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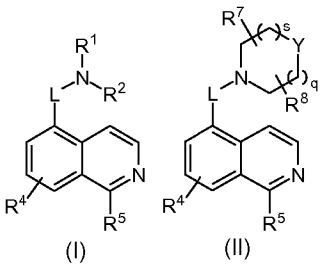

(57) Abstract: The present invention relates to new AGC kinase inhibitors, in particular to compounds of Formula (I) or (II) or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof, wherein R^1, R^2, R^4, R^5, R^7, R^8, q s, L, and Y have the meaning defined in the claims. In particular, the present invention relates to ROCK inhibitors, compositions, in particular pharmaceuticals, comprising such inhibitors, and to uses of such inhibitors in the treatment and prophylaxis of disease.

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KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to new kinase inhibitors, more specifically AGC kinases inhibitors, compositions, in particular pharmaceuticals, comprising such inhibitors, and to uses of such inhibitors in the treatment and prophylaxis of disease.

BACKGROUND OF THE INVENTION

AGC-family protein kinases are named after their family members protein kinase A (PKA), protein kinase G (PKG), and protein kinase C (PKC).

One AGC-kinase family of interest is Rho-associated coiled-coil forming protein serine/threonine kinase (ROCK), which is believed to be an effector of Ras-related small GTPase Rho. The Rho family consists of at least 10 members of small GTP binding proteins, including RhoA, B, C, D, E, F, G, Rac1, Rac2, Cdc42 and TC10. Two isoforms of ROCK are known: α (ROCKII) and β (ROCKI). ROCKI shows highest expression levels in non-neuronal tissues, such as heart, lung and skeletal muscles; whereas ROCKII is preferentially expressed in brain (hippocampus, cortex and cerebellum).

The Rho/Rho-kinase mediated pathway plays an important role in the signal transduction pathway of many agonists such as angiotensin II, 5-HT, NA, thrombin, endothelin-1, urotensin II, platelet-derived growth factor and ATP/ADP. Activation of ROCK leads to phosphorylation of various proteins: MLCP, MLC, LIMKs, CRMP2 and others. One of the main substrates is the myosin light chain MLC. Activation of MLC, together with the ROCK-induced inactivation of the MLCPhosphatase, leads to stimulation of actin-myosin interactions and subsequent cell contraction and stress fiber formation. ROCK also induces activation of LIMs resulting in an increase of actin filaments. Finally, ROCK activates the ERM protein complex and other proteins involved in cytoskeletal regulation.

ROCK associates with and activates the IKK complex. ROCK inhibitors prevent the degradation of the IKK complex and subsequent NF-κB activation induced by MPS and TNF. As a consequence, ROCK inhibitors decrease NF-κB transcription stimulated by pro-inflammatory mediators. NF-κB is a ubiquitously expressed family of transcription factors controlling the expression of numerous genes involved in immunity and inflammation. Therefore ROCK inhibitors provide a useful therapy to treat auto-immune and inflammatory diseases.

In conclusion, ROCKs play an important role in various cellular functions: such as smooth muscle contraction, actin cytoskeleton organization, platelet activation, downregulation of myosin phosphatase cell adhesion, -migration, -proliferation and -survival, thrombin-induced responses of aortic smooth muscle cells, hypertrophy of cardiomyocytes, bronchial smooth muscle contraction, smooth muscle contraction and cytoskeletal reorganization of non- muscle cells, activation of volume- regulated anion channels, neurite retraction, neutrophil chemotaxis, wound healing and cell transformation and gene expression.

More specifically, ROCK has been implicated in various diseases and disorders including hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia and atherosclerosis.

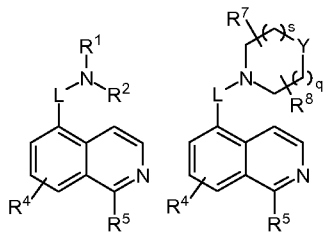
Accordingly, the development of inhibitors of ROCK would be useful as therapeutic agents for the treatment of disorders implicated in the ROCK pathway. Accordingly, there is a great need to develop inhibitors of ROCK that are useful in treating various diseases or conditions associated with ROCK activation, particularly given the inadequate treatments currently available for the majority of these disorders.

SUMMARY OF THE INVENTION

We have surprisingly found that the compounds described herein act as inhibitors of AGC-kinases and in particular of ROCK.

These compounds and pharmaceutically acceptable compositions thereof are useful for treating or lessening the severity of a variety of disorders, including allergic disorders such as asthma, cardiovascular diseases, vascular diseases, eye diseases, renal diseases, erectile dysfunction, inflammatory diseases, proliferative disorders; neurological disorders and diseases of the central nervous system (CNS), osteoporosis, renal diseases and AIDS.

Viewed from a first aspect, the invention provides a compound of Formula I or II or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof,



I II

wherein:

q is an integer selected from 0, 1 or 2,

s is an integer selected from 1 or 2,

R^1 is a group selected from aminoalkyl, alkylaminoalkyl, cycloalkyl, cycloalkylalkyl, aminocycloalkyl, aminocycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aminoheterocyclyl, aminoheterocyclylalkyl, each group being optionally substituted by one or more substituents selected from amino, hydroxyl, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, heterocyclyl,

R^2 is selected from hydrogen or alkyl, said alkyl being optionally substituted with one or more substituents selected from amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, heterocyclyl, alkoxy, cycloalkyl,

Y is $-C(R^3)R^6-$ or $-NR^3-$, wherein

R^3 is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl,

R^4 is selected from hydrogen, alkyl, alkoxy, cyano, nitro, halogen,

R^5 is hydrogen ,

R^6 is selected from hydrogen or alkyl,

L in Formula I is $–CR^9R^{10}-$ and L in Formula II is selected from $–CR^9R^{10}-$ or $–SO_2-$,

R^7 is hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 and R^8 are fused together and form an alkylene or alkyleneaminoalkylene optionally substituted with one or more substituent selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from alkyl, alkenyl, alkenyl, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylsulfonylaminoalkyl, alkylsulfonylamino, alkylcarbonyl, formylamino, formylaminoalkyl, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkoxyl, alkoxyalkyl, cyanoalkyl, aryloxyaralkyl, aralkylheteroaryl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl,

heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy, alkylsulfonyl, sulfo, alkylsulfonylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylthio, arylalkenylaminooxy, arylalkylaminooxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, aryloxy, aryloxyaralkyl, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, haloaryl, heteroaryl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylaralkyl, heteroarylcarbonylamino, heteroarylalkylaminooxy, hydroxyalkyl, or fused to the cycloalkyl, aryl, heterocyclyl substituent or heteroaryl may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each of said group being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more aryl, heteroaryl, cycloalkyl, or heterocyclyl ring,

said ring or fused ring being optionally substituted with one or more substituent selected from halo, alkenylaminooxy, alkoxy, alkyl, alkylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylsulfonyl, alkylsulfonylamino, alkylthio, amino, aralkyl, aryl, arylalkenylaminooxy, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, aryloxy, cyano, cycloalkyl, haloalkoxy, haloalkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyalkyl, nitro, oxo, sulfonyl, or fused to the cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkyloxycarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

with the proviso that when L is SO_2 in formula II, R^7 is not hydrogen or alkyl.

Viewed from a further aspect, the invention provides a pharmaceutical and/or veterinary composition comprising a compound of the invention.

Viewed from a still further aspect, the invention provides a compound of the invention for use in human or veterinary medicine.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of at least one disease and/or

disorder selected from the group comprising eye diseases; erectile dysfunction; cardiovascular diseases; vascular diseases; proliferative diseases; inflammatory diseases; neurological diseases and disease of the central nervous system (CNS); bronchial asthma; osteoporosis; renal diseases; and AIDS.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of eyes diseases including macular degeneration, retinopathy and glaucoma, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of inflammatory diseases, such as contact dermatitis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and/or for preventing, treating and/or alleviating complications and/or symptoms and/or inflammatory responses associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of cardiovascular and vascular diseases: including but not limited to acute stroke, congestive heart failure, cardiovascular ischemia, heart disease, cardiac remodeling, angina, coronary vasospasm, cerebral vasospasm, restenosis, hypertension, (pulmonary) hypertension, arteriosclerosis, thrombosis (including deep thrombosis); pulmonary vasoconstriction, and platelet related diseases, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith and/or alleviating complications and/or symptoms associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention, treatment and/or management of neurological and CNS disorders: including but not limited to stroke, multiple sclerosis, brain or spinal cord injury, inflammatory and demyelinating diseases such as Alzheimer´s disease, MS and neuropathic pain, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of proliferative diseases including but not limited to cancer of the brain (gliomas), breast, colon, intestine, skin, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate or thyroid; leukemia; sarcoma; lymphoma; melanoma; and/or for preventing, treating and/or alleviating complications and/or symptoms and/or inflammatory responses associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention in the preparation of a medicament for the prevention and/or treatment of erectile dysfunction, bronchial asthma, osteoporosis, renal diseases and AIDS, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

Viewed from a still further aspect, the invention provides the use of a compound of the invention, or a composition comprising such a compound, for inhibiting the activity of at least one kinase, in vitro or in vivo.

Viewed from a still further aspect, the invention provides the use of a compound of the invention, or a composition comprising such a compound, for inhibiting the activity of at least one ROCK kinase, for example ROCKII and/or ROCKI isoforms.

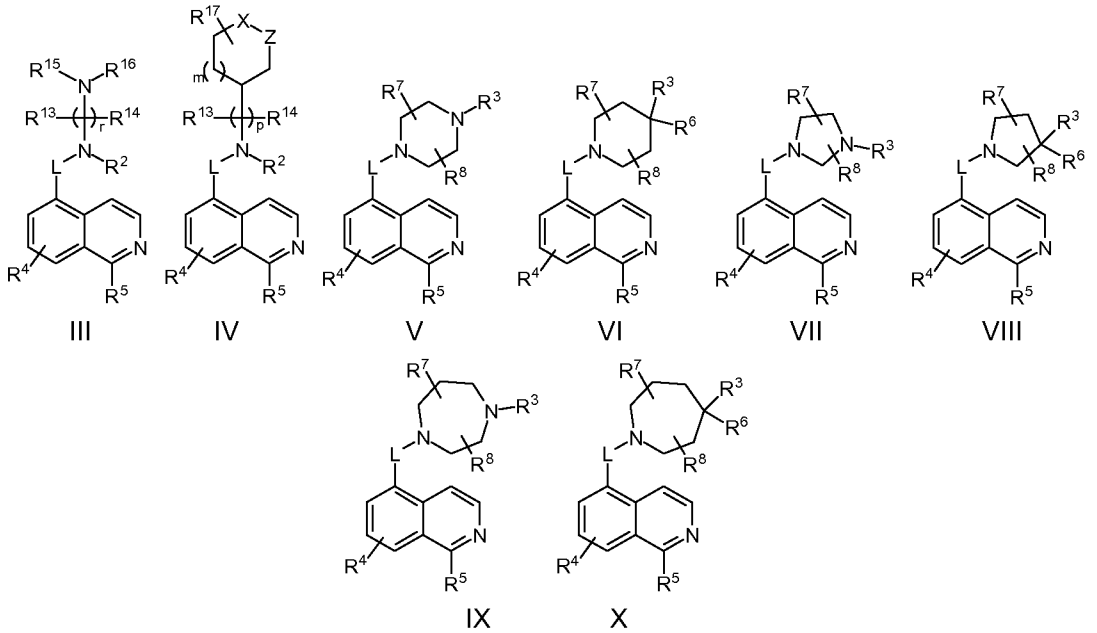
DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be further described. In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Unless a context dictates otherwise, asterisks are used herein to indicate the point at which a mono- or bivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

Undefined (racemic) asymmetric centers that may be present in the compounds of Formula I or II are interchangeably indicated by drawing a wavy bonds or a straight bond in order to visualize the undefined steric character of the bond.

In an embodiment, the present invention provides a compound of Formula I or II having one of the Formula III, IV, V, VI, VII, VIII, IX, or X,



wherein

r is an integer selected from 1, 2, 3, 4 or 5,

p is an integer selected from 0, 1 or 2,

m is an integer selected from 0 or 1,

R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, haloalkoxy, alkoxy, amino, aminoalkyl, alkylaminoalkyl,

R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl,

R^{17} is selected from hydrogen, hydroxyl, amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, heterocyclyl,

X and Z are each independently selected from $-C(R^{18})R^{19}-$ or $-NR^{18}-$, wherein R^{18} is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl, and R^{19} is selected from hydrogen or alkyl,

wherein R^2 is selected from hydrogen or alkyl, said alkyl being optionally substituted with one or more substituents selected from amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, heterocyclyl, alkoxy, cycloalkyl,

R^3 is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl,

R^4 is selected from hydrogen, alkyl, alkoxy, cyano, nitro, halogen,

R^5 is hydrogen ,

R^6 is selected from hydrogen or alkyl,

L in Formula III, IV, is $-CR^9R^{10}-$ and L in Formula V, VI, VII, VIII, IX, or X is selected from $-CR^9R^{10}-$ or $-SO_2-$,

R^7 is hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 and R^8 are fused together and form an alkylene or alkyleneaminoalkylene optionally substituted with one or more substituent selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from alkyl, alkenyl, alkenyl, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylsulfonylaminoalkyl, alkylsulfonylamino, alkylcarbonyl, formylamino, formylaminoalkyl, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkoxyl, alkoxyalkyl, cyanoalkyl, aryloxyaralkyl, aralkylheteroaryl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy, alkylsulfonyl, sulfo, alkylsulfonylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylthio, arylalkenylaminooxy, arylalkylaminooxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, aryloxy, aryloxyaralkyl, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, haloaryl, heteroaryl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylaralkyl, heteroarylcarbonylamino, heteroarylalkylaminooxy, hydroxyalkyl, or fused to the cycloalkyl, aryl, heterocyclyl substituent or heteroaryl may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each of said group being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more aryl, heteroaryl, cycloalkyl, or heterocyclyl ring,

said ring or fused ring being optionally substituted with one or more substituent selected from halo, alkenylaminooxy, alkoxy, alkyl, alkylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylsulfonyl, alkylsulfonylamino, alkylthio, amino, aralkyl, aryl, arylalkenylaminooxy, arylamino, arylaminosulfonyl, arylcarbonyl,

arylcarbonylamino, aryloxy, cyano, cycloalkyl, haloalkoxy, haloalkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyalkyl, nitro, oxo, sulfonyl, or fused to the cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkyloxycarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof, with the proviso that when L is SO_2 in formula V, VI, VII, VIII, IX, or X, R^7 is not hydrogen or alkyl.

In an embodiment, heterocyclyl is preferably selected from piperidinyl, azetidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, indolinyl, isoindolinyl, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 4H-quinolizinyl, 4aH-carbazolyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, , phthalazinyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrehydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothienyl, N- formylpiperazinyl, and morpholinyl,

preferably, aryl is selected from phenyl, biphenylyl, biphenylenyl, tetralinyl, azulenyl, naphthyl, indenyl, anthryl, or pyrenyl, and

preferably heteroaryl is selected from pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl.

In an embodiment, the present invention provides a compound of Formula I or II having one of the Formula III, IV, V, VI, VII, VIII, IX, or X,

r is an integer selected from 1, 2, 3, 4 or 5, preferably 1, 2 or 3, more preferably 1 or 2,

p is an integer selected from 0, 1 or 2, preferably, 0 or 1,

m is an integer selected from 0 or 1,

R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy, amino, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, preferably R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy, amino, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl, more preferably, R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, C_{1-6}alkyl, C_{6-10}aryl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy, amino, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl,

R^{15} and R^{16} are each independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, haloC_{1-6}alkyl, preferably R^{15} and R^{16} are each independently selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, haloC_{1-6}alkyl, more preferably R^{15} and R^{16} are each independently selected from hydrogen, C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, haloC_{1-6}alkyl, yet more preferably R^{15} and R^{16} are each independently selected from hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl,

R^{17} is selected from hydrogen, hydroxyl, amino, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino, heteroaryl, heteroarylC_{1-6}alkyl, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy, C_{3-6}cycloalkyl, heterocyclyl, preferably R^{17} is selected from hydrogen, hydroxyl, amino, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy, C_{3-6}cycloalkyl, heterocyclyl, more preferably R^{17} is selected from hydrogen, amino, C_{6-10}arylC_{1-4}alkyl, C_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkoxy,

X and Z are each independently selected from -C(R^{18})R^{19}- or -NR^{18}-, wherein R^{18} is hydrogen or a group selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, haloC_{6-10}arylC_{1-6}alkyl, amino, aminoC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, each group being optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{6-10}aryl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, amino, C_{1-6}alkoxy, heteroaryl, heterocyclyl, C_{3-6}cycloalkyl, and R^{19} is selected from hydrogen or C_{1-6}alkyl, preferably R^{18} is hydrogen or a group selected from C_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, haloC_{6-10}arylC_{1-6}alkyl, amino, aminoC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, preferably R^{18} is hydrogen or a group selected from C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, haloarylC_{1-6}alkyl, amino, aminoC_{1-6}alkyl,

wherein R^{2} is selected from hydrogen or C_{1-6}alkyl, said C_{1-6}alkyl being optionally substituted with one or more substituents selected from amino, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, C_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino, heteroaryl, heteroarylC_{1-6}alkyl, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, heterocyclyl,

C_{1-6}alkoxy, C_{3-6}cycloalkyl, preferably R^2 is selected from hydrogen or C_{1-6}alkyl, said C_{1-6}alkyl being optionally substituted with one or more substituents selected from amino, C_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylamino, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, more preferably R^2 is selected from hydrogen or C_{1-6}alkyl,

R^3 is hydrogen or a group selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, haloC_{6-10}arylC_{1-4}alkyl, amino, aminoC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, each group being optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{6-10}aryl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, amino, C_{1-6}alkoxy, heteroaryl, heterocyclyl, C_{3-6}cycloalkyl, preferably R^3 is hydrogen or a group selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, haloC_{6-10}arylC_{1-4}alkyl, amino, aminoC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4}alkyl, each group being optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{6-10}aryl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, preferably R^3 is hydrogen or a group selected from C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, haloC_{6-10}arylC_{1-4}alkyl, amino, aminoC_{1-6}alkyl, each group being optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{6-10}aryl, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy,,

R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, nitro, halogen, preferably R^4 is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, more preferably R^4 is hydrogen,

R^5 is hydrogen,

R^6 is selected from hydrogen or C_{1-6}alkyl,

L in Formula III or IV is $-CR^9R^{10}-$ and L in Formula V, VI, VII, VIII, IX, or X is selected from $-CR^9R^{10}-$ or $-SO_2-$,

