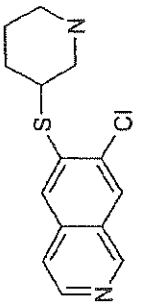
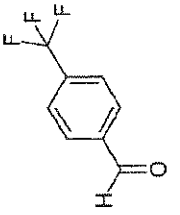
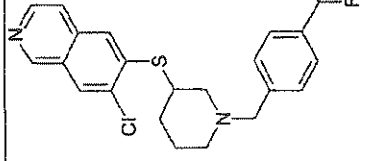
Example	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
375				1.10	375.4/377.4	B	7-Chloro-6-[1-(3,3,3-trifluoro-propyl)-piperidin-3-ylsulfanyl]-isoquinoline
376				1.26	375.5/377.5	B	7-Chloro-6-(1-cyclohexylmethyl-piperidin-3-ylsulfanyl)-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
377				1.04	361.1/3 63.1	B	7-Chloro-6-(1-cyclohexyl-piperidin-3-ylsulfanyl)-isoquinoline
378				1.17	403.0	B	7-Chloro-6-[1-(4-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
379				1.09	403.0	B	7-Chloro-6-[1-(3-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
380				1.12	403.1	B	7-Chloro-6-[1-(2-chloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
381				1.07	369.1/3 71.1	B	6-(1-Benzyl-piperidin-3-ylsulfanyl)-7-chloro-isoquinoline
382				1.21	437.1	B	7-Chloro-6-[1-(3,5-dichloro-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example	Amine	Carbonyl compound	Product	R_t [min]	Mass $[M+H^+]$	LCMS Method	Chemical name
383				1.07	537.1/539.2	B	2-Chloro-5-[3-(7-chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-benzenesulfonamide
384				1.00	533.2	B	3-[3-(7-Chloro-isoquinolin-6-ylsulfanyl)-piperidin-1-ylmethyl]-N-[1-dimethylamino-meth-(E)-ylidene]-4-methoxy-benzenesulfonamide

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
385				1.07	383.1/3 85.2	B	7-Chloro-6-[1-(4-methyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline
386				1.16	437.1/4 39.2	B	7-Chloro-6-[1-(4-trifluoromethyl-benzyl)-piperidin-3-ylsulfanyl]-isoquinoline

Example.	Amine	Carbonyl compound	Product	R_t [min]	Mass [M+H$^+$]	LCMS Method	Chemical name
387				0.85	370.1/372.2	B	7-Chloro-6-(1-pyridin-4-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline
388				0.83	370.1/372.2	B	7-Chloro-6-(1-pyridin-3-ylmethyl-piperidin-3-ylsulfanyl)-isoquinoline

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
99	++++
166	++++
169	++++
195	++++
196	+++++
199	+++++
207	+++++
213	++++
215	++++
218	+++++
220	+++++
226	+++++
234	++++
236	+++++
243	+++++

Compound No.	pIC50
246	++++
248	++++
249	+++++
251	++++
253	++++
259	+++++
269	+++++
271	+++++
277	+++++
279	++++
286	+++++
288	+++++
290	++++

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

+: $pIC50 \leq 3.0$

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

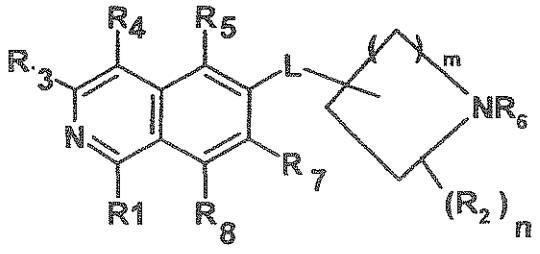
+++ $4.0 \leq pIC_{50} < 5.0$

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

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

Claims

1. A compound of the formula (I)



(I)

wherein

R_1 is H, OH or NH_2;

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

R_3 is

H,

halogen,

$(C_1$-$C_6)$alkyl,

$(C_1$-$C_6)$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,
$(C_2$-$C_6)$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 is
H;

