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(54) Title: DIHYDROFUOPYRIDINE DERIVATIVES AS RHO-KINASE INHIBITORS

(57) Abstract: The invention relates to compounds of formula (I) inhibiting Rho Kinase that are dihydrofuopyridine derivatives, methods of preparing such compounds, pharmaceutical compositions containing them and therapeutic use thereof. Particularly the compounds of the invention may be useful in the treatment of many disorders associated with ROCK enzymes mechanisms, such as pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

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DIHYDROFUROPYRIDINE DERIVATIVES AS RHO- KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to novel compounds inhibiting Rho Kinase (hereinafter ROCK Inhibitors); methods of preparing such compounds, pharmaceutical compositions containing them and therapeutic use thereof.

BACKGROUND OF THE INVENTION

The compounds of the invention are inhibitors of the activity or function of the ROCK-I and/or ROCK-II isoforms of the Rho-associated coiled-coil forming protein kinase (ROCK).

Rho-associated coiled-coil forming protein kinase (ROCK) belongs to the AGC (PKA/PKG/PKC) family of serine-threonine kinases. Two human isoforms of ROCK have been described, ROCK-I (also referred to as p160 ROCK or ROK β or ROCK1) and ROCK-II (ROK α or ROCK2) are approximately 160 kDa proteins containing an N-terminal Ser/Thr kinase domain, followed by a coiled-coil structure, a pleckstrin homology domain, and a cysteine-rich region at the C-terminus (Riento, K.; Ridley, A. J. Rocks: multifunctional kinases in cell behaviour. Nat. Rev. Mol. Cell Biol. 2003, 4, 446–456).

Both ROCK-II and ROCK-I are expressed in many human and rodent tissues including the heart, pancreas, lung, liver, skeletal muscle, kidney and brain (above Riento and Ridley, 2003). In patients with pulmonary hypertension, ROCK activity is significantly higher in both lung tissues and circulating neutrophils as compared with controls (Duong-Quy S, Bei Y, Liu Z, Dinh-Xuan AT. Role of Rho-kinase and its inhibitors in pulmonary hypertension. Pharmacol Ther. 2013;137(3):352-64). A significant correlation was established between neutrophil ROCK activity and the severity and duration of pulmonary hypertension (Duong-Quy et al., 2013).

There is now substantial evidence that ROCK is involved in many of the pathways that contribute to the pathologies associated with several acute and chronic pulmonary diseases, including asthma, COPD, bronchiectasis and ARDS/ALI. Given the biological effect of ROCK, selective inhibitors have the potential to treat a number of pathological mechanisms in respiratory diseases, such as smooth muscle hyper-reactivity, bronchoconstriction, airway inflammation and airway remodeling, neuromodulation and

exacerbations due to respiratory tract viral infection (Fernandes LB, Henry PJ, Goldie RG. Rho kinase as a therapeutic target in the treatment of asthma and chronic obstructive pulmonary disease. *Ther Adv Respir Dis.* 2007 Oct;1(1):25-33). Indeed the Rho kinase inhibitor Y-27632 causes bronchodilatation and reduces pulmonary eosinophilia trafficking and airways hyperresponsiveness (Gosens, R.; Schaafsma, D.; Nelemans, S. A.; Halayko, A. J. Rhokinase as a drug target for the treatment of airway hyperresponsiveness in asthma. *Mini-Rev. Med. Chem.* 2006, 6, 339–348). Pulmonary ROCK activation has been demonstrated in humans with idiopathic pulmonary fibrosis (IPF) and in animal models of this disease. ROCK inhibitors can prevent fibrosis in these models, and more importantly, induce the regression of already established fibrosis, thus indicating ROCK inhibitors as potential powerful pharmacological agents to halt progression of pulmonary fibrosis (Jiang, C.; Huang, H.; Liu, J.; Wang, Y.; Lu, Z.; Xu, Z. Fasudil, a rho-kinase inhibitor, attenuates bleomycin-induced pulmonary fibrosis in mice. *Int. J. Mol. Sci.* 2012, 13, 8293–8307).

Various compounds have been described in the literature as Rho Kinase Inhibitors. See e.g. WO2004/039796 disclosing phenylaminopyrimidine compounds derivatives; WO2006/009889 disclosing indazole compound derivatives; WO2010/032875 disclosing nicotinamide compounds derivatives; WO2009/079008 disclosing pyrazole derivatives; WO2014/118133 disclosing pyrimidine derivatives and, of the same Applicant of the present invention, WO2018/115383 disclosing bicyclic dihydropyrimidine and WO 2018/138293, WO 2019/048479, WO 2019/121223, WO 2019/121233, WO 2019/121406, WO 2019/238628, WO 2020/016129 disclosing tyrosine-amide compounds derivatives and analogues.

The compounds disclosed exhibit substantial structural differences from the compounds of the present invention.