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, hydroxyl, C_{1-6}alkyloxycarbonyl, carboxyl, aminoC_{1-6}alkyl, amino, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{3-6}cycloalkylC_{1-6}alkyl, or fused to said C_{6-10}aryl, arylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{3-6}cycloalkylC_{1-4}alkyl, group may be one or more C_{3-6}cycloalkyl, C_{6-10}aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, C_{1-6}alkoxy, C_{1-6}alkyl, amino, cyano, nitro, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkylamino, preferably R^7 is hydrogen or a group selected from C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, hydroxyl, C_{1-6}alkyloxycarbonyl, carboxyl, aminoC_{1-6}alkyl, amino, C_{6-10}aryl, C_{6-10}arylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{3-6}cycloalkylC_{1-6}alkyl, or fused to said C_{6-10}aryl, arylC_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, heterocyclylC_{1-4}alkyl, C_{3-6}cycloalkyl, or C_{3-6}cycloalkylC_{1-4}alkyl, group may be one or more C_{3-6}cycloalkyl, C_{6-10}aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, C_{1-6}alkoxy, C_{1-6}alkyl, amino, cyano, nitro, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkylamino,

or R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from C_{1-6}alkyl, C_{6-10}aryl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, hydroxyl, C_{1-6}alkyloxycarbonyl, carboxyl, aminoC_{1-6}alkyl, amino, heteroaryl, C_{6-10}arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, C_{1-6}alkyl, amino, cyano, nitro, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkylamino,

or R^7 and R^8 are fused together and form an C_{1-6}alkylene or C_{1-6}alkyleneaminoC_{1-6}alkylene optionally substituted with one or more substituent selected from hydroxyl, C_{1-6}alkoxy, C_{1-6}alkyl, amino, cyano, nitro, halo, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or C_{1-6}alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyl, amino, aminoC_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-6}alkylsulfonylaminoC_{1-6}alkyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonyl, formylamino, formylaminoC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, C_{1-6}alkoxyl, C_{1-6}alkoxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{6-10}aryloxyC_{6-10}arylC_{1-6}alkyl, C_{6-10}arylC_{1-6}alkylheteroaryl, hydroxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylC_{6-10}arylC_{1-6}alkyl, or fused to said C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, or heteroarylC_{6-10}arylC_{1-6}alkyl group may be one or more C_{3-6}cycloalkyl, C_{6-10}aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy, amino, C_{1-6}alkylamino, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{2-6}alkenylaminooxy, C_{1-6}alkylsulfonyl, sulfo, C_{1-6}alkylsulfonylamino, C_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxyaminoC_{2-6}alkenyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylthio, C_{6-10}arylC_{2-6}alkenylaminooxy, C_{6-10}arylC_{1-6}alkylaminooxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkyl, heterocyclyl, C_{6-10}aryl, C_{6-10}arylC_{1-6}alkyl, C_{6-10}aryloxy, C_{6-10}aryloxyC_{6-10}arylC_{1-6}alkyl, C_{6-10}arylamino, C_{6-10}arylaminosulfonyl, C_{6-10}arylcarbonyl, C_{6-10}arylcarbonylamino, haloC_{6-10}aryl, heteroaryl, heteroarylC_{2-6}alkenylaminooxy, heteroarylC_{1-6}alkyl, heteroarylC_{6-10}arylC_{1-6}alkyl, heteroarylcarbonylamino, heteroarylC_{1-6}alkylaminooxy, hydroxyC_{1-6}alkyl, or fused to the C_{3-6}cycloalkyl, C_{6-10}aryl, heterocyclyl substituent or heteroaryl may be one or more C_{3-6}cycloalkyl, C_{6-10}aryl, heterocyclyl or heteroaryl,

each of said group being optionally substituted by one or more further substituent selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylheteroaryl, C_{1-6}alkylsulfonyl, C_{6-10}arylC_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylamino, C_{6-10}aryloxy, cyano, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more C_{6-10}aryl, heteroaryl, C_{3-8}cycloalkyl, or heterocyclyl ring,

said ring or fused ring being optionally substituted with one or more substituent selected from halo, C_{2-6}alkenylaminooxy, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylaminosulfonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxyaminoC_{2-6}alkenyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylthio, amino, C_{6-10}arylC_{1-6}alkyl, C_{6-10}aryl, C_{6-10}arylC_{2-6}alkenylaminooxy, C_{6-10}arylamino, C_{6-10}arylaminosulfonyl, C_{6-10}arylcarbonyl, C_{6-10}arylcarbonylamino, C_{6-10}aryloxy, cyano, cycloalkyl, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylC_{2-6}alkenylaminooxy, heteroarylC_{1-6}alkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyC_{1-6}alkyl, nitro, oxo, sulfonyl, or fused to the C_{3-8}cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, C_{6-10}aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylheteroaryl, C_{1-6}alkylsulfonyl, C_{6-10}arylC_{1-6}alkyl, C_{6-10}aryl, arylamino, aryloxy, cyano, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or a stereoisomer, tautomer, racemic, metabolite, pro- or predrug, salt, hydrate, or solvate thereof, with the proviso that when L is SO_2 in formula V, VI, VII, VIII, IX, or X, R^7 is not hydrogen or C_{1-6}alkyl.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

The term "alkyl" by itself or as part of another substituent refers to a hydrocarbyl radical of Formula C_nH_{2n+1} wherein n is a number greater than or equal to 1. Generally, alkyl groups of this invention comprise from 1 to 20 carbon atoms, more preferably from 1 to 10 carbon atoms, still more preferably 1 to 8 carbon atoms, in particular 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-4}alkyl means an alkyl of one to four carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers, heptyl and its isomers, octyl and its isomers, nonyl and its isomers; decyl and its isomers. C_1-C_6 alkyl includes all linear, branched alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, and hexyl and its isomers.

The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 4 substituents, or example 1, 2, 3 or 4 substituents or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents

include halogen, hydroxyl, carbonyl, nitro, amino, oximes, imines, azido, hydrazino, cyano, alkyl, aryl, heteroaryl, cycloalkyl, acyl, alkylamino, alkoxy, thio, alkylthio, carboxylic acid, acylamino, alkyl esters, carbamates, thioamides, urea, sulfonamides and the like.

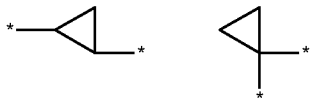
When the term "alkyl" is used as a suffix following another term, as in "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one or two (preferably one) substituent(s) selected from the other, specifically-named group, also as defined herein. The term "hydroxyalkyl" refers to a -R^a-OH group wherein R^a is alkylene as defined herein. For example, "hydroxyalkyl" includes 2-hydroxyethyl, 1-(hydroxymethyl)-2-methylpropyl, 3,4-dihydroxybutyl, and so forth. "Alkoxyalkyl" refers to an alkyl group substituted with one to two of OR', wherein R' is alkyl as defined below. For example, “aralkyl” or “arylalkyl” refers to a substituted alkyl group as defined above wherein at least one of the alkyl substituents is an aryl as defined below, such as benzyl. For example, “heteroarylalkyl” refers to a substituted alkyl group as defined above wherein at least one of the alkyl substituents is a heteroaryl as defined below, such as pyridinyl.

The term “cycloalkyl group" as used herein is a cyclic alkyl group, that is to say, a monovalent, hydrocarbyl group having 1, 2 or 3 cyclic structure. Cycloalkyl includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups containing 1 to 3 rings, including monocyclic, bicyclic or polycyclic alkyl groups. Cycloalkyl groups may comprise 3 or more carbon atoms in the ring and generally, according to this invention comprise from 3 to 10, more preferably from 3 to 8 carbon atoms still more preferably from 3 to 6 carbon atoms. The further rings of multi-ring cycloalkyls may be either fused, bridged and/or joined through one or more spiro atoms. Cycloalkyl groups may also be considered to be a subset of homocyclic rings discussed hereinafter. Examples of cycloalkyl groups, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl with cyclopropyl being particularly preferred. An “optionally substituted cycloalkyl” refers to a cycloalkyl having optionally one or more substituents (for example 1 to 3 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl. When the suffix "ene" is used in conjunction with a cyclic group, this is intended to mean the cyclic group as defined herein having two single bonds as points of attachment to other groups.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylmethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene. Similarly, where alkenyl groups as defined above and alkynyl groups as defined above, respectively, are divalent radicals having single bonds for attachment to two other groups, they are termed "alkenylene" and "alkynylene" respectively.

Generally, alkylene groups of this invention preferably comprise the same number of carbon atoms as their alkyl counterparts. "Cycloalkylene" herein refers to a saturated homocyclic hydrocarbyl biradical of Formula C_nH_{2n-2}. Cycloalkylene groups of this invention preferably comprise the same

number of carbon atoms as their cycloalkyl radical counterparts. Where an alkylene or cycloalkylene biradical is present, connectivity to the molecular structure of which it forms part may be through a common carbon atom or different carbon atom, preferably a common carbon atom. To illustrate this applying the asterisk nomenclature of this invention, a C_3 alkylene group may be for example *-$CH_2CH_2CH_2$-*, *-CH(-CH_2CH_3)-* or *-CH_2CH(-CH_3)-*. Likewise a C_3 cycloalkylene group may be



Where a cycloalkylene group is present, this is preferably a C_3-C_6 cycloalkylene group, more preferably a C_3 cycloalkylene (i.e. cyclopropylene group) wherein its connectivity to the structure of which it forms part is through a common carbon atom. Cycloalkylene and alkylene biradicals in compounds of the invention may be, but preferably are not, substituted.

The term “alkenyl" as used herein refers to an unsaturated hydrocarbyl group, which may be linear, branched or cyclic, comprising one or more carbon-carbon double bonds. Alkenyl groups thus comprise two or more carbon atoms, preferably between 2 and 20 carbon atoms, more preferably between 2 and 10 carbon atoms, still more preferably between 2 and 8 carbon atoms, for example, between 2 and 6 carbon atoms. Similarly to cycloalkyl groups, cycloalkenyl groups may be considered to be a subset of homocyclic rings discussed hereinafter. Examples of alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2-heptenyl and its isomers, 2-octenyl and its isomers, 2,4-pentadienyl and the like. An optionally substituted alkenyl refers to an alkenyl having optionally one or more substituents (for example 1, 2 or 3 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl. Similarly to cycloalkyl groups, cycloalkenyl groups may be considered to be a subset of homocyclic rings discussed hereinafter.

The term “alkynyl" as used herein, similarly to alkenyl, refers to a class of monovalent unsaturated hydrocarbyl groups, wherein the unsaturation arises from the presence of one or more carbon-carbon triple bonds. Alkynyl groups typically, and preferably, have the same number of carbon atoms as described above in relation to alkenyl groups. Examples alkynyl groups are ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl and its isomers, 2-hexynyl and its isomers, 2-heptynyl and its isomers, 2-octynyl and its isomers and the like. An optionally substituted alkynyl refers to an alkynyl having optionally one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl. Similarly to cycloalkyl groups, cycloalkynyl groups may be considered to be a subset of homocyclic rings discussed hereinafter.

The term “homocyclic ring" as used herein is a ring wherein the ring atoms comprise only carbon atoms. Examples of homocyclic rings thus include cycloalkyl, cycloalkenyl and cycloalkynyl, with cycloalkyl and cycloalkenyl being preferred. Where a ring carbon atom is replaced with a heteroatom, preferably nitrogen, oxygen of sulfur, the heteroatom-containing ring resultant from

such a replacement is referred to herein as a heterocyclic ring. More than one carbon atom in a ring may be replaced so forming heterocyclic ring having a plurality of heteroatoms.

The terms "heterocyclyl" or "heterocyclo" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 13 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. An optionally substituted heterocyclic refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or for example 1, 2, 3 or 4), selected from those defined above for substituted aryl.

Exemplary heterocyclic groups include piperidinyl, azetidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, indolinyl, isoindolinyl, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 4H-quinolizinyl, 4aH-carbazolyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, phthalazinyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrehydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothienyl, N- formylpiperazinyl, and morpholinyl.

The term “aryl" as used herein refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphthalene or anthracene) or linked covalently, typically containing 5 to 8 atoms; wherein at least one ring is aromatic. The aromatic ring may optionally include one to three additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of aryl comprise phenyl, biphenylyl, biphenylenyl, 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-azulenyl, 1- or 2-naphthyl, 1-, 2- or 3-indenyl, 1-, 2- or 9-anthryl, 1- 2-, 3-, 4- or 5-acenaphtylenyl, 3-, 4- or 5-acenaphtenyl, 1-, 2-, 3-, 4- or 10-phenanthryl, 1- or 2-pentalenyl, 1, 2-, 3- or 4-fluorenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, dibenzo[a,d]cylcoheptenyl, 1-, 2-, 3-, 4- or 5-pyrenyl.

The aryl ring can optionally be substituted by one or more aromatic substituents. An “optionally substituted aryl” refers to an aryl having optionally one or more substituents (for example 1 to 5

substituents, or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents are selected from halogen, hydroxyl, oxo, nitro, amino, hydrazine, aminocarbonyl, azido, cyano, alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkylalkyl, alkylamino, alkoxy, -SO_2-NH_2, aryl, heteroaryl, arylalkyl, haloalkyl, haloalkoxy, alkyloxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, -SO_2R^{15}, alkylthio, carboxy, and the like, wherein R^{15} is alkyl or cycloalkyl.

The term "arylene" as used herein is intended to include divalent carbocyclic aromatic ring systems such as phenylene, biphenylylene, naphthylene, anthracenylene, phenanthrenylene, fluorenylene, indenylene, pentalenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.

Where a carbon atom in an aryl group is replaced with a heteroatom, the resultant ring is referred to herein as a heteroaryl ring.

The term “heteroaryl” as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 3 rings which are fused together or linked covalently, typically containing 5 to 8 atoms; at least one of which is aromatic in which one or more carbon atoms in one or more of these rings can be replaced by oxygen, nitrogen or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. Non-limiting examples of a heterocyclyl include: pyrrolyl, furanyl (or furyl), thiophenyl (or thienyl), pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl.

In particular, non-limiting examples of heteroaryl can be 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1,3,4-thiadiazolyl, 1- or 5-tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-

thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 1-, 3-, 4- or 5-isobenzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 3-, 4- or 5-isobenzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2- or 3-pyrazinyl, 1,4-oxazin-2- or -3-yl, 1,4-dioxin-2- or -3-yl, 1,4-thiazin-2- or -3-yl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazin-2-, -4- or -6-yl, thieno[2,3-b]furan-2-, -3-, -4-, or -5-yl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 1-, 2-thianthrenyl, 3-, 4- or 5-isobenzofuranyl, 1-, 2-, 3-, 4- or 9-xanthenyl, 1-, 2-, 3- or 4-phenoxathiinyl, 2-, 3-pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-indolizinyl, 2-, 3-, 4- or 5-isoindolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 6-, 7- or 8-purinyl, 4-, 5- or 6-phthalazinyl, 2-, 3- or 4-naphthyridinyl, 2-, 5- or 6-quinoxalinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 1-, 2-, 3- or 4-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl(quinolyl), 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl(isoquinolyl), 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 6- or 7-pteridinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-carbolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-phenanthridinyl, 1-, 2-, 3- or 4-acridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-(1,7)phenanthrolinyl, 1- or 2-phenazinyl, 1-, 2-, 3-, 4-, or 10-phenothiazinyl, 3- or 4-furazanyl, 1-, 2-, 3-, 4-, or 10-phenoxazinyl, or additionally substituted derivatives thereof.

An “optionally substituted heteroaryl” refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents), selected from those defined above for substituted aryl.

The term “oxo” as used herein refers to the group =O.

The term “alkoxy" as used herein refers to a radical having the Formula -OR wherein R is alkyl. Preferably, alkoxy is C_1-C_{10} alkoxy or C_1-C_6 alkoxy. Where the oxygen atom in an alkoxy group is substituted with sulfur, the resultant radical is referred to as thioalkoxy. Haloalkoxy is an alkoxy group wherein one or more hydrogen atoms in the alkyl group are substituted with halo.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term “cycloalkylalkyl” by itself or as part of another substituent refers to a group having one of the aforementioned cycloalkyl groups attached to one of the aforementioned alkyl chains. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term “heterocyclyl-alkyl” by itself or as part of another substituents refers to a group having one of the aforementioned heterocyclyl group attached to one of the aforementioned alkyl group, i.e., to a group $–R^b$-R^c wherein R^b is alkylene or alkylene substituted by alkyl group and R^c is a heterocyclyl group.

The term “acyl” by itself or as part of another substituent refers to an alkanoyl group having 2 to 6 carbon atoms or a phenylalkanoyl group whose alkanoyl moiety has 1 to 4 carbon atoms, i.e. a carbonyl group linked to a radical such as, but not limited to, alkyl, aryl, more particularly, the group $–COR^{10}$, wherein R^{10} can be selected from alkyl, aryl, substituted alkyl, or substituted aryl, as defined herein. The term acyl therefore encompasses the group alkylcarbonyl ($–COR^{10}$), wherein R^{10} is alkyl. Preferably, acyl is C_2-C_{11} acyl or C_2-C_7 acyl. Where the oxygen atom is an acyl group is substituted with sulfur, the resultant radical is referred to as thioacyl. Said acyl can be exemplified by acetyl, propionyl, butyryl, valeryl and pivaloyl, benzoyl, phenylacetyl, phenylpropionyl and phenylbutytyl.

The term “amino” refers to the group $–NH_2$.

The term “alkylamino” by itself or as part of another substituent refers to a group consisting of an amino groups attached to one or two independently selected and optionally substituted alkyl groups, cycloalkyl groups, arylalkyl or cycloalkylalkyl groups i.e., alkyl amino refers to $–N(R^8)(R^9)$ wherein R^8 and R^9 are each independently selected from hydrogen, cycloalkyl, arylalkyl, cycloalkylalkyl or alkyl. Non-limiting examples of alkylamino groups include methylamino ($NHCH_3$), ethylamino ($NHCH_2CH_3$), n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-hexylamino, and the like.

The term “aminoalkyl” refers to the group $-R^b-NR^dR^e$ wherein R^b is alkylene or substituted alkylene, R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is hydrogen or alkyl as defined herein.

The term “aminocarbonyl” refers to the group $-(C=O)-NH_2$.

The term "alkylaminocarbonyl" refers to a group $-(C=O)-NR^dR^e$ wherein R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is alkyl or substituted alkyl as defined herein.

The term “alkylaminocarbonylamino” refers to a group $-NH(C=O)-NR^dR^e$ or $-NR'(C=O)-NR^dR^e$ wherein R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is alkyl or substituted alkyl as defined herein, wherein R’ is alkyl or substituted alkyl.

The term "carboxy" or “carboxyl” refers to the group $-CO_2H$. Thus, a carboxyalkyl is an alkyl group as defined above having at least one substituent that is $-CO_2H$.

The term "alkoxycarbonyl" refers to a carboxy group linked to an alkyl radical i. e. to form $–C(=O)OR^{10}$, wherein R^{10} is as defined above for acyl.

The term “alkylcarbonyloxy” refers to a $–O-C(=O)R^{11}$ wherein R^{11} is as defined above for alkyl.

The term “alkylcarbonylamino” refers to an group of Formula -NH(C=O)R or -NR'(C=O)R, wherein R and R’ are each independently alkyl or substituted alkyl.

The term “alkylcarbonylaminoalkyl” refers to a group $-R^b-NR^d-C(=O)-R^e$ wherein R^b is alkylene or substituted alkylene, R^d is hydrogen or alkyl as defined herein, and R^e is alkyl as defined herein.

The term “alkoxy” by itself or as part of another substituent refers to a group consisting of an oxygen atom attached to one optionally substituted straight or branched alkyl group. Non-limiting examples of suitable alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, hexanoxy and the like.

The term “alkylthio” by itself or as part of another substituent refers to a group consisting of a sulfur atom attached to one optionally substituted alkyl group. Non-limiting examples of alkylthio groups include methylthio (SCH_3), ethylthio (SCH_2CH_3), n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-hexylthio, and the like.

The term “acylamino” by itself or as part of another substituent refers to a group consisting of an amino group attached to one or two independently selected acyl groups as described before. In case the two acyl groups of a dicarboxylic acid are attached to the amino group these represent imides such as phtalimides, maleimides and the like, and are encompassed in the meaning of the term acylamino.

The term “halo” or “halogen” as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term “haloalkoxy” alone or in combination refers to a group of Formula -O-alkyl wherein the alkyl group is substituted by 1, 2 or 3 halogen atoms. For example, "haloalkoxy" includes $-OCF_3$ and $-OCHF_2$.

The term “sulfonyl” alone or in combination refers to a group of Formula $-SO_2-R^z$ wherein R^z is alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl as defined herein. As used herein the term alkylsulfonyl is a group of formula $-SO_2-R^z$ wherein R^z is alkyl.

The term “sulfonamide” alone or in combination refers to a group of Formula $-SO_2$-NRR wherein each R independently is hydrogen or alkyl as defined herein.

The term “alkylsulfonylamino” alone or in combination refers to a group of Formula $-NR^d-SO_2-R$ wherein R^d is hydrogen or alkyl as defined herein, and R is alkyl as defined herein.

Whenever the term “substituted” is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using “substituted” is replaced with a selection from the indicated group, provided that the indicated atom’s normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

Where groups may be optionally substituted, such groups may be substituted with once or more, and preferably once or twice. Substituents may be selected from, for example, the group comprising halo, hydroxyl, oxo, nitro, amido, carboxy, amino, cyano haloalkoxy, and haloalkyl.

As used herein the terms such as “alkyl, aryl, or cycloalkyl, each being optionally substituted with” or “alkyl, aryl, or cycloalkyl, optionally substituted with” refers to optionally substituted alkyl, optionally substituted aryl and optionally substituted cycloalkyl.

Whenever used in the present invention the term “compounds of the invention” or a similar term is meant to include the compounds of general Formula I or II and any subgroup thereof. This term also refers to the compounds as depicted in Tables 1 to 9 and their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, pro-drugs, esters and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

The terms described above and others used in the specification are well understood to those in the art.