R',
(C_1-C_8)alkyl,
(C_1-C_6)alkylene-R',
(C_1-C_6)alkylene-O-(C_1-C_6)alkyl,
(C_1-C_6)alkylene-O-R',
(C_1-C_6)alkylene-CH[R']$_2$,
(C_1-C_6)alkylene-C(O)-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';

R_7 is
H,
halogen,
CN,
NO_2,

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

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

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

R',

$(C_2\text{-}C_6)$alkenylene-$(C_6\text{-}C_{10})$aryl,

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

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

NH_2,

NH-R',

NH-SO_2H,

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

NH-SO_2-R',

SO_2-NH_2,

SO_2-NHR',

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

NH-C(O)-R',

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

C(O)OH, or

C(O)O-$(C_1\text{-}C_6)$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]-$(CH_2)p$ or N[$(C_1\text{-}C_3)$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;

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,

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

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

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

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

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

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

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

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

wherein in residues R_4, R_5, 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 $CON(CH_3)_2$;

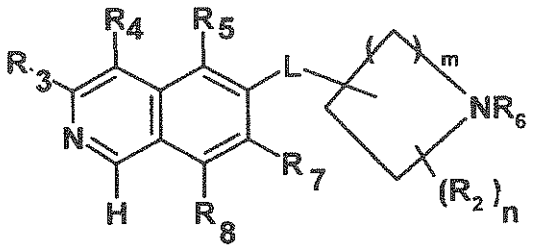
wherein in residues R_2 to R_8 alkyl or alkylene can optionally be substituted one or more times by halogen;

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, $C(O)\text{-}(C_1\text{-}C_6)$alkyl, $C(O)\text{-}(C_6\text{-}C_{10})$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-$C(O)\text{-}(C_1\text{-}C_6)$alkyl, PO_3H_2, SO_3H, $SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$alkyl, $SO_2N[(C_1\text{-}C_6)alkyl]_2$, S-$(C_1\text{-}C_6)$alkyl; SO-$(C_1\text{-}C_6)$alkyl, SO_2-$(C_1\text{-}C_6)$alkyl, $SO_2\text{-}N{=}CH\text{-}N[(C_1\text{-}C_6)alkyl]_2$, $C(NH)(NH_2)$, NH_2, NH-$(C_1\text{-}C_6)$alkyl, $N[(C_1\text{-}C_6)alkyl]_2$, NH-$C(O)\text{-}(C_1\text{-}C_6)$alkyl, NH-$C(O)O\text{-}(C_1\text{-}C_6)$alkyl, NH-$SO_2\text{-}(C_1\text{-}C_6)$alkyl, NH-$SO_2\text{-}(C_6\text{-}C_{10})$aryl, NH-$SO_2\text{-}(C_5\text{-}C_{10})$heterocyclyl, $N(C_1\text{-}C_6)alkyl\text{-}C(O)\text{-}(C_1\text{-}C_6)$alkyl, $N(C_1\text{-}C_6)alkyl\text{-}C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $N(C_1\text{-}C_6)alkyl\text{-}C(O)\text{-}NH\text{-}(C_1\text{-}C_6)$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, $C(O)O\text{-}(C_1\text{-}C_6)$alkyl, $CONH_2$, $(C_1\text{-}C_6)alkylene\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)alkylene\text{-}O\text{-}(C_6\text{-}C_{10})$aryl, or O-$(C_1\text{-}C_6)alkylene\text{-}(C_6\text{-}C_{10})$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-C_{10})aryl and (C_5-C_{10})heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group;

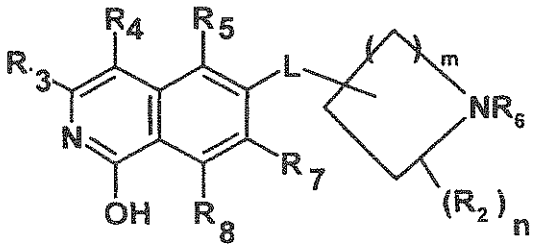
or their stereoisomeric and/or tautomeric forms and/or their pharmaceutically acceptable salts.