Preferred features of the compounds of this invention are now set forth.

In a particular embodiment, in compounds of Formula I, II, III, IV, V, VI, VII, VIII, IX, X, L is $-CR^9R^{10}-$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X, Y, Z, r, s, p, q, m have the same meaning as that defined above. Preferably, L is $-CR^9R^{10}-$, R^9 and R^{10} are each independently selected from hydrogen or alkyl,

and heterocyclyl is selected from piperidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, indolinyl, isoindolinyl, 2H-pyrrolyl, pyrrolinyl, pyrrolidinyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, pyrazolinyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, thietanyl, dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrehydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothienyl, N-formylpiperazinyl, and morpholinyl,

preferably aryl is selected from phenyl, biphenylyl, biphenylenyl, naphthyl, or indenyl,

preferably heteroaryl is selected from pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, indolyl,

indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, thienopyridinyl, purinyl, benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl. More preferably, L is CH_2.

In another particular embodiment, in compounds of Formula II, III, IV, V, VI, VII, VIII, IX, X, L is $-SO_2-$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X, Y, Z, r, s, p, q, m have the same meaning as that defined above.

According to an embodiment of the present invention, in compounds of Formula II, V, VI, VII, VIII, IX and X, R^7 is hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino, and

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined above.

According to another embodiment of the present invention, in compounds of Formula II, V, VI, VII, VIII, IX and X, R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from alkyl, alkenyl, alkenyl, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylsulfonylaminoalkyl, alkylsulfonylamino, alkylcarbonyl, formylamino, formylaminoalkyl, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkoxyl, alkoxyalkyl, cyanoalkyl, aryloxyaralkyl, aralkylheteroaryl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy, alkylsulfonyl, sulfo, alkylsulfonylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylthio, arylalkenylaminooxy, arylalkylaminooxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, aryloxy, aryloxyaralkyl, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, haloaryl, heteroaryl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylaralkyl, heteroarylcarbonylamino, heteroarylalkylaminooxy, hydroxyalkyl, or fused to the cycloalkyl, aryl, heterocyclyl substituent or heteroaryl may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each of said group being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

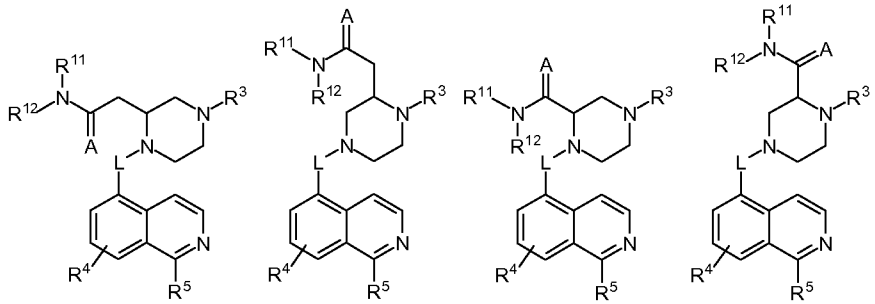
or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more aryl, heteroaryl, cycloalkyl, or heterocyclyl ring,

said ring or fused ring being optionally substituted with one or more substituent selected from halo, alkenylaminooxy, alkoxy, alkyl, alkylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylsulfonyl, alkylsulfonylamino, alkylthio, amino, aralkyl, aryl, arylalkenylaminooxy, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, aryloxy, cyano, cycloalkyl, haloalkoxy, haloalkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyalkyl, nitro, oxo, sulfonyl, or fused to the cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkyloxycarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined above.

According to another embodiment of the present invention, in compounds of Formula II, V, VI, VII, VIII, IX and X, R^7 and R^8 are fused together and form an alkylene or alkyleneaminoalkylene optionally substituted with one or more substituent selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined above.

According to an embodiment of the present invention, some preferred compounds of Formula II or V are compounds having one of the structural Formula V1, V2, V3, V4:



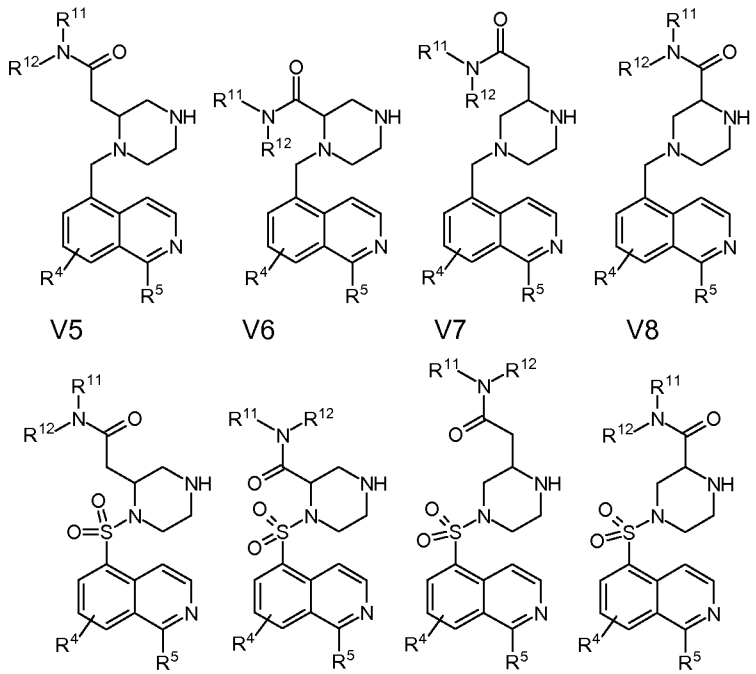
V1 V2 V3 V4

wherein R^3, R^4, R^5, R^{11}, R^{12}, L and A have the same meaning as that defined above.

In a particular embodiment, in compounds of formula V1, V2, V3, V4, A is O and R^3, R^4, R^5, R^{11}, R^{12}, L have the same meaning as that defined above.

In another particular embodiment, in compounds of formula V1, V2, V3, V4, A is S and R^3, R^4, R^5, R^{11}, R^{12}, L have the same meaning as that defined above.

According to another embodiment of the present invention, some preferred compounds of Formula II, V, V1, V2, V3, V4, are compounds of Formula:



V5 V6 V7 V8

V9 V10 V11 V12

wherein R^4, R^5, R^{11}, R^{12} have the same meaning as that defined above.

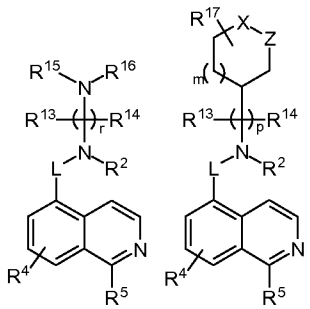
According to an embodiment of the present invention, in compounds of Formula VI, VII, VIII, IX or X, R^7 is preferably hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl,

aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino, and

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined above.

In another particular embodiment, compounds of Formula I, have structural Formula III or IV,



III IV

wherein

r is an integer selected from 1, 2, 3, 4 or 5, preferably 1, 2, 3, or 4,

p is an integer selected from 0, 1 or 2, preferably 0 or 1

m is an integer selected from 0 or 1,

R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, haloalkoxy, alkoxy, amino, aminoalkyl, alkylaminoalkyl, preferably R^{13} and R^{14} are each independently selected from hydrogen or alkyl,

R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl, preferably R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl,

R^{17} is selected from hydrogen, hydroxyl, amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, heterocyclyl, preferably, R^{17} is selected from hydrogen, hydroxyl, amino, aryl, arylalkyl, alkyl,

X and Z are each independently selected from $-C(R^{18})R^{19}-$ or $-NR^{18}-$, wherein R^{18} is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl,

cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl, and R^{19} is selected from hydrogen or alkyl,

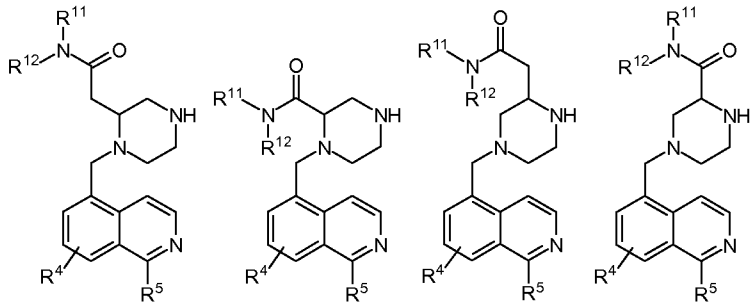
R^2 is selected from hydrogen or alkyl, said alkyl being optionally substituted with one or more substituents selected from amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, heterocyclyl, alkoxy, cycloalkyl,

R^4 is selected from hydrogen, alkyl, alkoxy, cyano, nitro, halogen,

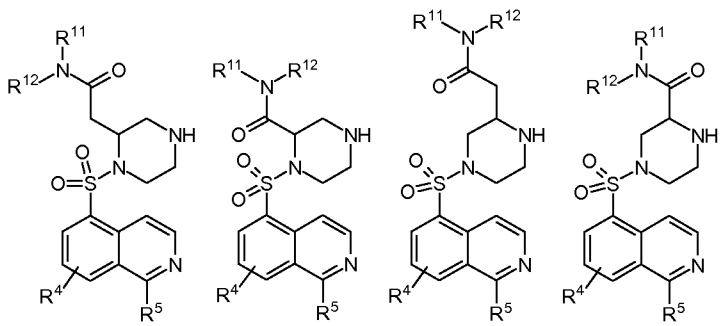
R^5 is selected from hydrogen , and

L is $–CR^9R^{10}$-; wherein R^9 and R^{10} are each independently selected from hydrogen or alkyl.

According to another embodiment of the present invention, some preferred compounds of Formula II, V, V1, V2, V3, V4, are compounds of Formula:



V5 V6 V7 V8



V9 V10 V11 V12

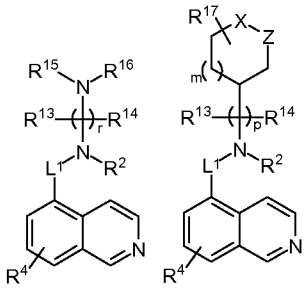
wherein R^4, R^5 are each independently hydrogen and

R^{11} is hydrogen or alkyl,

R^{12} is hydrogen or a group selected from alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy.

In an embodiment, some preferred compounds of Formula II, V, V1, V2, V3, V4, are compounds of Formula V5, V6, V7, V8, V9, V10, V11, V12, wherein aryl is phenyl or naphthyl, wherein heterocyclyl is selected from piperazinyl, piperidinyl, pyrrolidinyl, diazepanyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolidinyl, indolinyl, dioxolanyl, and wherein heteroaryl is selected from indolyl, benzoxazolyl, furanyl, thiazolyl, piridinyl, thienyl, pyrazolyl, or imidazolyl.

According to another embodiment of the present invention, some preferred compounds of Formula III or IV, are compounds of Formula:



III1 IV1

r is an integer selected from 1 or 2,

p is an integer selected from 0, 1 or 2,

m is an integer selected from 0 or 1,

R^{13} and R^{14} are each independently selected from hydrogen or alkyl,

R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl,

R^{17} is selected from hydrogen, hydroxyl, amino, aryl, arylalkyl, alkyl,

X and Z are each independently selected from $-C(R^{18})R^{19}-$ or $-NR^{18}-$, wherein R^{18} is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl, and R^{19} is selected from hydrogen or alkyl,

R^2 is selected from hydrogen or alkyl,

R^4 is selected from hydrogen or halogen, and

L^1 is $-CR^9R^{10}-$, wherein R^9 and R^{10} are each independently selected from hydrogen or CH_3. Preferably, L is CH_2.

It is clear to a person skilled in the art that the compounds of Formula I or II may contain at least one asymmetric center and thus may exist as different stereoisomeric forms. The absolute

configuration of each asymmetric center that may be present in the compounds of Formula I or II may be indicated by the stereochemical descriptors R and S.

The compounds of the invention may be in the form of pharmaceutically and/or veterinary acceptable salts, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the prior art referred to below).

When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention. When the compounds of the invention contain a hydrogen-donating heteroatom (e.g. NH), the invention also covers salts and/or isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

In addition, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention in its broadest sense also included non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention. For example, salts formed with optically active acids or bases may be used to form diastereoisomeric salts that can facilitate the separation of optically active isomers of the compounds of Formula I or II above.

The invention also generally covers all pharmaceutically acceptable predrugs and prodrugs of the compounds of Formula I or II, for which general reference is made to the prior art cited hereinbelow.

The term “pro-drug” as used herein means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug. The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th Ed, McGraw-Hill, Int. Ed. 1992, “Biotransformation of Drugs”, p 13-15) describing pro-drugs generally is hereby incorporated. Pro-drugs of the compounds of the invention can be prepared by modifying functional groups present in said component in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent component. Typical examples of pro-drugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference. Pro-drugs are characterized by increased bio-availability and are readily metabolized into the active inhibitors *in vivo*. The term “pre-drug”, as used herein, means any compound that will be modified to form a drug species, wherein the modification may take place either inside or outside of the body, and either before or after the pre-drug reaches the area of the body where administration of the drug is indicated.

As described, above, some of the compounds of the invention may contain one or more asymmetric carbon atoms that serve as a chiral center, which may lead to different optical forms

(e.g. enantiomers or diastereoisomers). The invention comprises all such optical forms in all possible configurations, as well as mixtures thereof.

More generally, from the above, it will be clear to the skilled person that the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, E/Z-isomers, stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

The compounds of Formula I or II may be prepared as described in the experimental section below using methods and chemistries with which those skilled in the art shall be familiar.

It will also be clear that when the desired compounds of the invention, and/or the starting materials, precursors and/or intermediates used in the preparation thereof, contain functional groups that are sensitive to the reaction conditions used in the preparation of the compounds of the invention (i.e. that would undergo undesired reactions under those conditions if they were not suitably protected) can be protected during said reaction with one or more suitable protective group, which protective group can then be suitably removed after either completion of said reaction and/or as a later or final step in the preparation of the compounds of the invention. Protected forms of the inventive compounds are included within the scope of the present invention. Suitable protective groups, as well as methods and conditions for inserting them and removing them, will be clear to the skilled person and are generally described in the standard handbooks of organic chemistry, such as Greene and Wuts, "*Protective groups in organic synthesis*", 3rd Edition, Wiley and Sons, 1999, which is incorporated herein by reference in its entirety. It will also be clear to the skilled person that compounds of the invention in which one or more functional groups have been protected with suitable functional groups can find use as intermediates in the production and/or synthesis of the compounds of the invention, and as such form a further aspect of the invention.

Generally, the compounds of the invention can be prepared from aldehyde (such as, but not limited to isoquinoline-5-carbaldehyde) or carboxylic acid-containing intermediates 1 to 8 described hereinafter which may be reacted with complementary reactive molecules so as to form the desired compound. The intermediates and complementary reactive molecules are either commercially available or may be easily prepared by the skilled person.

The compounds of the invention may be used for the inhibition of kinases in vitro or in vivo, preferably in vitro, for modulating biological pathways and/or processes in which such kinases are involved; and/or to prevent and/or treat diseases or disorders in which such kinases, pathways and/or processes are involved.

According to one preferred, but non-limiting embodiment, the compounds of the invention may be used to inhibit (at least one isoform of) ROCK; and as such may be used for any purposes known per se for inhibitors of ROCK.

In the invention, particular preference is given to compounds of Formula I or II above that in the inhibition assay for ROCK described below inhibit ROCK with an IC_{50} value of less than 100 μM, preferably less than 50 μM, more preferably less than 10 μM, preferably less than 5 μM, even more preferably less than 1μM, preferably less than 0.1 μM, and in particular less than 10 nM, for example less than or 1 nM, as determined by a suitable assay, such as the assay used in the Examples below.

The present invention also relates to the use of the compounds of Formula I or II above in (the preparation of a composition for) inhibiting at least one kinase, in particular for inhibiting at least one isoform of ROCK, more in particular for inhibiting ROCK I and/or ROCK II isoforms. As used herein, the term “ROCKI” can also be referred as ROK-β, p160ROCK, or Rho-kinase β and the term “ROCKII” can also be referred as ROK-α or Rho-kinase α. Said inhibition may be effected in vitro and/or in vivo, and when effected in vivo, is preferably effected in a selective manner, as defined above.

The present invention also relates to a compound of Formula I or II, for use in the prevention and/or treatment of at least one disease and/or disorder selected from the group comprising eye diseases; erectile dysfunction; cardiovascular diseases; vascular diseases; inflammatory diseases; proliferative diseases; neurological diseases and disease of the central nervous system (CNS); bronchial asthma; osteoporosis; renal diseases; and AIDS.

According to an embodiment, the invention provides a method for treating or lessening the severity of a ROCK-mediated disease or condition in a patient comprising the step of administering to said patient a compound according to the present invention.

The term "ROCK-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which is known to play a role. The term "ROCK-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ROCK inhibitor. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which ROCK is known to play a role.

According to particularly preferred embodiments, the compounds of the invention are preferably used in the prevention and/or treatment of at least one disease or disorder, preferably in which at least one isoform of ROCK is involved. According to an even more particularly preferred embodiment, the compounds of the invention may be used in the prevention and/or treatment of at least one disease or disorder in which the ROCK I or ROCK II is involved, such as, such as inflammatory diseases, chronic obstructive bladder disease (COBD) and the related erectile dysfunction as well as in diabetes related ED.

Specifically, the present invention relates to the use of a compound according to the invention for the preparation of a medicament for treating or lessening the severity of a disease or condition selected from eye disease or disorder (such as but not limited to retinopathy, glaucoma and degenerative retinal diseases such as macular degeneration and retinitis pigmentosa), kidney

disease (such as but not limited to renal dysfunction), and bladder dysfunction (such as but not limited to chronic obstructive bladder disease), erectile dysfunction (such as but not limited to bladder disease related erectile dysfunction and diabetes related erectile dysfunction) neurological and CNS (brain) disease or disorder (such as but not limited to Alzheimer, meningitis, convulsions), hypertension, lung disease (such as but not limited to asthma, fibrosis, pneumonia, cystic fibrosis, respiratory distress syndrome), premature birth, cancer (such as but not limited to cancer of the brain (gliomas), breast, colon, head and neck, prostate, kidney, lung, intestine, nerve, skin, pancreas, liver, uterus, ovary, brain, thyroid gland; leukemia; lymphoma, and melanoma), cardiovascular and vascular (blood vessel, artery) disease or disorder (such as but not limited to cerebrovascular contraction, ischemia, reperfusion, pulmonary vasoconstriction, acute stroke, congestive heart failure, cardiovascular ischemia, heart disease, cardiac remodeling, hypoxia peripheral circulation disorder, atherosclerosis, thrombosis, aneurism, and hemorrhage), blood disease (such as but not limited to sepsis, eosinophilia, endotoxemia), musculoskeletal disease (such as but not limited to spasm), infection, allergy and autoimmune diseases or disorders, AIDS, bone disease (such as but not limited to osteoporosis), inflammatory diseases, diabetes (such as but not limited to hyperglycemia), obesity and pancreas disease.

For example, the compounds of the invention may be used in the prevention and/or treatment of diseases and disorders such as:

- Cardiovascular and vascular diseases: including but not limited to acute stroke, congestive heart failure, cardiovascular ischemia, heart disease, cardiac remodeling, angina, coronary vasospasm, cerebral vasospasm, restenosis, hypertension, (pulmonary) hypertension, pulmonary vasoconstriction, arteriosclerosis, thrombosis (including deep thrombosis) and platelet related diseases.

- Neurological and CNS disorders: including but not limited to stroke, multiple sclerosis, brain or spinal cord injury, inflammatory and demyelinating diseases such as Alzheimer´s disease, MS and neuropathic pain. The present compounds are therefore suitable for preventing neurodegeneration and stimulating neurogeneration in various neurological disorders.

- Proliferative diseases: such as cancer including but not limited to cancer of the brain (gliomas), breast, colon, intestine, skin, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate, or thyroid; leukemia; sarcoma; lymphoma; and melanoma.

- Inflammatory diseases: including but not limited to contact dermatitis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease and ulcerative colitis. Preferably, the compound may be used in (the preparation of a medicament for) the prevention and/or treatment of Inflammatory diseases selected from contact dermatitis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease and ulcerative colitis and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

In addition, the compounds of the invention may be used in the prevention and/or treatment of diseases and disorders such as erectile dysfunction; bronchial asthma; osteoporosis; renal

diseases; AIDS; eye diseases such as glaucoma, macular degeneration and retinopathy, . Preferably, the compound may be used in the prevention and/or treatment of glaucoma and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

The present invention therefore relates to a method of treating or lessening the severity of a disease or condition selected from cardiovascular and vascular diseases: including but not limited to acute stroke, congestive heart failure, cardiovascular ischemia, heart disease, cardiac remodeling, angina, coronary vasospasm, cerebral vasospasm, pulmonary vasoconstriction, restenosis, hypertension, (pulmonary) hypertension, arteriosclerosis, thrombosis (including deep thrombosis) and platelet related diseases; neurological and CNS disorders: including but not limited to stroke, multiple sclerosis, spinal or brain cord injury, brain or spinal cord injury, inflammatory and demyelinating diseases such as Alzheimer´s disease, MS and neuropathic pain; proliferative diseases such as cancer including but not limited to cancer of the brain (gliomas), breast, colon, intestine, skin, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate or thyroid cancer; leukemia; sarcoma; lymphoma; melanoma; erectile dysfunction; bronchial asthma; osteoporosis; eye diseases such as glaucoma, macular degeneration and retinopathy; renal diseases; AIDS; preterm labor; vascular smooth muscle cell proliferation; myocardial hypertrophy; malignoma; ischemia/reperfusion-induced injury; endothelial dysfunction; Crohn's Disease and colitis; neurite outgrowth; Raynaud's Disease; benign prostatic hyperplasia; and atherosclerosis, wherein said method comprises administering to a patient in need thereof a compound or a composition according to the present invention.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form or a pro-drug or pre-drug, such as an ester. As used herein and unless otherwise stated, the term “solvate” includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates, solvates, etc. and the preparation thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate,

propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. In addition, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl–bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds.

By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration (including ocular), for administration by inhalation, by a skin patch, by an implant, by a suppository, etc.. Such suitable administration forms – which may be solid, semi-solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, eye drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic

polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β- or γ-cyclodextrins (CDs) or ethers and mixed ethers thereof wherein one or more of the hydroxyl groups of the anhydroglucose units of the cyclodextrin are substituted with alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyalkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyalkyl, particularly carboxymethyl or carboxyethyl; alkylcarbonyl, particularly acetyl; alkoxycarbonylalkyl or carboxyalkoxyalkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; alkylcarbonyloxyalkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl- β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl- β-CD, and in particular 2-hydroxypropyl- β-CD (2-HP- β-CD). The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. Although the formulations described therein are with antifungal active ingredients, they are equally interesting for formulating the compounds. Said formulations may also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors. In particular, the present invention encompasses a pharmaceutical composition comprising an effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin. The present invention also encompasses cyclodextrin complexes consisting of a compound according to the invention and a cyclodextrin.

Particular reference is made to the compositions, formulations (and carriers, excipients, diluents, etc. for use therein), routes of administration etc., which are known per se for analogous pyridinocarboxamides, such as those described in US-A-4,997,834 and EP-A-0 370 498.

For the treatment of pain, the compounds of the invention may be used locally or systemically. For local administration, the compounds may advantageously be used in the form of a spray, ointment or transdermal patch or another suitable form for topical, transdermal and/or intradermal administration; and for systemic administration, the compounds of the invention may advantageously be administered orally.

For ophthalmic application, solutions, gels, tablets and the like are often prepared using a physiological saline solution, gel or excipient as a major vehicle. Ophthalmic formulations should preferably be prepared at a comfortable pH with an appropriate buffer system.

More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. The term "a solid dispersion" also comprises dispersions that are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-propyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

It may further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Said beads comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antiretroviral agent and (c) a seal-coating polymer layer. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

The preparations may be prepared in a manner known per se, which usually involves mixing at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, ocular, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound of the Formula I or II above that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram body weight day of the patient per day, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778,US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Thus, in a further aspect, the invention relates to a composition, and in particular a composition for pharmaceutical use, that contains at least one compound of the invention (i.e. a compound that has been identified, discovered and/or developed using a nematode or method as described herein) and at least one suitable carrier (i.e. a carrier suitable for pharmaceutical use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

The compositions are of value in the veterinary field, which for the purposes herein not only includes the prevention and/or treatment of diseases in animals, but also – for economically important animals such as cattle, pigs, sheep, chicken, fish, etc. – enhancing the growth and/or weight of the animal and/or the amount and/or the quality of the meat or other products obtained from the animal. Thus, in a further aspect, the invention relates to a composition for veterinary use that contains at least one compound of the invention (e.g. a compound that has been identified, discovered and/or developed using a nematode or method as described herein) and at least one suitable carrier (i.e. a carrier suitable for veterinary use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limited the scope of the invention in any way.

EXAMPLES

Analytical (or preparative) techniques:

Unless indicated otherwise, the purity of the compounds was confirmed by liquid chromatography/mass spectrometry (LC/MS), as follows:

- HPLC system: Waters 2690 with photodiode array detector Waters 996; Column: C18; Gradient: solvent A (H_2O/formic acid 26.5 nM) 0%, to solvent B (CH_3CN/formic acid 17 nM) 80% in 3 min. Flow: 2.75 ml/min.

- Mass spectrometer: Micromass Platform LC. Ionization: electrospray (polarity: negative and positive).

Unless indicated otherwise, purification by preparative HPLC, was performed on a Shimadzu SCL-10A (UV detection at 215 and 254 nm, detector SPD-10A) using C-18 column (Nucleosil, 100Å, 100µm, 20 x 200 mm) and different gradients (water, acetonitrile, formic acid).

Chiral HPLC (analytical and preparative) was performed on a Shimadzu SCL-10A (UV detection at 215 and 254 nm, detector SPD-10A) using different column such as Chiralcel OD-H (tris-3,5-dimethylphenylcarbamate, 46 x 250 or 100 x 250 mm, 5 µm), Chiralcel OJ (tris-methylbenzoate, 46 x 250 or 100 x 250 mm, 5 µm), Chiralpak AD (tris-3,5-dimethylphenylcarbamate, 46 x 250 mm, 10 µm) and Chiralpak AS (tris-(S)-1-phenylethylcarbamate, 46 x 250 mm, 10 µm) from Chiral Technologies Europe (Illkirch, France):

- Eluent: mixture of solvent such as ethanol, 1-propanol, 2-propanol, methanol, butanol, pentane, hexane, heptane, cyclohexane, diisopropylethyamine, triethylamine.
- Flow: between 1 and 50 ml/min.

NMR spectra were determined on a Varian Mercury 300 MHz NMR using the indicated solvent as an internal reference. Melting points were determined on a Büchi B-540 and are non-corrected. All reagents used either were obtained commercially or were prepared in a manner known per se.

Attribution of the configuration:

The Cahn-Ingold-Prelog system was used to attribute the absolute configuration of chiral center, in which the four groups on an asymmetric carbon are ranked to a set of sequences rules. Reference is made to Cahn; Ingold; Prelog *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 385-415.

Name of the molecule

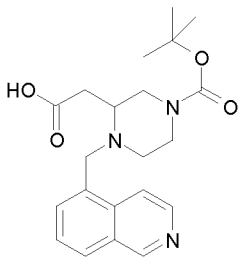
The software MDL ISIS™ / Draw 2.5 was used to assign the name of the molecules.

Example 1

The following intermediates and general procedures were used to prepare the compounds described herein.

Intermediates:

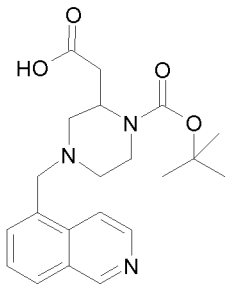
Intermediate 1: 3-carboxymethyl-4-isoquinolin-5-ylmethyl-piperazine-1-carboxylic acid tert-butyl ester.



To a solution of isoquinoline-5-carbaldehyde (1.35 g) in DCM, were successively added a solution of 3-methoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester (1.1 eq.) in DCM (25 ml) and $NaBH(OAc)_3$ (2.5 eq.). The reaction mixture was stirred at RT for 24 hours. diluted in DCM and 1M sodium bicarbonate. After separation, the organic layer was washed with brine, dried with magnesium sulfate, filtered off and evaporated. The residue was by chromatography on C-18 (water/CH3CN 100/0 to 40/60) to afford the intermediate methyl ester as a white powder (56 % yield).

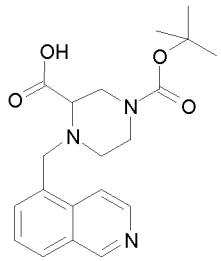
The methyl ester (1.92 g) was dissolved in a mixture of MeOH (20 ml) and water (20 ml). Lithium hydroxide hydrate (5 eq.) was added and the reaction mixture was stirred at 60°C for 30 minutes and then, was concentrated. The resulting solution, was diluted with aqueous citric acid solution (pH 5, 50 ml) and then slowly acidified to pH 4-5 with 2N hydrochloric acid. The compound was extracted with DCM (250 ml). The organic layer was dried over magnesium sulfate, filtered off and evaporated. The title compound was obtained as a white powder (80 % yield) and was used without further purification (mp: 104-106°C).

Intermediate 2: 2-carboxymethyl-4-isoquinolin-5-ylmethyl-piperazine-1-carboxylic acid tert-butyl ester.



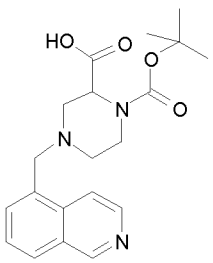
The title compound was obtained using the protocol described for Intermediate 1, starting from 2-methoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester (27 % overall yield).

Intermediate 3: 4-isoquinolin-5-ylmethyl-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester.



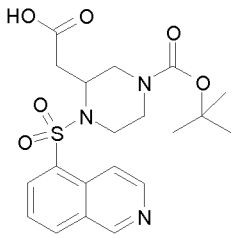
The title compound was obtained using the protocol described for Intermediate 1, starting from piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (52 % overall yield).

Intermediate 4: 4-isoquinolin-5-ylmethyl-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester.



The title compound was obtained using the protocol described for Intermediate 5, starting from piperazine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (64 % overall yield).

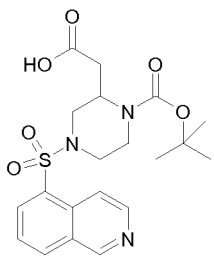
Intermediate 5: 3-carboxymethyl-4-(isoquinoline-5-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester.



To a solution of isoquinoline-5-sulfonyl chloride hydrochloride (930 mg) in THF (20 ml) were added DIPEA (2.2 eq.) and (3-methoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester (1 eq.). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was taken in DCM. The DCM layer was washed with 1N sodium carbonate and then, with brine. The organic layer was evaporated and the residue was purified by chromatography on C-18 (water/CH_3CN 100/0 to 50/50) to afford the intermediate methyl ester as a white powder (66 % yield).

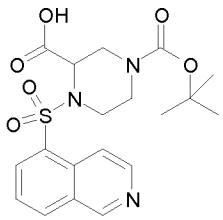
The methyl ester (1.0 g) was dissolved in a mixture of MeOH (20 ml) and water (20 ml). Lithium hydroxide hydrate (5 eq.) was added and the reaction mixture was stirred at 60°C for 30 minutes and then, was concentrated. The resulting solution, was diluted with aqueous citric acid solution (pH 5, 50 ml) and then slowly acidified to pH 4-5 with 2N hydrochloric acid. The compound was extracted with DCM (250 ml). The organic layer was dried over magnesium sulfate, filtered off and evaporated. The title compound was obtained as a white powder (72 % yield) and was used without further purification (mp: 119-121°C).

Intermediate 6: 2-carboxymethyl-4-(isoquinoline-5-sulfonyl)-piperazine-1-carboxylic acid tert-butyl ester.



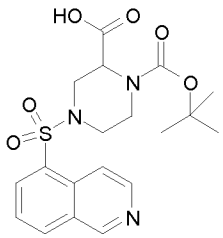
The title compound was obtained using the protocol described for Intermediate 5, starting from 2-methoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester (29 % overall yield).

Intermediate 7: 4-(isoquinoline-5-sulfonyl)-piperazine-1,3-dicarboxylic acid 1-tert-butyl ester.



The title compound was obtained using the protocol described for Intermediate 5, starting from piperazine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (30 % overall yield).

Intermediate 8: 4-(isoquinoline-5-sulfonyl)-piperazine-1,2-dicarboxylic acid 1-tert-butyl ester.



The title compound was obtained using the protocol described for Intermediate 5, starting from piperazine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (55 % overall yield).

General procedures:

Protocol A:

To a solution of the corresponding aldehyde (1 eq.) in DCM (0.25 M) were successively added the corresponding amine (1 to 1.1 eq.) in DCM (0.25 M) and sodium triacetoxyborohydride (2.5 eq.). The reaction mixture was stirred at RT for 16 to 24 hours. Sodium carbonate 1 M was then added, and the reaction mixture was further stirred at RT for 1 hour. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered off, and finally evaporated. The residue was purified by flash chromatography on silica gel or on C-18.

Deprotection of tert-butoxycarbonylamino group (when applicable): The product was dissolved in freshly distillated 1,4-dioxane. HCl gas was bubbled in the solution for 10 to 30 minutes. The solvent was then evaporated and the final compound was dried under vacuum.

Protocol B:

To a solution of the corresponding carboxylic acid (5.25 µmol) in DMF (0.437 M) with DIEA (3 eq) was added 1 eq of a solution of TBTU / HOBt (1 / 0.2) in DMF (0.4 M). The reaction mixture was stirred at RT for 3 to 10 minutes and a solution of the corresponding amine (1 eq) in DMF (0.1 M) at neutrality (with DIEA). The reaction mixture was stirred at RT for 3 hours, and then 0.7 eq of a solution of TBTU / HOBt (1 / 0.2) in DMF (0.4 M) was added. After 4 hours the reaction mixture was evaporated.

Deprotection of tert-butoxycarbonylamino group: a mixture of DCM and trifluoroacetic acid (1 / 1; 100 µl) was added to the residue. The solution was stirred at RT for 2 hours, and then evaporated under reduced pressure. Compounds were used without further purification.

Protocol C:

To a solution of the corresponding carboxylic acid (1 eq) in DMF (0.25 M) with DIEA (3 eq) was added TBTU (1.3 eq) and HOBt (0.3 eq). The reaction mixture was stirred at RT for 3 to 10 minutes and the corresponding amine (1 eq) was added. The reaction mixture was stirred at RT for 3 hours to 3 days. The solvent was evaporated. The residue was partitioned between EtOAc and 2N Na_2CO_3 (or 1N NaOH). The product was extracted with EtOAc. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated.

Alternative protocol: To a solution of the corresponding carboxylic acid (1 eq) in a mixture DMF/DCM (0.25 M) were successively added DCC (1 eq), HOBt (1 eq) and DIEA (3 eq). The solution was stirred at RT for 30 minutes before the addition of the corresponding amine (1 eq). The reaction mixture was stirred at RT for 2 hours to 3 days. The solvent was evaporated. The residue was partitioned between DCM and water. The product was extracted with DCM. The organic layer was separated, washed with 2N Na_2CO_3 (or 1N NaOH), brine, dried over magnesium sulfate, and evaporated.

Deprotection of tert-butoxycarbonylamino group: The crude product was dissolved in freshly distillated 1,4-dioxane. HCl gas was bubbled in the solution for 10 to 30 minutes. The solvent was evaporated and then, the residue was purified by preparative HPLC.

Biological activity

The compounds were tested for inhibition of human ROCKα/ROCKII mix.

The inhibition assays were performed with a fluorescence polarization (FP) assay using the commercially available ROCK IMAP Kit from Molecular Devices (Product ID. No. R8093), essentially in accordance with the protocol supplied by the manufacturer. The S6 ribosomal protein-derived substrate used was (FI)-AKRRRLSSLRA, also obtained from Molecular Devices (Product ID No. R7184). The enzyme mix ROCKα/ROCKII was obtained from Upstate Biotechnology (Product ID No 14-451).

In summary, all compounds were screened in the wells of a 384 well plate for enzymatic inhibition with concentrations varying from 100µM to 0.3nM using a stepwise 3 (or 2)-fold dilution. Y-27632 (commercially available from Tocris) was used as a reference (0.4 µM).

To perform the assay, 1µl of a solution of the compound to be tested in DMSO (at each concentration) was added to 2 µl of a solution of the enzyme in 10mM Tris-HCl , 10mM $MgCl_2$, 0.1% BSA, 0.05% NaN_3, pH 7,2. The final concentration of the enzyme was 2.6nM.

After incubating for 30 minutes at RT, 2 µl of a mixture of ATP and the protein substrate in 10mM Tris-HCl, 10mM $MgCl_2$, 0.1% BSA, 0.05% NaN_3, pH 7.2 was added. The final concentration of the ATP was 10 µM and final concentration of protein substrate was 0.2 µM.

After incubating for 60 minutes at RT, 12 µl of the IMAP Binding Solution (mix of the IMAP Binding Buffer A (1x) and the IMAP Binding Reagent (from the ROCK IMAP kit)) was added.

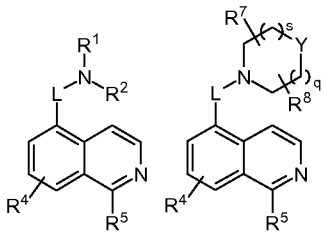
The mixture thus obtained (total volume: 17 µl) was incubated for 60 minutes at RT, upon which the fluorescence polarization was measured using an automated plate reader (Perkin Elmer, Model Envision 2100-0010 HTS) with FP filters: excitation filter FITC FP 480 and emission filters FITC FP P-pol 535 and FITC FP S-pol 535 (Perkin-Elmer). The results were fitted to a curve using the XL-Fit algorithm and IC50 values were calculated for each fitted curve, again using the XL-Fit algorithm.

The IC_{50} value for the reference compound (Y compound Y-27632) was 0.4µM.

Compounds of the invention

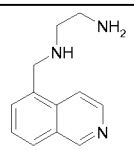
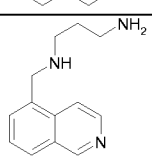
In the tables 1 to 9 that are set forth below, exemplary compounds of the invention are set out in tabulated form. In these tables, the name of the compound, an arbitrarily assigned compound number and structural information are set out. In addition, the protocol by which the compounds were made is provided and the IC_{50} value obtained (in accordance with the protocol set forth above) is represented as follows: "+++" means IC_{50} below 0.1 µM; "++" means IC_{50} between 0.1 and 1 µM; "+" means IC_{50} between 1 and 50 µM.

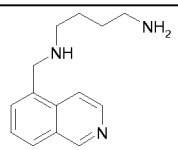
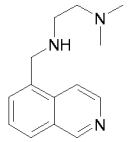
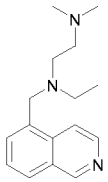
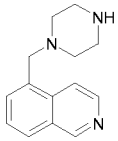
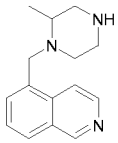
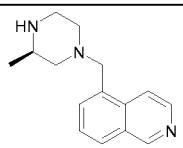
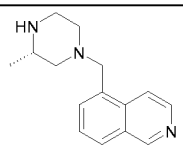
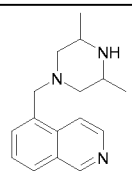
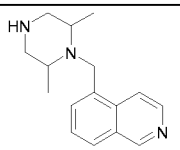
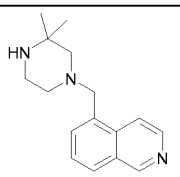
Table 1 shows the results for compounds of Formula I or II. As used herein the term "ND" means "not determined".