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



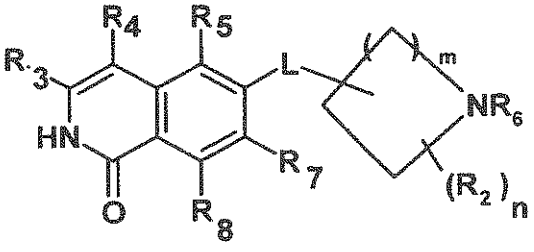
(II)

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, $(C_1$-$C_4)$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-$(C_5$-$C_6)$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 $(C_1$-$C_4)$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-$(C_6$-$C_{10})$aryl and $(C_1$-$C_6)$-alkylene-$(C_5$-$C_{10})$-heterocyclyl.

17. A compound according to one of claims 1 to 16, wherein 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-$(C_6\text{-}C_{10})$aryl and $(C_1\text{-}C_6)$-alkylene-$(C_5\text{-}C_{10})$-heterocyclyl.

18. A compound according to one of claims 1 to 17, wherein 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.

19. A compound according to one of claims 1 to 18, wherein R_5 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_6\text{-}C_{10})$aryl, or $(C_5\text{-}C_{10})$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 16, wherein 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.

24. A compound according to one of claims 1 to 23, wherein R_7 is H, halogen, CN, $(C_1\text{-}C_4)$alkyl, O-$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, phenyl, cyclopropyl or $(C_5\text{-}C_6)$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 is
H,
$(C_1$-$C_6)$alkyl,
R',
$(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$aryl,
$(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl,

$(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl,
$(C_1$-$C_6)$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'.

37. A compound according to any of claims 1 to 36, wherein R_6 is
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,

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

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

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

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

38. A compound according to any of claims 1 to 37, wherein R_6 is

H,

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

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

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

$(C_6\text{-}C10)$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)NH-$(C_1\text{-}C_6)$alkyl,

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

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,

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

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

39. A compound according to any of claims 1 to 38, wherein R_6 is

H,

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

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

$(C_1\text{-}C_4)$alkylene-O-$(C_1\text{-}C_4)$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,

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

$C(O)(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl.

40. A compound according to any of claims 1 to 39, wherein R_6 is

H;

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

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

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

$(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl wherein heterocyclyl is unsubstituted or substituted one or more times by $(C_1\text{-}C_4)$alkyl;

$(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl wherein aryl is unsubstituted or substituted one or more times by halogen, $(C_1\text{-}C_4)$alkyl, O-$(C_1\text{-}C_4)$alkyl, SO_2-$(C_1\text{-}C_4)$alkyl or SO_2-N[$(C_1\text{-}C_6)$alkyl]$_2$.

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

43. A compound according to any of claims 1 to 42, wherein R_6 is H.

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

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

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

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

48. A compound according to one of claims 1 to 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 is H, R', $(C_1$-$C_8)$alkyl, $(C_1$-$C_6)$alkylene-R', $(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylene-O-R', $(C_1$-$C_6)$alkylene-$CH[R']_2$, $(C_1$-$C_6)$alkylene-$C(O)NH_2$, $(C_1$-$C_6)$alkylene-C(O)NH-R', $(C_1$-$C_6)$alkylene-$C(O)N[(C_1$-$C_4)$alkyl$]_2$, $(C_1$-$C_6)$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)NH-$(C_1$-$C_6)$alkyl, $C(O)N[(C_1$-$C_6)$alkyl$]_2$, C(O) $(C_1$-$C_6)$alkylene-C_3-$C_8)$cycloalkyl, C(O) $(C_1$-$C_6)$alkylene-C_5-$C_{10})$heterocyclyl, or C(O) $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl;

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

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 $N(C_1$-$C_6)$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 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)$(C_3$-$C_8)$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, 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 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_2-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_8)cycloalkyl, (C_1-C_8)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_{10})heterocyclyl, C(O)(C_1-C_3)alkylene-(C_5-C_{10})heterocyclyl or C(O)(C_1-C_3)alkylene-(C_6-C_{10})aryl;

R_7 is H, halogen, CN, (C_1-C_4)alkyl, O(C_1-C_4)alkyl, (C_2-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 NH or S.

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, physiologically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.