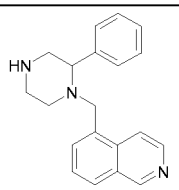
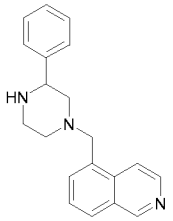
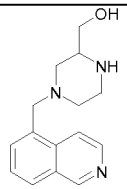
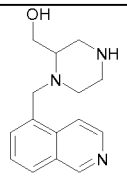
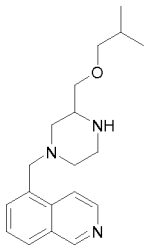
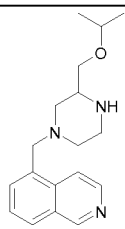
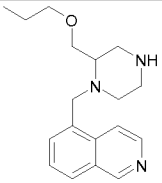
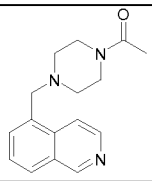


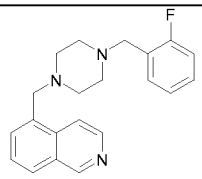
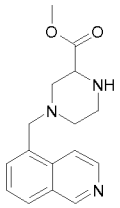
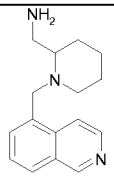
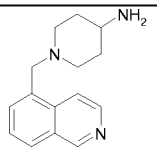
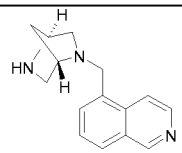
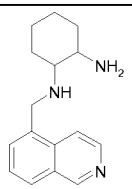
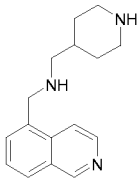
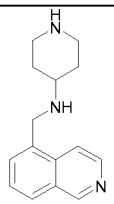
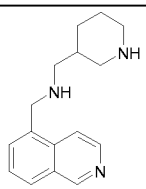
I II

Table 1

Name	Compound	Structure	IC_{50} (µM) ROCK
N'1'-Isoquinolin-5-ylmethyl-ethane-1,2-diamine	Compound 1		+
N'1'-Isoquinolin-5-ylmethyl-propane-1,3-diamine	Compound 2		+

Name	Compound	Structure	IC_{50} (μM) ROCK
N'1'-Isoquinolin-5-ylmethyl-butane-1,4-diamine	Compound 3		+
N'-Isoquinolin-5-ylmethyl-N,N-dimethyl-ethane-1,2-diamine	Compound 4		nd
N-Ethyl-N-isoquinolin-5-ylmethyl-N',N'-dimethyl-ethane-1,2-diamine	Compound 5		+
5-Piperazin-1-ylmethyl-isoquinoline	Compound 6		++
5-(2-Methyl-piperazin-1-ylmethyl)-isoquinoline	Compound 7		++
5-((R)-3-Methyl-piperazin-1-ylmethyl)-isoquinoline	Compound 8		+
5-((S)-3-Methyl-piperazin-1-ylmethyl)-isoquinoline	Compound 9		++
5-(3,5-Dimethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 10		++
5-(2,6-Dimethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 11		+
5-(3,3-Dimethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 12		++

Name	Compound	Structure	IC_{50} (μM) ROCK
5-(2-phenyl-piperazin-1-ylmethyl)-isoquinoline	Compound 13		+
5-(3-phenyl-piperazin-1-ylmethyl)-isoquinoline	Compound 14		+
(4-Isoquinolin-5-ylmethyl-piperazin-2-yl)-methanol	Compound 15		++
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-methanol	Compound 16		++
5-(3-Isobutoxymethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 17		nd
5-(3-Isopropoxymethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 18		+
5-(2-Propoxymethyl-piperazin-1-ylmethyl)-isoquinoline	Compound 19		+
1-(4-Isoquinolin-5-ylmethyl-piperazin-1-yl)-ethanone	Compound 20		+

Name	Compound	Structure	IC_{50} (μM) ROCK
5-[4-(2-Fluoro-benzyl)-piperazin-1-ylmethyl]-isoquinoline	Compound 21		+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid methyl ester	Compound 22		+
C-(1-Isoquinolin-5-ylmethyl-piperidin-2-yl)-methylamine	Compound 23		+
1-Isoquinolin-5-ylmethyl-piperidin-4-ylamine	Compound 24		+
5-[(1S,4S)-1-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)methyl]-isoquinoline	Compound 25		+
N-Isoquinolin-5-ylmethyl-cyclohexane-1,2-diamine	Compound 26		+
Isoquinolin-5-ylmethyl-piperidin-4-ylmethyl-amine	Compound 27		nd
Isoquinolin-5-ylmethyl-piperidin-4-yl-amine	Compound 28		nd
Isoquinolin-5-ylmethyl-piperidin-3-ylmethyl-amine	Compound 29		+

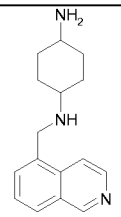
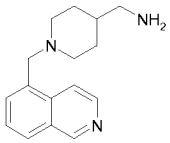
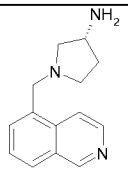
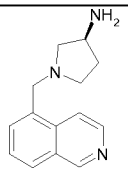
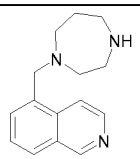
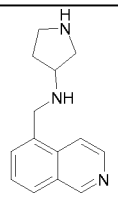
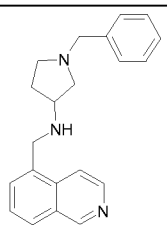
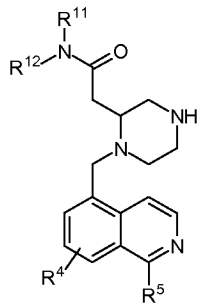
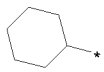
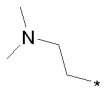
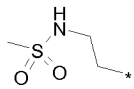
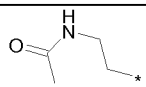
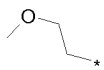
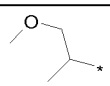
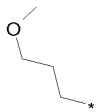
Name	Compound	Structure	IC_{50} (μM) ROCK
N-Isoquinolin-5-ylmethyl-cyclohexane-1,4-diamine	Compound 30		nd
C-(1-Isoquinolin-5-ylmethyl-piperidin-4-yl)-methylamine	Compound 31		+
(R)-1-Isoquinolin-5-ylmethyl-pyrrolidin-3-ylamine	Compound 32		+
(S)-1-Isoquinolin-5-ylmethyl-pyrrolidin-3-ylamine	Compound 33		+
5-[1,4]Diazepan-1-ylmethyl-isoquinoline	Compound 34		++
Isoquinolin-5-ylmethyl-pyrrolidin-3-yl-amine	Compound 35		+
(1-Benzyl-pyrrolidin-3-yl)-isoquinolin-5-ylmethyl-amine	Compound 36		+

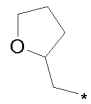
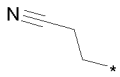
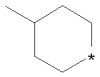
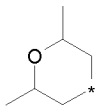
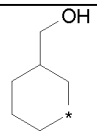
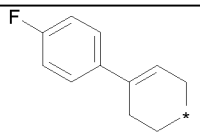
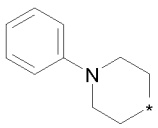
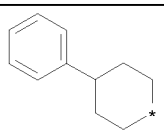
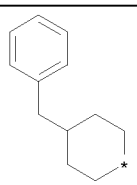
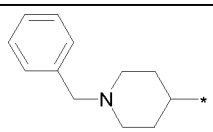
Table 2 shows the results for compounds of Formula V5 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V5 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 1 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.

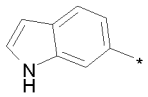
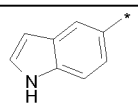
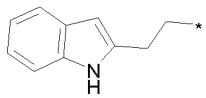
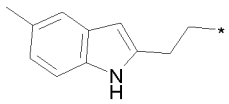
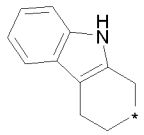
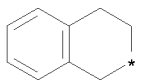
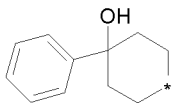
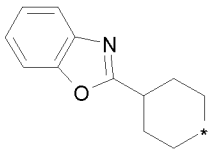
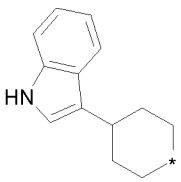
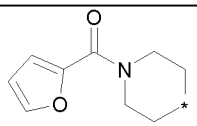
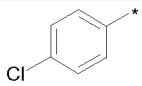
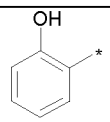
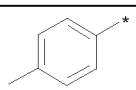


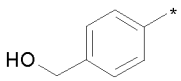
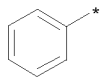
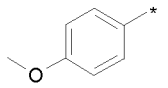
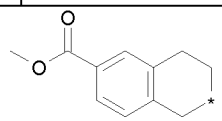
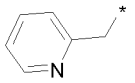
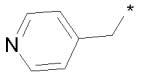
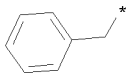
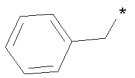
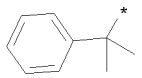
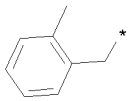
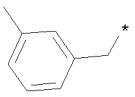
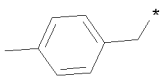
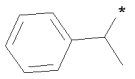
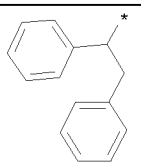
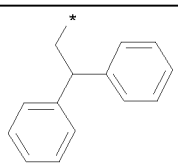
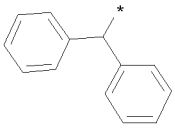
V5

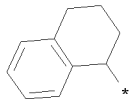
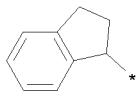
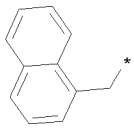
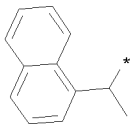
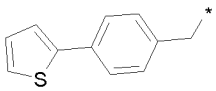
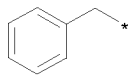
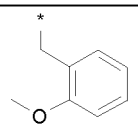
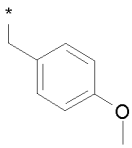
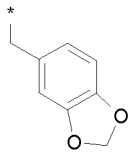
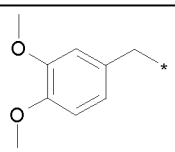
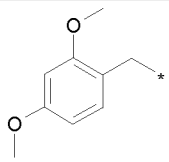
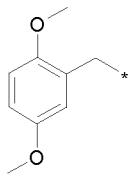
Table 2

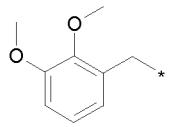
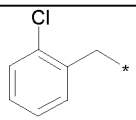
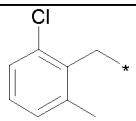
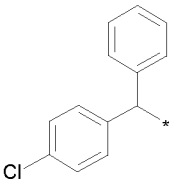
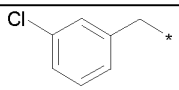
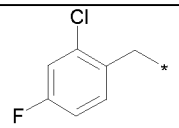
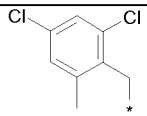
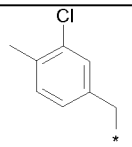
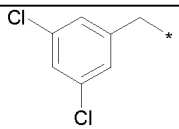
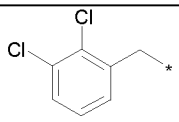
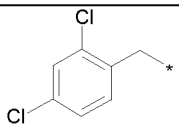
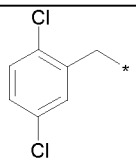
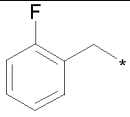
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(1,1-dimethyl-propyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 37	-H		B	nd
N-cyclopropylmethyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 38	-H		B	nd
N-ethyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 39	-H		B	nd
N-cyclohexyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 40	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-methyl-N-propyl-acetamide	Compound 41	$-CH_3$		B	nd
N-Cyclopropylmethyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-propyl-acetamide	Compound 42			B	nd
N-(2-dimethylamino-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 43	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-methanesulfonylamino-ethyl)-acetamide	Compound 44	-H		B	nd
N-(2-acetylamino-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 45	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-methoxy-ethyl)-acetamide	Compound 46	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(2-methoxy-1-methyl-ethyl)-acetamide	Compound 47	-H		B	nd
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(3-methoxy-propyl)-acetamide	Compound 48	-H		B	nd

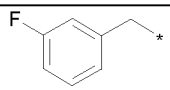
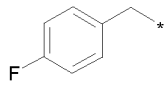
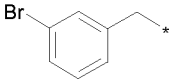
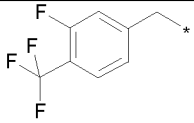
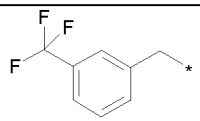
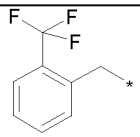
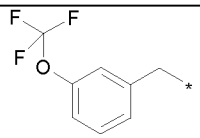
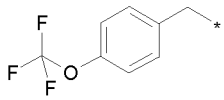
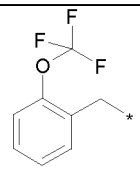
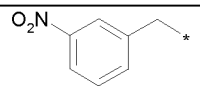
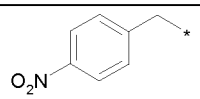
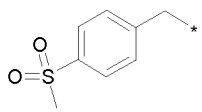
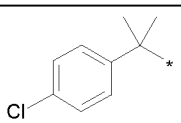
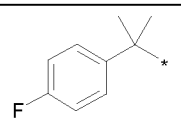
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(tetrahydro-furan-2-ylmethyl)-acetamide	Compound 49	-H		B	nd
N-(2-cyano-ethyl)-*N*-cyclopropyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 50			B	nd
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-1-pyrrolidin-1-yl-ethanone	Compound 51			B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-1-(4-methyl-piperidin-1-yl)-ethanone	Compound 52			B	nd
1-(3,6-dihydro-2H-pyridin-1-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 53			B	nd
1-(2,6-dimethyl-morpholin-4-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 54			B	nd
1-(morpholin-4-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 55			B	nd
1-(3-hydroxymethyl-piperidin-1-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 56			B	nd
1-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 57			B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-1-(4-phenyl-piperazin-1-yl)-ethanone	Compound 58			B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-1-(4-phenyl-piperidin-1-yl)-ethanone	Compound 59			B	+
1-(4-benzyl-piperidin-1-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 60			B	+
N-(1-Benzyl-piperidin-4-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 61	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-methoxy-acetamide	Compound 62	-H		B	+

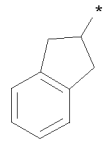
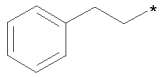
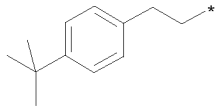
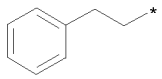
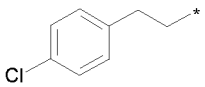
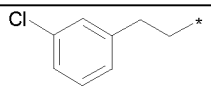
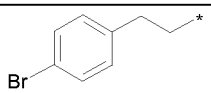
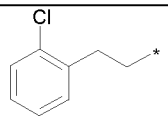
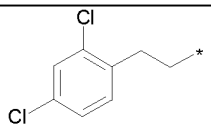
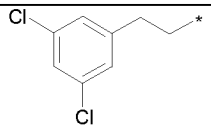
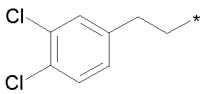
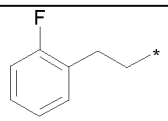
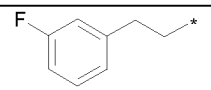
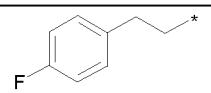
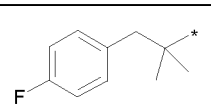
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(1*H*-indol-6-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 63	-H		B	++
N-(1*H*-indol-5-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 64	-H		B	nd
N-[2-(1*H*-indol-2-yl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 65	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-[2-(5-methyl-1H-indol-3-yl)-ethyl]-acetamide	Compound 66	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-1-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone	Compound 67			B	nd
1-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 68			B	nd
1-(4-Hydroxy-4-phenyl-piperidin-1-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 69			B	++
1-(4-Benzooxazol-2-yl-piperidin-1-yl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 70			B	nd
1-[4-(1*H*-Indol-3-yl)-piperidin-1-yl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 71			B	+
1-[4-(furan-2-carbonyl)-piperazin-1-yl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-ethanone	Compound 72			B	+
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-1-thiazolidin-3-yl-ethanone	Compound 73			B	nd
N-(4-chloro-phenyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 74	-H		C	++
N-(2-hydroxy-phenyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 75	-H		B	++
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-p-tolyl-acetamide	Compound 76	-H		B	++

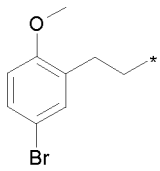
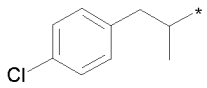
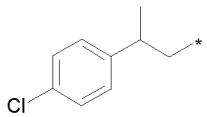
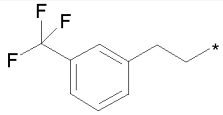
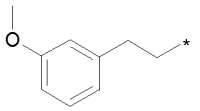
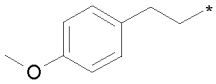
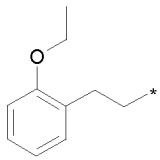
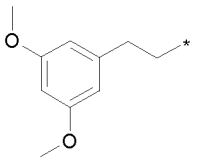
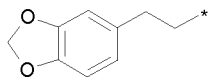
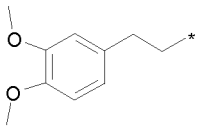
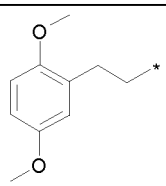
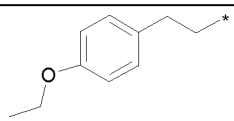
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(4-hydroxymethyl-phenyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 77	-H		C	+++
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-phenyl-acetamide	Compound 78	-H		B	++
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(4-methoxy-phenyl-acetamide	Compound 79	-H		B	++
2-[2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetyl]-1,2,3,4-tetrahydro-isoquinoline-6-carboxylic acid methyl ester	Compound 80			B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-pyridin-2-ylmethyl-acetamide	Compound 81	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-pyridin-2-ylmethyl-acetamide	Compound 82	-H		B	nd
N-benzyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-methyl-acetamide	Compound 83	$-CH_3$		B	+
N-benzyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 84	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(1-methyl-1-phenyl-ethyl)-acetamide	Compound 85	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-methyl-benzyl)-acetamide	Compound 86	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(3-methyl-benzyl)-acetamide	Compound 87	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(4-methyl-benzyl)-acetamide	Compound 88	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(1-phenyl-ethyl)-acetamide	Compound 89	-H		B	nd
N-(1,2-diphenyl-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 90	-H		B	nd
N-(2,2-diphenyl-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 91	-H		B	+
N-benzhydryl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 92	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide	Compound 93	-H		B	+
N-indan-1-yl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 94	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(1-naphthalen-1-yl-methyl)-acetamide	Compound 95	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(1-naphthalen-1-yl-ethyl)-acetamide	Compound 96	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(4-thiophen-2-yl-benzyl)-acetamide	Compound 97	-H		B	nd
N-benzyl-*N*-(2-cyano-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 98			B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(2-methoxy-benzyl-acetamide	Compound 99	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(4-methoxy-benzyl-acetamide	Compound 100	-H		B	+
N-benzo[1,3]dioxol-5-ylmethyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 101	-H		B	+
N-(3,4-dimethoxy-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 102	-H		B	nd
N-(2,4-dimethoxy-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 103	-H		B	nd
N-(2,5-dimethoxy-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 104	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(2,3-dimethoxy-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 105	-H		B	nd
N-(2-chloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 106	-H		B	+
N-(2-chloro-6-methyl-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 107	-H		B	+
N-[(4-chloro-phenyl)-phenyl-methyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 108	-H		B	nd
N-(3-chloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 109	-H		B	+
N-(2-chloro-4-fluoro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 110	-H		B	+
N-(2,4-dichloro-6-methyl-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 111	-H		B	++
N-(3-chloro-4-methyl-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 112	-H		B	+
N-(3,5-dichloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 113	-H		B	+
N-(2,3-dichloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 114	-H		B	+
N-(2,4-dichloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 115	-H		B	+
N-(2,5-dichloro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 116	-H		B	+
N-(2-fluoro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 117	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(3-fluoro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 118	-H		B	+
N-(4-fluoro-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 119	-H		B	+
N-(3-bromo-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 120	-H		B	+
N-(3-fluoro-4-trifluoromethyl-benzyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 121	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(3-trifluoromethyl-benzyl)-acetamide	Compound 122	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-trifluoromethyl-benzyl)-acetamide	Compound 123	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-trifluoromethoxy-benzyl)-acetamide	Compound 124	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(4-trifluoromethoxy-benzyl)-acetamide	Compound 125	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(2-trifluoromethoxy-benzyl)-acetamide	Compound 126	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(3-nitro-benzyl)-acetamide	Compound 127	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-(4-nitro-benzyl)-*N*-propyl-acetamide	Compound 128			B	nd
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(4-methanesulfonyl-benzyl)-acetamide	Compound 129	-H		B	nd
N-[1-(4-chloro-phenyl)-1-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 130	-H		B	+
N-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 107	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-indan-2-yl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 108	-H		B	+
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-phenethyl-acetamide	Compound 109	-H		B	+
N-[2-(4-*tert*-Butyl-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 110	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-methyl-N-phenethyl-acetamide	Compound 111	-CH_3		B	nd
N-[2-(4-chloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 112	-H		B	+
N-[2-(3-chloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 113	-H		B	+
N-[2-(4-bromo-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 114	-H		B	+
N-[2-(2-chloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 115	-H		B	+
N-[2-(2,4-dichloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 116	-H		B	+
N-[2-(3,5-dichloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 117	-H		B	+
N-[2-(3,4-dichloro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 118	-H		B	+
N-[2-(2-fluoro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 119	-H		B	+
N-[2-(3-fluoro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 120	-H		B	+
N-[2-(4-fluoro-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 121	-H		B	+
N-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 122	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-[2-(3-bromo-6-methoxy-phenyl)-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 123	-H		B	nd
N-[2-(4-chloro-phenyl)-1-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-pip erazin-2-yl)-acetamide	Compound 124	-H		B	+
N-[2-(4-chloro-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-pip erazin-2-yl)-acetamide	Compound 125	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide	Compound 126	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-[2-(3-methoxy-phenyl)-ethyl]-acetamide	Compound 127	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-[2-(4-methoxy-phenyl)-ethyl]-acetamide	Compound 128	-H		B	+
N-[2-(2-ethoxy-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-pip erazin-2-yl)-acetamide	Compound 129	-H		B	nd
N-[2-(3,5-dimethoxy-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 130	-H		B	nd
N-(2-benzo[1,3]dioxol-5-yl-ethyl)-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 131	-H		B	+
N-[2-(3,4-dimethoxy-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 132	-H		B	nd
N-[2-(2,5-dimethoxy-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 133	-H		B	nd
N-[2-(4-ethoxy-phenyl)-2-methyl-ethyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 134	-H		B	nd

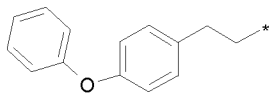
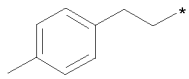
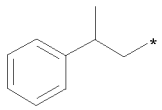
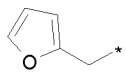
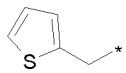
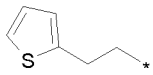
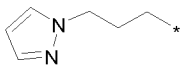
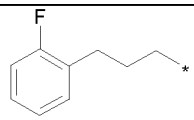
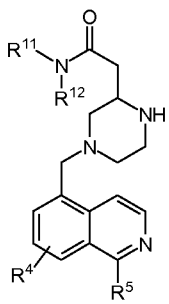
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-[2-(3-phenoxy-phenyl)-ethyl]-acetamide	Compound 135	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-N-[2-(4-methyl-phenyl)-ethyl]-acetamide	Compound 136	-H		B	nd
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(2-phenyl-propyl)-acetamide	Compound 137	-H		B	+
N-furan-2-ylmethyl-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 138	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)- *N*-thiophene-2-ylmethyl-acetamide	Compound 139	-H		B	+
2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)- *N*-thiophene-2-yl-ethyl-acetamide	Compound 140	-H		B	+
2-(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(3-pyrazol-1-yl-propyl)-acetamide	Compound 141	-H		B	+
N-[3-(2-Fluoro-phenyl)-propyl]-2-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 142	-H		B	+

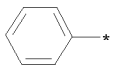
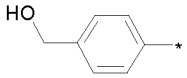
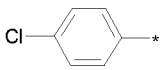
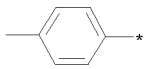
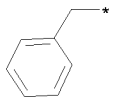
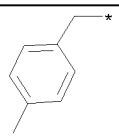
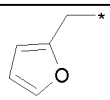
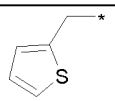
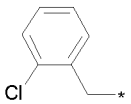
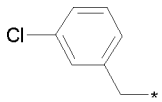
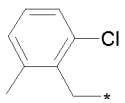
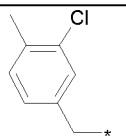
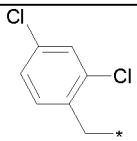
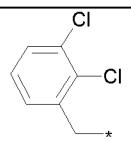
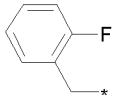
Table 3 shows the results for compounds of Formula V7 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V7 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 2 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.



V7

Table 3

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-phenyl-acetamide	Compound 143	-H		B	++
N-(4-hydroxymethyl-phenyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 144	-H		B	+
N-(4-chloro-phenyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 145	-H		B	++
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- *N*-*p*-tolyl-acetamide	Compound 146	-H		B	++
N-benzyl-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 147	-H		B	+
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(4-methyl-benzyl)-acetamide	Compound 148	-H		B	+
N-furan-2-ylmethyl-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 149	-H		B	+
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- *N*-thiophen-2-ylmethyl-acetamide	Compound 150	-H		B	+
N-(2-chloro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 151	-H		B	+
N-(3-chloro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 152	-H		B	+
N-(2-chloro-6-methyl-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 153	-H		B	+
N-(3-chloro-4-methyl-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 154	-H		B	+
N-(2,4-dichloro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 155	-H		B	+
N-(2,3-dichloro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 156	-H		B	+
N-(2-fluoro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 157	-H		B	+

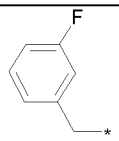
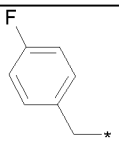
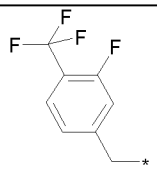
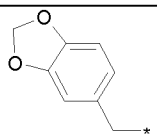
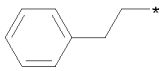
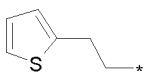
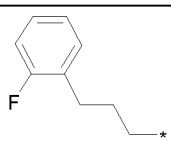
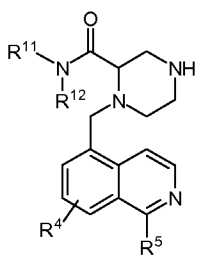
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(3-fluoro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 158	-H		B	+
N-(4-fluoro-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 159	-H		B	+
N-(3-fluoro-4-trifluoromethyl-benzyl)-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-acetamide	Compound 160	-H		C	++
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(3,4-methylenedioxy-benzyl)-acetamide	Compound 161	-H		B	+
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-phenethyl-acetamide	Compound 162	-H		B	+
2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)-*N*-(2-thiophen-2-yl-ethyl)-acetamide	Compound 163	-H		B	+
N-[3-(2-fluoro-phenyl)-propyl]-2-(4-isoquinolin-5-ylmethyl-piperazin-2-yl)- acetamide	Compound 164	-H		B	+

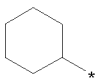
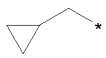
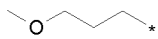
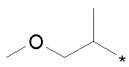
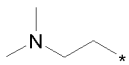
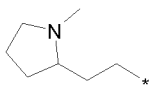
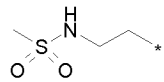
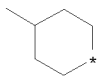
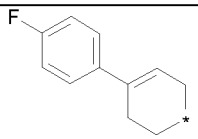
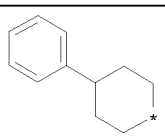
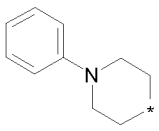
Table 4 shows the results for compounds of Formula V6 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V6 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 3 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.

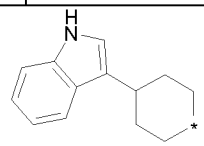
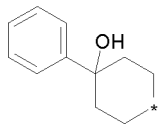
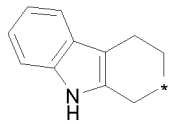
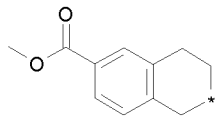
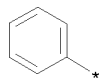
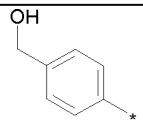
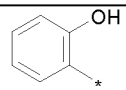
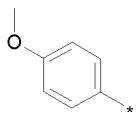
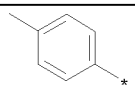
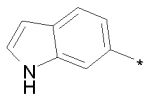
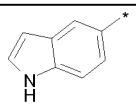
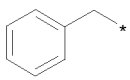
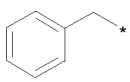


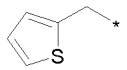
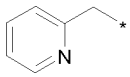
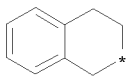
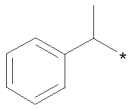
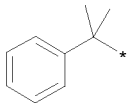
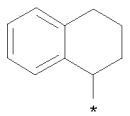
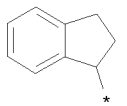
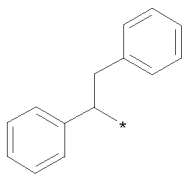
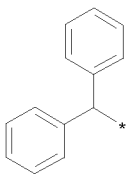
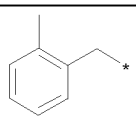
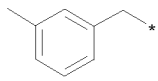
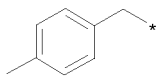
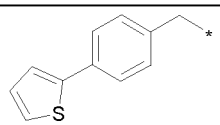
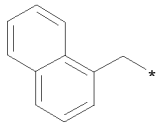
V6

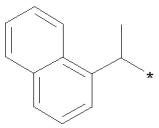
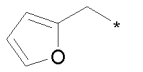
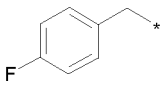
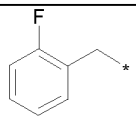
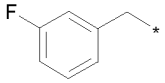
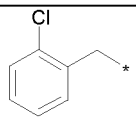
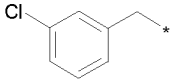
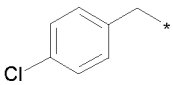
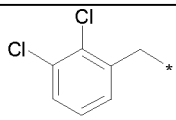
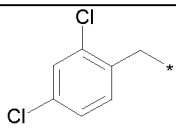
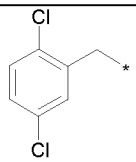
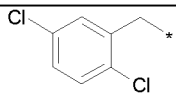
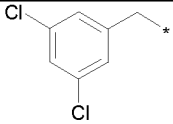
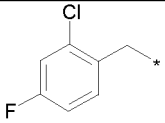
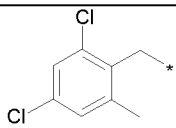
Table 4

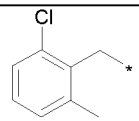
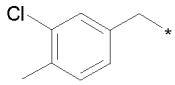
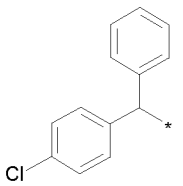
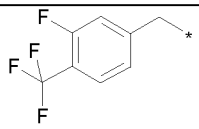
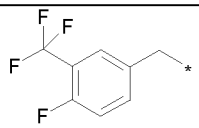
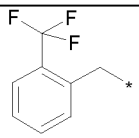
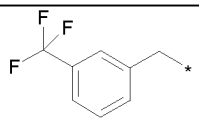
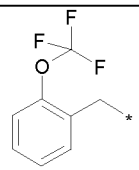
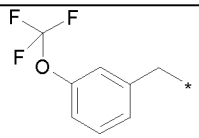
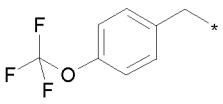
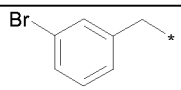
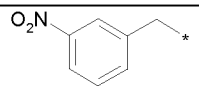
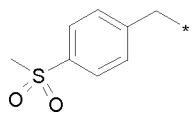
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK

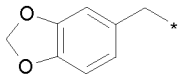
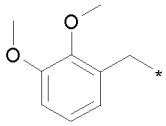
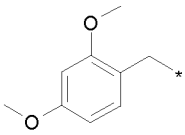
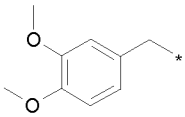
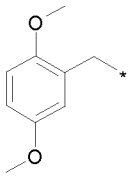
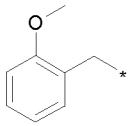
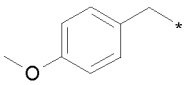
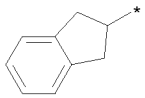
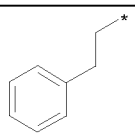
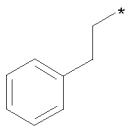
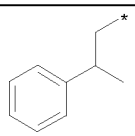
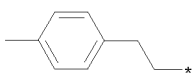
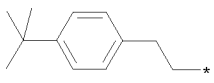
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid ethylamide	Compound 165	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1,1-dimethyl-propyl)-amide	Compound 166	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid cyclohexylamide	Compound 167	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid cyclopropylmethyl-amide	Compound 168	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-methyl-amide	Compound 169	$-CH_3$		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (3-methoxy-propyl)-amide	Compound 170	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-methoxy-1-methyl-ethyl)-amide	Compound 171	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-dimethylamino-ethyl)-amide	Compound 172	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide	Compound 173	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-methanesulfonylamino-ethyl)-amide	Compound 174	-H		B	+
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-(4-methyl-piperidin-1-yl)-methanone	Compound 175			B	+
((3,6-Dihydro-2H-pyridin-1-yl)-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-methanone	Compound 176			B	nd
[4-(4-Fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-(1-naphthalen-1-ylmethyl-piperazin-2-yl)-methanone	Compound 177			B	+
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-(4-phenyl-piperidin-1-yl)-methanone	Compound 178			B	+
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-(4-phenyl-piperazin-1-yl)-methanone	Compound 179			B	+

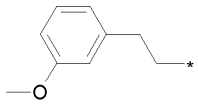
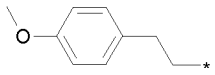
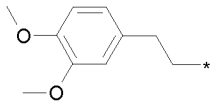
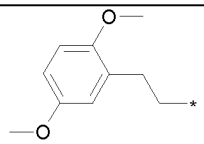
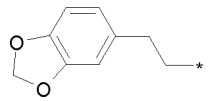
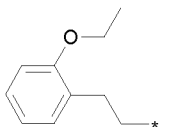
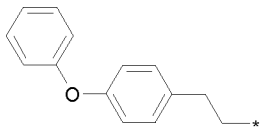
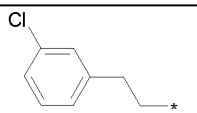
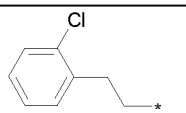
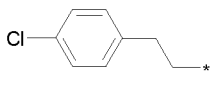
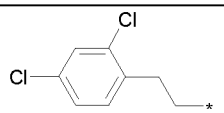
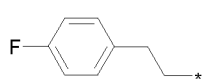
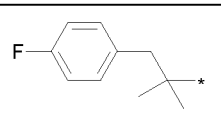
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
[4-(1*H*-Indol-3-yl)-piperidin-1-yl]-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-methanone	Compound 180			B	+
(4-Hydroxy-4-phenyl-piperidin-1-yl)-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-methanone	Compound 181			B	+
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-morpholin-4-yl-methanone	Compound 182			B	nd
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-thiazolidin-3-yl-methanone	Compound 183			B	+
(1-Isoquinolin-5-ylmethyl-piperazin-2-yl)-(1,3,4,9-tetrahydro-β-carbolin-2-yl)-methanone	Compound 184			B	+
2-(1-Isoquinolin-5-ylmethyl-piperazine-2-carbonyl)-1,2,3,4-tetrahydro-isoquinoline-6-carboxylic acid methyl ester	Compound 185			B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid phenylamide	Compound 186	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (4-hydroxymethyl-phenyl)-amide	Compound 187	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-hydroxy-phenyl)-amide	Compound 188	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (4-methoxy-phenyl)-amide	Compound 189	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid p-tolyl-amide	Compound 190	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1*H*-indol-6-yl)-amide	Compound 191	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1H-indol-5-yl)-amide	Compound 192	-H		B	nd
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid benzyl-methyl-amide	Compound 193	$-CH_3$		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid benzylamide	Compound 194	-H		B	++

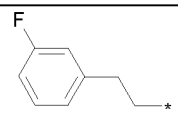
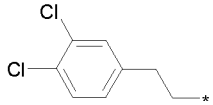
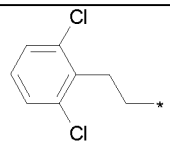
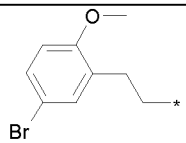
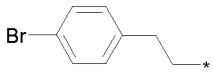
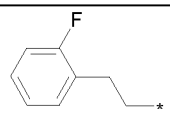
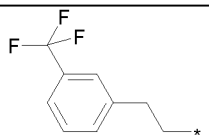
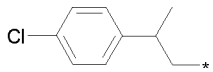
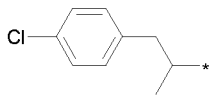
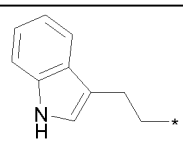
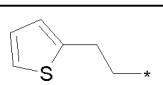
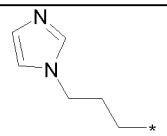
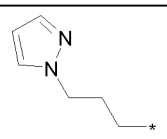
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Naphthalen-1-ylmethyl-piperazine-2-carboxylic acid (thiophen-2-ylmethyl)-amide	Compound 195	-H		B	++
1-Naphthalen-1-ylmethyl-piperazine-2-carboxylic acid (pyridin-2-ylmethyl)-amide	Compound 196	-H		B	+
(3,4-Dihydro-1H-isoquinolin-2-yl)-(1-isoquinolin-5-ylmethyl-piperazin-2-yl)-methanone	Compound 197	-H		B	nd
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1-phenyl-ethyl)-amide	Compound 198	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1-methyl-1-phenyl-ethyl)-amide	Compound 199	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide	Compound 200	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid indan-1-ylamide	Compound 201	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1,2-diphenyl-ethyl)-amide	Compound 202	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid benzhydryl-amide	Compound 203	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-methyl-benzylamide	Compound 204	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-methyl-benzylamide	Compound 205	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methyl-benzylamide	Compound 206	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-thiophen-2-yl-benzylamide	Compound 207	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (naphthalen-1-ylmethyl)-amide	Compound 208	-H		B	++

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide	Compound 209	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (furan-2-ylmethyl)-amide	Compound 210	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-fluoro-benzylamide	Compound 211	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-fluoro-benzylamide	Compound 212	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-fluoro-benzylamide	Compound 213	-H		C	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-benzylamide	Compound 214	-H		C	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-chloro-benzylamide	Compound 215	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-chloro-benzylamide	Compound 216	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,3-dichloro-benzylamide	Compound 217	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dichloro-benzylamide	Compound 218	-H		C	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,5-dichloro-benzylamide	Compound 219	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3,6-dichloro-benzylamide	Compound 220	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3,5-dichloro-benzylamide	Compound 221	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-4-fluoro-benzylamide	Compound 222	-H		C	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dichloro-6-methyl-benzylamide	Compound 223	-H		C	++

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-6-methyl-benzylamide	Compound 224	-H		C	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-chloro-4-methyl-benzylamide	Compound 225	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [(4-chloro-phenyl)-phenyl-methyl]-amide	Compound 226	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-fluoro-6-trifluoromethyl-benzylamide	Compound 227	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide	Compound 228	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-trifluoromethyl-benzylamide	Compound 229	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-trifluoromethyl-benzylamide	Compound 230	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-trifluoromethoxy-benzylamide	Compound 231	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-trifluoromethoxy-benzylamide	Compound 232	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-trifluoromethoxy-benzylamide	Compound 233	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-bromo-benzylamide	Compound 234	-H		B	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-nitro-benzylamide	Compound 235	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methanesulfonyl-benzylamide	Compound 236	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide	Compound 237	-H		C	+++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,3-dimethoxy-benzylamide	Compound 238	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dimethoxy-benzylamide	Compound 239	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3,4-dimethoxy-benzylamide	Compound 240	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,5-dimethoxy-benzylamide	Compound 241	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-methoxy-benzylamide	Compound 242	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methoxy-benzylamide	Compound 243	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid indan-2-ylamide	Compound 244	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid phenethyl-amide	Compound 245	H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid methyl-phenethyl-amide	Compound 246	$-CH_3$		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-phenyl-propyl)-amide	Compound 247	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-methyl-phenyl)-ethyl]-amide	Compound 248	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-tert-butyl-phenyl)-ethyl]-amide	Compound 249	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-methoxy-phenyl)-ethyl]-amide	Compound 250	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide	Compound 251	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide	Compound 252	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2,5-dimethoxy-phenyl)-ethyl]-amide	Compound 253	-H		B	nd
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-benzo[1,3]dioxol-5-yl-ethyl)-amide	Compound 254	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-ethoxy-phenyl)-ethyl]-amide	Compound 255	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-phenoxy-phenyl)-ethyl]-amide	Compound 256	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-chloro-phenyl)-ethyl]-amide	Compound 257	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-chloro-phenyl)-ethyl]-amide	Compound 258	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-chloro-phenyl)-ethyl]-amide	Compound 259	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide	Compound 260	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide	Compound 261	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-fluoro-phenyl)-1,1-dimethyl-ethyl]-amide	Compound 262	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-fluoro-phenyl)-ethyl]-amide	Compound 263	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3,4-dichloro-phenyl)-ethyl]-amide	Compound 264	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2,6-dichloro-phenyl)-ethyl]-amide	Compound 265	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-bromo-6-methoxy-phenyl)-ethyl]-amide	Compound 266	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-bromo-phenyl)-ethyl]-amide	Compound 267	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide	Compound 268	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-trifluoromethyl-phenyl)-ethyl]-amide	Compound 269	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-chloro-phenyl)-propyl]-amide	Compound 270	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-chloro-phenyl)-1-methyl-ethyl]-amide	Compound 271	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(1H-indol-3-yl)-ethyl]-amide	Compound 272	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide	Compound 273	-H		B	++
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (3-imidazol-1-yl-propyl)-amide	Compound 274	-H		B	+
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (3-pyrazol-1-yl-propyl)-amide	Compound 275	-H		B	+

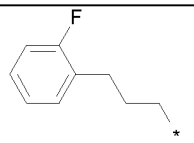
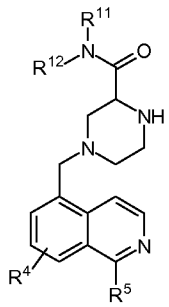
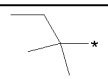
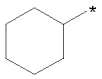
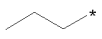
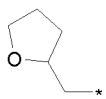
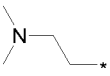
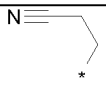
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [3-(2-fluoro-phenyl)-propyl]-amide	Compound 276	-H		B	++

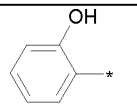
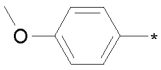
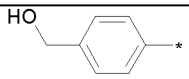
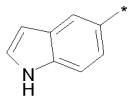
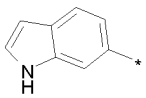
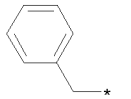
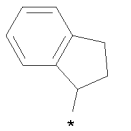
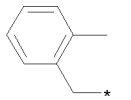
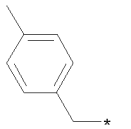
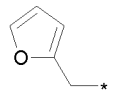
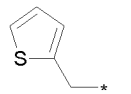
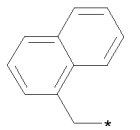
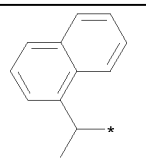
Table 5 shows the results for compounds of Formula V8 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V8 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 4 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.

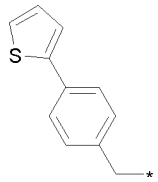
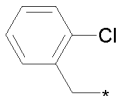
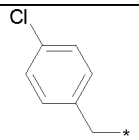
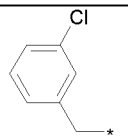
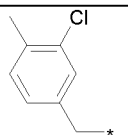
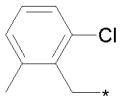
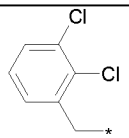
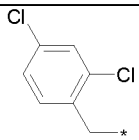
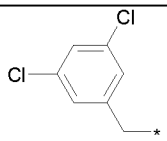
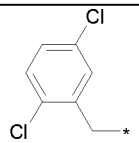
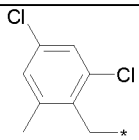


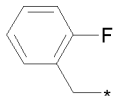
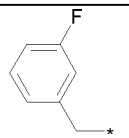
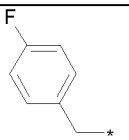
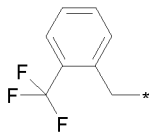
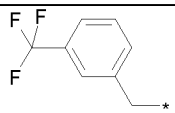
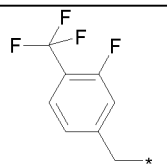
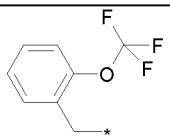
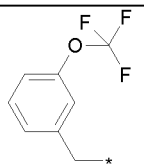
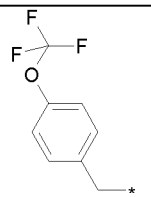
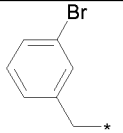
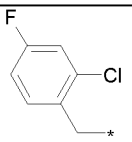
V8

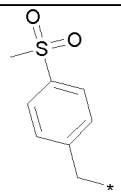
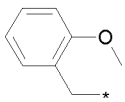
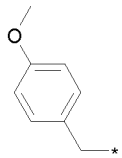
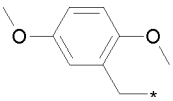
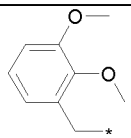
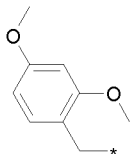
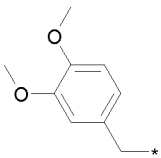
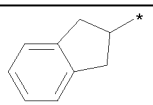
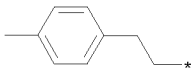
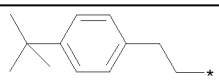
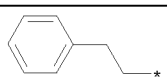
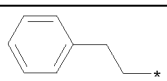
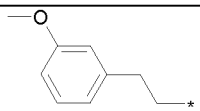
Table 5

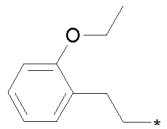
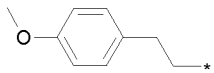
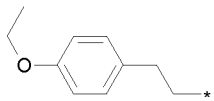
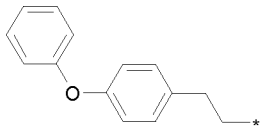
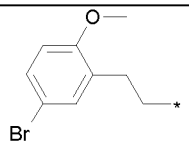
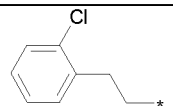
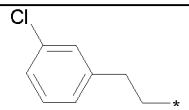
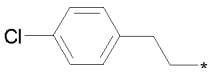
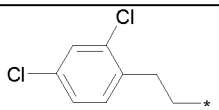
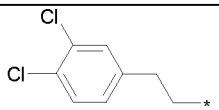
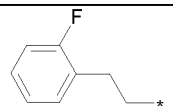
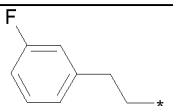
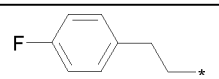
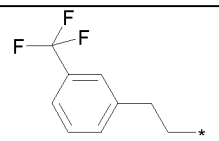
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid ethylamide	Compound 277	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1,1-dimethyl-propyl)-amide	Compound 278	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid cyclohexyl-amide	Compound 279	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid methyl-propyl-amide	Compound 280	-CH_3		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid cyclopropylmethyl-amide	Compound 281	-H		B	nd
4-Naphthalen-1-ylmethyl-piperazine-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide	Compound 282	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-dimethylamino-ethyl)-amide	Compound 283	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-cyano-ethyl)-amide	Compound 284	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid p-tolylamide	Compound 285	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-hydroxy-phenyl)-amide	Compound 286	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (4-methoxy-phenyl)-amide	Compound 287	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (4-hydroxymethyl-phenyl)-amide	Compound 288	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1*H*-indol-5-yl)-amide	Compound 289	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1*H*-indol-6-yl)-amide	Compound 290	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid benzylamide	Compound 291	-H		B	nd
1-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid indan-1-ylamide	Compound 292	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-methyl-benzylamide	Compound 293	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methyl-benzylamide	Compound 294	-H		B	nd
4-isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (furan-2-ylmethyl)-amide	Compound 295	-H		B	nd
4-isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (thiophen-2-ylmethyl)-amide	Compound 296	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (naphthalen-1-ylmethyl)-amide	Compound 297	-H		B	+
4-isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (1-naphthalen-1-yl-ethyl)-amide	Compound 298	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-thiophen-2-yl-benzylamide	Compound 299	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-benzylamide	Compound 300	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-chloro-benzylamide	Compound 301	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-chloro-benzylamide	Compound 302	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-chloro-4-methyl-benzylamide	Compound 303	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-6-methyl-benzylamide	Compound 304	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,3-dichloro-benzylamide	Compound 305	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dichloro-benzylamide	Compound 306	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3,5-dichloro-benzylamide	Compound 307	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,5-dichloro-benzylamide	Compound 308	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dichloro-6-methyl-benzylamide	Compound 309	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-fluoro-benzylamide	Compound 310	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-fluoro-benzylamide	Compound 311	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-fluoro-benzylamide	Compound 312	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-trifluoromethyl-benzylamide	Compound 313	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-trifluoromethyl-benzylamide	Compound 314	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-fluoro-4-trifluoromethyl-benzylamide	Compound 315	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-trifluoromethoxy-benzylamide	Compound 316	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-trifluoromethoxy-benzylamide	Compound 317	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-trifluoromethoxy-benzylamide	Compound 318	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3-bromo-benzylamide	Compound 319	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-chloro-4-fluoro-benzylamide	Compound 320	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methanesulfonyl-benzylamide	Compound 321	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2-methoxy-benzylamide	Compound 322	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 4-methoxy-benzylamide	Compound 323	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,5-dimethoxy-benzylamide	Compound 324	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,3-dimethoxy-benzylamide	Compound 325	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 2,4-dimethoxy-benzylamide	Compound 326	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid 3,4-dimethoxy-benzylamide	Compound 327	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid indan-2-ylamide	Compound 328	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-methyl-phenyl)-ethyl]-amide	Compound 329	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-*tert*-butyl-phenyl)-ethyl]-amide	Compound 330	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid phenethyl-amide	Compound 331	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid methyl-phenethyl-amide	Compound 332	-CH_3		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-methoxy-phenyl)-ethyl]-amide	Compound 333	-H		B	nd

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-ethoxy-phenyl)-ethyl]-amide	Compound 334	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-methoxy-phenyl)-ethyl]-amide	Compound 335	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-ethoxy-phenyl)-ethyl]-amide	Compound 336	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-phenoxy-phenyl)-ethyl]-amide	Compound 337	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-bromo-6-methoxy-phenyl)-ethyl]-amide	Compound 338	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-chloro-phenyl)-ethyl]-amide	Compound 339	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-chloro-phenyl)-ethyl]-amide	Compound 340	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-chloro-phenyl)-ethyl]-amide	Compound 341	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide	Compound 342	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3,4-dichloro-phenyl)-ethyl]-amide	Compound 343	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(2-fluoro-phenyl)-ethyl]-amide	Compound 344	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-fluoro-phenyl)-ethyl]-amide	Compound 345	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(4-fluoro-phenyl)-ethyl]-amide	Compound 346	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [2-(3-trifluoromethyl-phenyl)-ethyl]-amide	Compound 347	-H		B	nd

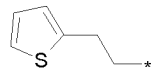
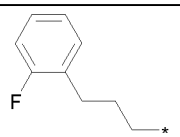
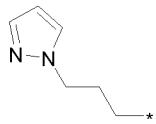
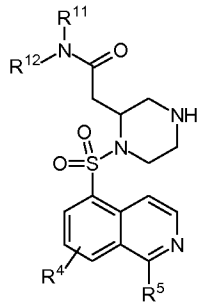
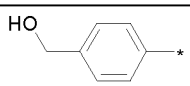
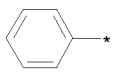
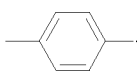
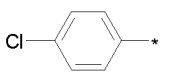
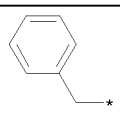
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide	Compound 348	-H		B	+
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid [3-(2-fluoro-phenyl)-propyl]-amide	Compound 349	-H		B	nd
4-Isoquinolin-5-ylmethyl-piperazine-2-carboxylic acid (3-pyrazol-1-yl-propyl)-amide	Compound 350	-H		B	nd

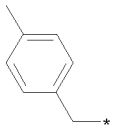
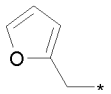
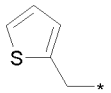
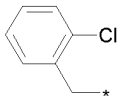
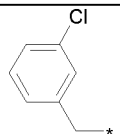
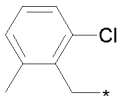
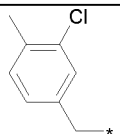
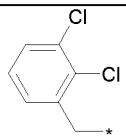
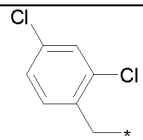
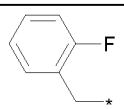
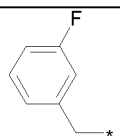
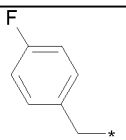
Table 6 shows the results for compounds of Formula V9 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V9 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 5 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.



V9

Table 6

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(4-hydroxymethyl-phenyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 351	-H		B	+
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]- *N*-phenyl-acetamide	Compound 352	-H		B	+
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]- *N*-p-tolyl-acetamide	Compound 353	-H		B	+
N-(4-chloro-phenyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 354	-H		B	+
N-benzyl-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 355	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]- *N*-(4-methyl-benzyl)-acetamide	Compound 356	-H		B	+
N-furan-2-ylmethyl-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 357	-H		B	+
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-thiophen-2-ylmethyl-acetamide	Compound 358	-H		B	+
N-(2-chloro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 359	-H		B	+
N-(3-chloro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 360	-H		B	+
N-(2-chloro-6-methyl-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 361	-H		B	+
N-(3-chloro-4-methyl-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 362	-H		B	+
N-(2,3-dichloro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 363	-H		B	+
N-(2,4-dichloro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 364	-H		B	+
N-(2-fluoro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 365	-H		B	+
N-(3-fluoro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 366	-H		B	+
N-(4-fluoro-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 367	-H		B	+

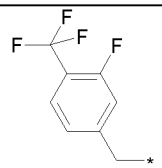
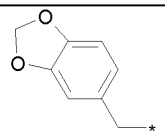
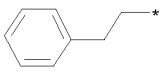
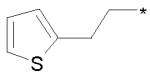
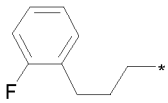
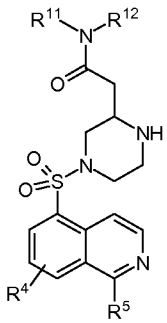
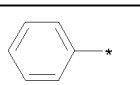
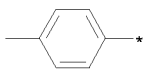
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(3-fluoro-4-trifluoromethyl-benzyl)-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 368	-H		B	+
N-benzo[1,3]dioxol-5-ylmethyl-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 369	-H		B	+
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-phenethyl-acetamide	Compound 370	-H		B	+
2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-(2-thiophen-2-yl-ethyl)-acetamide	Compound 371	-H		B	+
N-[3-(2-fluoro-phenyl)-propyl]-2-[1-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 372	-H		B	+

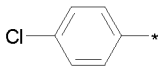
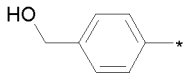
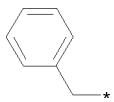
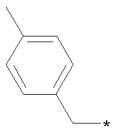
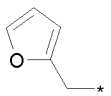
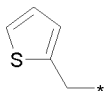
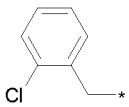
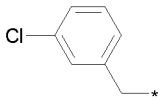
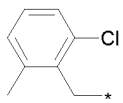
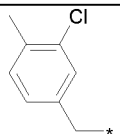
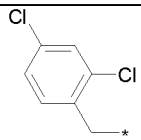
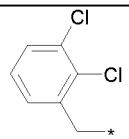
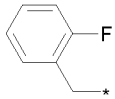
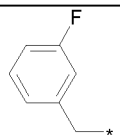
Table 7 shows the results for compounds of Formula V11 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V11 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 6 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.



V11

Table 7

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-phenyl-acetamide	Compound 373	-H		B	+
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-*p*-tolyl-acetamide	Compound 374	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(4-chloro-phenyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 375	-H		B	+
N-(4-hydroxymethyl-phenyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 376	-H		B	+
N-benzyl-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 377	-H		B	+
e2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]- *N*-(4-methyl-benzyl)-acetamide	Compound 378	-H		B	+
N-furan-2-ylmethyl-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 379	-H		B	+
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-thiophen-2-ylmethyl-acetamide	Compound 380	-H		B	+
N-(2-chloro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 381	-H		B	+
N-(3-chloro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 382	-H		B	+
N-(2-chloro-6-methyl-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 383	-H		B	+
N-(3-chloro-4-methyl-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 384	-H		B	+
N-(2,4-dichloro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 385	-H		B	+
N-(2,3-dichloro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 386	-H		B	+
N-(2-fluoro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 387	-H		B	+
N-(3-fluoro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 388	-H		B	+

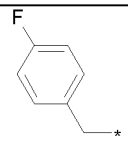
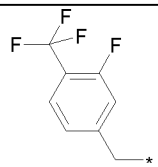
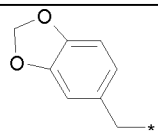
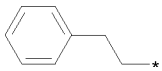
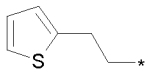
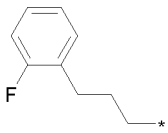
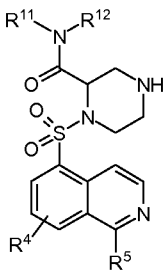
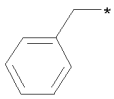
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
N-(4-fluoro-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 389	-H		B	+
N-(3-fluoro-4-trifluoromethyl-benzyl)-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 390	-H		B	+
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]- *N*-(3,4-methylenedioxy-benzyl)-acetamide	Compound 391	-H		B	+
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-phenethyl-acetamide	Compound 392	-H		B	+
2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-*N*-(2-thiophen-2-yl-ethyl)-acetamide	Compound 393	-H		B	+
N-[3-(2-fluoro-phenyl)-propyl]-2-[4-(isoquinoline-5-sulfonyl)-piperazin-2-yl]-acetamide	Compound 394	-H		B	+

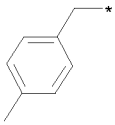
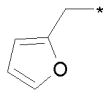
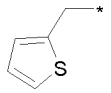
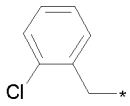
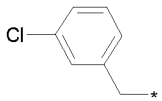
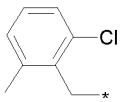
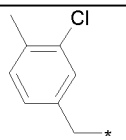
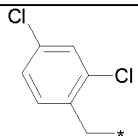
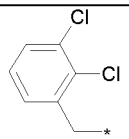
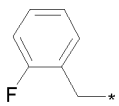
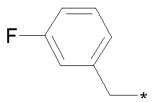
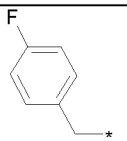
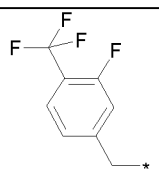
Table 8 shows the results for compounds of Formula V10 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V10 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 7 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.



V10

Table 8

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid benzylamide	Compound 395	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 4-methyl-benzylamide	Compound 396	-H		B	++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (furan-2-ylmethyl)-amide	Compound 397	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (thiophen-2-ylmethyl)-amide	Compound 398	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-chloro-benzylamide	Compound 399	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-chloro-benzylamide	Compound 400	-H		B	++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-chloro-6-methyl-benzylamide	Compound 401	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-chloro-4-methyl-benzylamide	Compound 402	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2,4-dichloro-benzylamide	Compound 403	-H		B	++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2,3-dichloro-benzylamide	Compound 404	-H		B	++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-fluoro-benzylamide	Compound 405	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-fluoro-benzylamide	Compound 406	-H		B	++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 4-fluoro-benzylamide	Compound 407	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-fluoro-4-trifluoromethyl-benzylamide	Compound 408	-H		B	+++

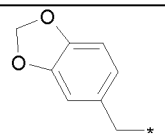
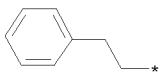
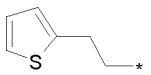
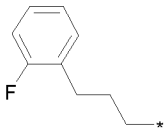
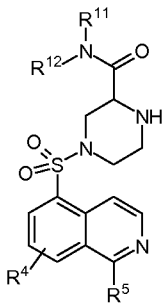
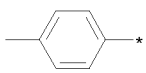
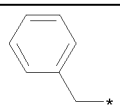
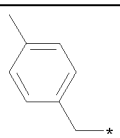
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3,4-methylenedioxy-benzylamide	Compound 409	-H		B	+++
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid phenethyl-amide	Compound 410	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide	Compound 411	-H		B	+
1-(isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid [3-(2-fluoro-phenyl)-propyl]--amide	Compound 412	-H		B	++

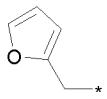
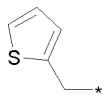
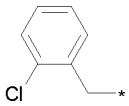
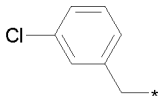
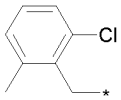
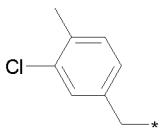
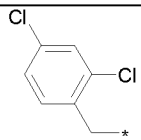
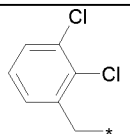
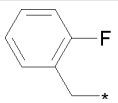
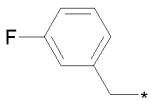
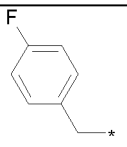
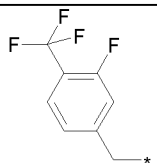
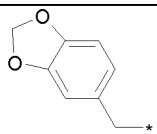
Table 9 shows the results for compounds of Formula V12 wherein R^4 and R^5 are each independently hydrogen. As used herein the term "ND" means "not determined" and Pr means "protocol". Compounds of Formula V12 wherein R^4 and R^5 are each independently hydrogen were prepared starting from Intermediate 8 and from the corresponding amine $HNR^{11}R^{12}$ following the general protocol B or C.

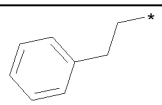
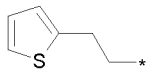
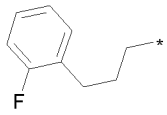


V12

Table 9

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid p-tolyl-amide	Compound 413	-H		B	++
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid benzylamide	Compound 414	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 4-methyl-benzylamide	Compound 415	-H		B	+

Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (furan-2-ylmethyl)-amide	Compound 416	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (thiophen-2-ylmethyl)-amide	Compound 417	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-chloro-benzylamide	Compound 418	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-chloro-benzylamide	Compound 419	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-chloro-6-methyl-benzylamide	Compound 420	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-chloro-4-methyl-benzylamide	Compound 421	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2,4-dichloro-benzylamide	Compound 422	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2,3-dichloro-benzylamide	Compound 423	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 2-fluoro-benzylamide	Compound 424	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-fluoro-benzylamide	Compound 425	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 4-fluoro-benzylamide	Compound 426	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3-fluoro-4-trifluoromethyl-benzylamide	Compound 427	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid 3,4-methylenedioxy-benzylamide	Compound 428	-H		B	+

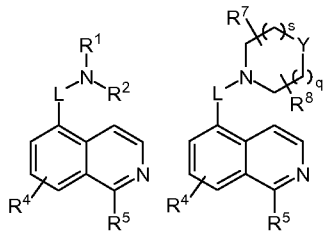
Name	Compound	R^{11}	R^{12}	Pr	IC_{50} (μM) ROCK
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid phenethyl-amide	Compound 429	-H		B	+
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid (2-thiophen-2-yl-ethyl)-amide	Compound 430	-H		B	++
4-(Isoquinoline-5-sulfonyl)-piperazine-2-carboxylic acid [3-(2-fluoro-phenyl)-propyl]-amide	Compound 431	-H		B	+

The present invention encompasses compounds 1 to 431 and stereoisomers, tautomers, racemics or a pharmaceutically acceptable salt and/or solvate thereof.

All patents, patent applications, and published references cited herein are hereby incorporated by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments, it will be understood by those skilled in the art that various changes in form and details may be made without departing from the scope of the invention encompassed by the claims.

CLAIMS:

1. A compound of Formula I or II or a stereoisomer, tautomer, racemic, salt, hydrate, or solvate thereof,



I II

wherein:

q is an integer selected from 0, 1 or 2,

s is an integer selected from 1 or 2,

R^1 is a group selected from aminoalkyl, alkylaminoalkyl, cycloalkyl, cycloalkylalkyl, aminocycloalkyl, aminocycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aminoheterocyclyl, aminoheterocyclylalkyl, each group being optionally substituted by one or more substituents selected from amino, hydroxyl, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, heterocyclyl,

R^2 is selected from hydrogen or alkyl, said alkyl being optionally substituted with one or more substituents selected from amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, heterocyclyl, alkoxy, cycloalkyl,

Y is $-C(R^3)R^6-$ or $-NR^3-$, wherein

R^3 is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl,

R^4 is selected from hydrogen, alkyl, alkoxy, cyano, nitro, halogen,

R^5 is hydrogen,

R^6 is selected from hydrogen or alkyl,

L in Formula I is $–CR^9R^{10}-$ and L in Formula II is selected from $–CR^9R^{10}-$ or $–SO_2-$,

R^7 is hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each

group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

or R^7 and R^8 are fused together and form an alkylene or alkyleneaminoalkylene optionally substituted with one or more substituent selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from alkyl, alkenyl, alkenyl, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylsulfonylaminoalkyl, alkylsulfonylamino, alkylcarbonyl, formylamino, formylaminoalkyl, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkoxyl, alkoxyalkyl, cyanoalkyl, aryloxyaralkyl, aralkylheteroaryl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy, alkylsulfonyl, sulfo, alkylsulfonylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylthio, arylalkenylaminooxy, arylalkylaminooxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, aryloxy, aryloxyaralkyl, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, haloaryl, heteroaryl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylaralkyl, heteroarylcarbonylamino, heteroarylalkylaminooxy, hydroxyalkyl, or fused to the cycloalkyl, aryl, heterocyclyl substituent or heteroaryl may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

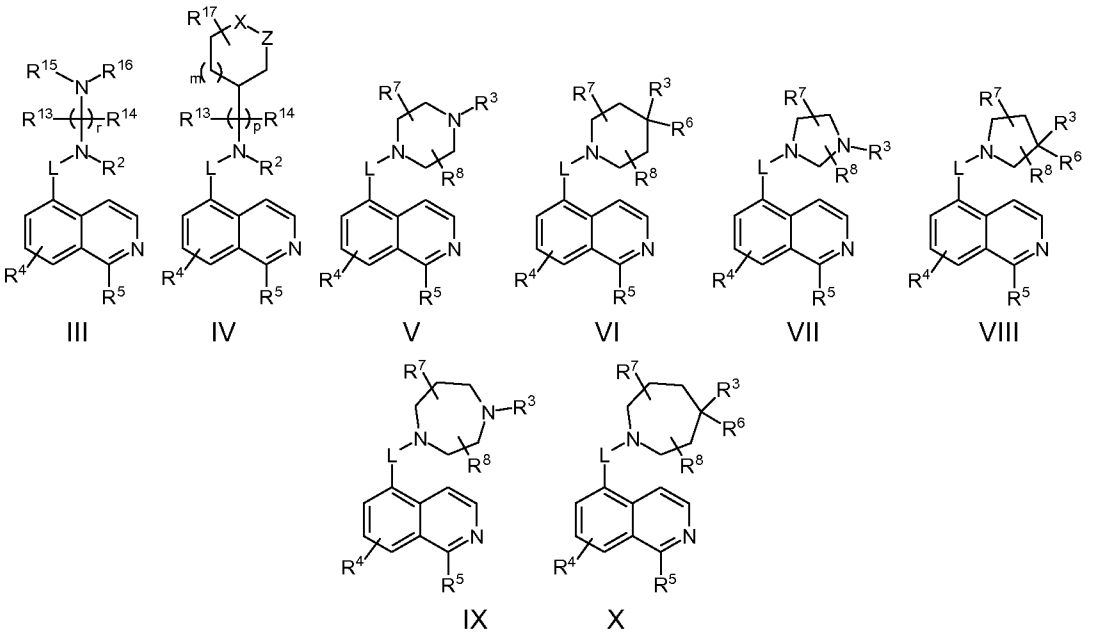
each of said group being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more aryl, heteroaryl, cycloalkyl, or heterocyclyl ring,

said ring or fused ring being optionally substituted with one or more substituent selected from halo, alkenylaminooxy, alkoxy, alkyl, alkylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylsulfonyl, alkylsulfonylamino, alkylthio, amino, aralkyl, aryl, arylalkenylaminooxy, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, aryloxy, cyano, cycloalkyl, haloalkoxy, haloalkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyalkyl, nitro, oxo, sulfonyl, or fused to the cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkyloxycarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

with the proviso that when L is SO_2 in formula II, R^7 is not hydrogen or alkyl.

2. The compound according to claim 1, having one of the Formula III, IV, V, VI, VII, VIII, IX, or X



III IV V VI VII VIII

IX X

wherein

r is an integer selected from 1, 2, 3, 4 or 5,

p is an integer selected from 0, 1 or 2,

m is an integer selected from 0 or 1,

R^{13} and R^{14} are each independently selected from hydrogen, hydroxyl, cyano, nitro, alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, haloalkoxy, alkoxy, amino, aminoalkyl, alkylaminoalkyl,

R^{15} and R^{16} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, haloalkyl,

R^{17} is selected from hydrogen, hydroxyl, amino, aryl, arylalkyl, alkyl, aminoalkyl, alkylamino, heteroaryl, heteroarylalkyl, halogen, haloalkyl, haloalkoxy, alkoxy, cycloalkyl, heterocyclyl,

X and Z are each independently selected from $-C(R^{18})R^{19}-$ or $-NR^{18}-$, wherein R^{18} is hydrogen or a group selected from alkyl, alkylcarbonyl, aryl, arylalkyl, haloarylalkyl, amino, aminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, each group being optionally substituted by one or more substituents selected from alkyl, aryl, halo, haloalkyl, haloalkoxy, amino, alkoxy, heteroaryl, heterocyclyl, cycloalkyl, and R^{19} is selected from hydrogen or alkyl,

wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, and L have the same meaning as that defined in claim 1.

3. The compound according to claim 1 or 2, wherein L is $-CR^9R^{10}-$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

4. The compound according to claim 3, wherein L is $-CH_2-$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

5. The compound according to claim 1 or 2, wherein L is $-SO_2-$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

6. The compound according to any of claims 1 to 5, wherein R^7 is hydrogen or a group selected from alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, or aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, or fused to said aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino, and

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

7. The compound according to any of claims 1 to 5, wherein R^7 is $-(C(R^9)R^{10})_p-C(=A)-N(R^{11})R^{12}$, wherein p is 0 or 1, A is an oxygen or sulfur atom;

R^8 is hydrogen or a group selected from alkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkyl, hydroxyl, alkyloxycarbonyl, carboxyl, aminoalkyl, amino, heteroaryl, aralkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, each group being optionally substituted with one or more substituents selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino,

R^9 and R^{10} are each independently selected from hydrogen or alkyl,

R^{11} and R^{12} are each independently hydrogen or a group selected from alkyl, alkenyl, alkenyl, amino, aminoalkyl, alkylamino, alkylaminoalkyl, alkylsulfonylaminoalkyl, alkylsulfonylamino, alkylcarbonyl, formylamino, formylaminoalkyl, alkylcarbonylamino, alkylcarbonylaminoalkyl, alkoxyl, alkoxyalkyl, cyanoalkyl, aryloxyaralkyl, aralkylheteroaryl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, heteroarylarylalkyl, or fused to said cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or heteroarylarylalkyl group may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each group being optionally substituted with one or more substituent selected from halo, oxo, hydroxyl, nitro, cyano, or a group selected from alkyl, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, alkenylaminooxy, alkylsulfonyl, sulfo, alkylsulfonylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylthio, arylalkenylaminooxy, arylalkylaminooxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, aryl, aralkyl, aryloxy, aryloxyaralkyl, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, haloaryl, heteroaryl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylaralkyl, heteroarylcarbonylamino, heteroarylalkylaminooxy, hydroxyalkyl, or fused to the cycloalkyl, aryl, heterocyclyl substituent or heteroaryl may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl,

each of said group being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl,

or R^{11} and R^{12} may together with the common nitrogen atom to which they are attached form a heterocyclic or heteroaryl ring, said ring being optionally fused with one or more aryl, heteroaryl, cycloalkyl, or heterocyclyl ring,

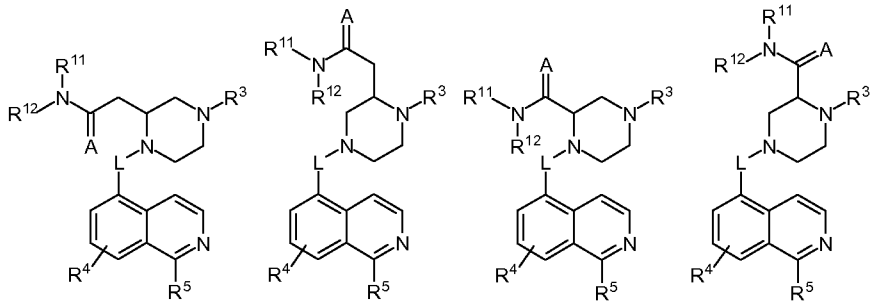
said ring or fused ring being optionally substituted with one or more substituent selected from halo, alkenylaminooxy, alkoxy, alkyl, alkylamino, alkylaminosulfonyl, alkylcarbonyl, alkylcarbonylamino, alkyloxyaminoalkenyl, alkyloxycarbonyl, alkylsulfonyl, alkylsulfonylamino, alkylthio, amino, aralkyl, aryl, arylalkenylaminooxy, arylamino, arylaminosulfonyl, arylcarbonyl, arylcarbonylamino, aryloxy, cyano, cycloalkyl, haloalkoxy,

haloalkyl, haloaryl, heteroaryl, heteroarylcarbonyl, heteroarylalkenylaminooxy, heteroarylalkyl, heteroarylcarbonylamino, heterocyclyl, hydroxyalkyl, nitro, oxo, sulfonyl, or fused to the cycloalkyl, aryl, heterocyclyl or heteroaryl substituent may be one or more cycloalkyl, aryl, heterocyclyl or heteroaryl, each of said substituent being optionally substituted by one or more further substituent selected from halo, alkoxy, alkyl, alkylamino, alkylcarbonyl, alkyloxycarbonyl, alkylheteroaryl, alkylsulfonyl, aralkyl, aryl, arylamino, aryloxy, cyano, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocyclyl, hydroxyl, nitro, oxo, or sulfonyl

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

8. The compound according to any of claims 1 to 5, wherein R^7 and R^8 are fused together and form an alkylene or alkyleneaminoalkylene optionally substituted with one or more substituent selected from hydroxyl, alkoxy, alkyl, amino, cyano, nitro, halo, haloalkyl, haloalkoxy, alkylamino, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, L, X, Y, Z, r, s, p, q, m have the same meaning as that defined in any one of the preceding claims.

9. The compound according to any of claim 1 to 5 and 7, having one of the Formula V1, V2, V3, V4



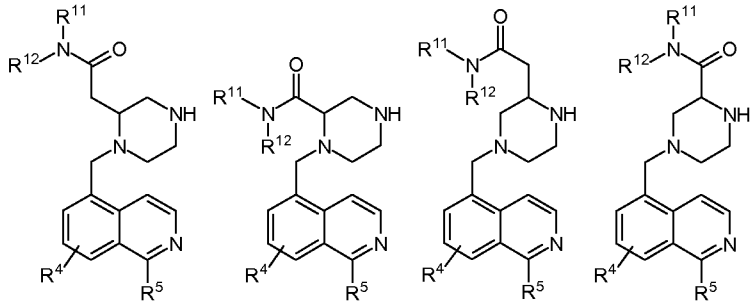
V1 V2 V3 V4

wherein R^3, R^4, R^5, R^{11}, R^{12}, L and A have the same meaning as that defined in any one of the preceding claims.

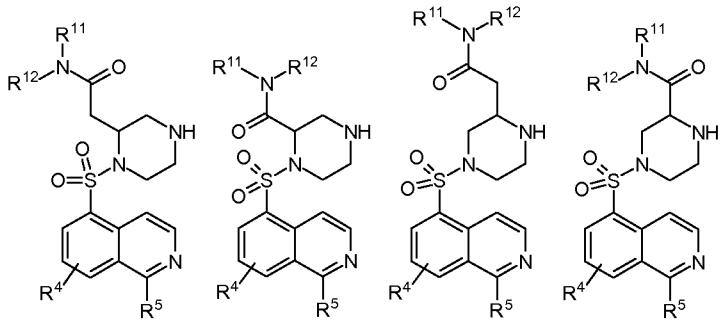
10. The compound according to claim 9, wherein A is O, and R^3, R^4, R^5, R^{11}, R^{12}, L have the same meaning as that defined in any one of the preceding claims.

11. The compound according to claim 9, wherein A is S, and R^3, R^4, R^5, R^{11}, R^{12}, L have the same meaning as that defined in any one of the preceding claims.

12. The compound according to any of claim 1 to 5 and 7, 9 and 10 having one of the Formula



V5 V6 V7 V8



V9 V10 V11 V12

wherein R^4, R^5, R^{11}, R^{12} have the same meaning as that defined in any one of the preceding claims.

13. A pharmaceutical and/or veterinary composition comprising a compound as defined in any of claims 1 to 12.

14. A pharmaceutical and/or veterinary composition according to claim 13 comprising at least one compound according to any one of claims 1 to 12 and at least one carrier, excipient or diluent acceptable for pharmaceutical and/or veterinary purposes.

15. The compound according to any one of claims 1 to 12 for use as a medicament.

16. Use of a compound according to any of claims 1 to 12 in the preparation of a medicament for the prevention and/or treatment of at least one disease and/or disorder selected from the group comprising eye diseases; erectile dysfunction; cardiovascular diseases; vascular diseases; inflammatory diseases; proliferative diseases; neurological diseases and disease of the central nervous system (CNS); bronchial asthma; osteoporosis; renal diseases; and AIDS.

17. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention and/or treatment of eyes diseases including retinopathy, macular degeneration and glaucoma, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

18. Use of a compound according to claim 17 for the preparation of a medicament for the prevention and/or treatment of glaucoma, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

19. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention and/or treatment of cardiovascular and vascular diseases selected from the group comprising acute stroke, congestive heart failure, cardiovascular ischemia, heart disease, cardiac remodeling, angina, coronary vasospasm, cerebral vasospasm, pulmonary vasoconstriction, restenosis, hypertension, pulmonary hypertension, arteriosclerosis, thrombosis including deep thrombosis, and platelet related diseases, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

20. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention, treatment and/or management of neurological and CNS disorders selected from the group comprising stroke, multiple sclerosis, brain or spinal cord injury, inflammatory and demyelinating diseases such as Alzheimer´s disease, MS and neuropathic pain, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

21. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention and/or treatment of cancer selected from the group comprising cancer of the brain (gliomas), breast, colon, intestine, skin, head and neck, kidney, lung, liver, ovarian, pancreatic, prostate, or thyroid, leukemia; lymphoma; sarcoma; melanoma; and/or for preventing, treating and/or alleviating complications and/or symptoms and/or inflammatory responses associated therewith.

22. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention and/or treatment of erectile dysfunction, bronchial asthma, osteoporosis, inflammatory diseases, renal diseases and AIDS, and/or for preventing, treating and/or alleviating complications and/or symptoms associated therewith.

23. Use of a compound according to any of claims 1 to 12 for the preparation of a medicament for the prevention and/or treatment of inflammatory diseases selected from the group comprising contact dermatitis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and/or for preventing, treating and/or alleviating complications and/or symptoms and/or inflammatory responses associated therewith.

24. A method for inhibiting the activity of at least one kinase, *in vitro* or *in vivo* using a compound according to any of claims 1 to 12, or a composition comprising such compound.

25. The method of claim 24 wherein said use is *in vitro*.

26. The method of claim 24 or claim 25 wherein the at least one kinase is ROCK.

27. The method according to claim 26 in which the at least one kinase is chosen from the alpha and/or beta isoforms of ROCK.

28. The method according to claim 27 in which the at least one kinase is chosen from the alpha isoform of ROCK.