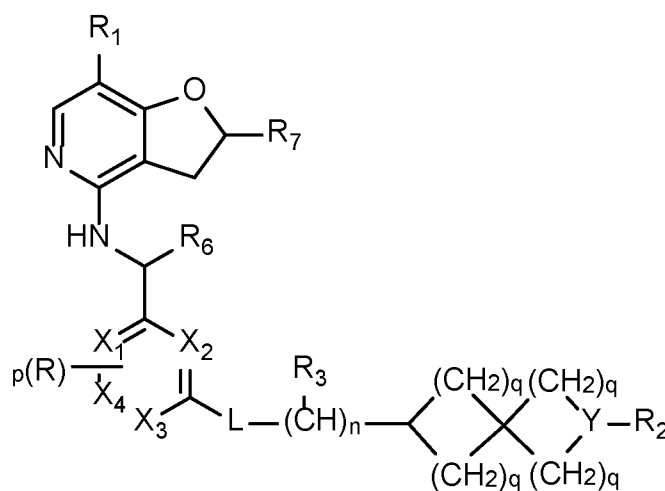
There remains a potential for developing novel and pharmacologically improved ROCK inhibitors in many therapeutic areas.

In view of the number of pathological responses which are mediated by ROCK enzymes, there is a continuing need for inhibitors of such enzymes which can be useful in the treatment of many disorders. The present invention relates to novel compounds differing from the structures disclosed in the art at least for a common new core scaffold. In fact the invention relates to compounds that are characterized by the

2,3-dihydrofuro[3,2-c]pyridine moiety, particularly 2,3-dihydrofuro[3,2-c]pyridin-4-amine, particularly preferably N-(3-(((2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)formamide and 3-(((2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide derivatives, particularly N-linked spirocyclic derivatives of such compounds, which are inhibitors of ROCK-I and ROCK-II isoforms of the Rho-associated coiled-coil forming protein kinase (ROCK) that have therapeutically desirable characteristics, particularly promising in the field of respiratory diseases but not excluding other fields such as that of immune system disorders including Graft-versus-host disease (GVHD), and specifically for some pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH) and specifically pulmonary arterial hypertension (PAH). The compounds of the invention may be prepared for administration by any route consistent with their pharmacokinetic properties. The compound of the invention are active as inhibitors of ROCK-I and ROCK-II isoforms, they are potent and have advantageously other improved properties such as selectivity and other in vitro properties indicative for a preferred route of administration.

SUMMARY OF THE INVENTION

The present invention is directed to a class of compounds, acting as inhibitors of the Rho Kinase (ROCK), of formula (I)



I

Wherein the variables X_1 , X_2 , X_3 and X_4 , p , R , R_1 , L , n , R_2 and R_3 , R_6 and R_7 , q and

Y are as defined in the detailed description of the invention; or pharmaceutically acceptable salts and solvates thereof.

In one aspect, the present invention refers to a compound of formula (I) for use as a medicament. In one aspect the present invention provides the use of a compound of the invention for the manufacture of a medicament.

In a further aspect, the present invention provides the use of a compound of the invention for the preparation of a medicament for the treatment of any disease associated with ROCK enzyme mechanisms, that is to say characterized by ROCK enzyme aberrant activity and/or wherein an inhibition of activity is desirable and in particular through the selective inhibition of the ROCK enzyme isoforms over other Kinases.

In another aspect, the present invention provides a method for prevention and/or treatment of any disease associated with ROCK enzyme mechanisms as above defined, said method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

In a Particular aspect the compounds of the invention are used alone or combined with other active ingredients and may be administered for the prevention and/or treatment of immune system disorders including Graft-versus-host disease (GVHD), and for pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH) and specifically pulmonary arterial hypertension (PAH).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term “Pharmaceutically acceptable salts” refers to derivatives of compounds of formula (I) wherein the parent compound is suitably modified by converting any of the free acid or basic group, if present, into the corresponding addition salt with any base or acid conventionally intended as being pharmaceutically acceptable.

Suitable examples of said salts may thus include mineral or organic acid addition salts of basic residues such as amino groups, as well as mineral or organic basic addition salts of acid residues such as carboxylic groups.

Cations of inorganic bases which can be suitably used to prepare salts of the invention comprise ions of alkali or alkaline earth metals such as potassium, sodium, calcium or magnesium. Those obtained by reacting the main compound, functioning as a

base, with an inorganic or organic acid to form a salt comprise, for example, salts of hydrochloric, hydrobromic, sulfuric, phosphoric, methane sulfonic, camphor sulfonic, acetic, oxalic, maleic, fumaric, succinic and citric acids.

Many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates” which are a further object of the invention. Polymorphs and crystalline forms of compounds of formula (I), or of pharmaceutically acceptable salts, or solvates thereof are a further object of the invention.

The term “Halogen” or “halogen atoms” includes fluorine, chlorine, bromine, and iodine atom ; meaning Fluoro, Chloro, Bromo, Iodo as substituent.

The term “(C₁-C₆)Alkyl” refers to straight-chained or branched alkyl groups wherein the number of carbon atoms is in the range 1 to 6. Particular alkyl groups are for example methyl, ethyl, n-propyl, isopropyl, t-butyl, 3-methylbutyl and the like.

The expressions “(C₁-C₆)Haloalkyl” refer to the above defined “(C₁-C₆)alkyl” groups wherein one or more hydrogen atoms are replaced by one or more halogen atoms, which can be the same or different from each other. Examples include halogenated, poly-halogenated and fully halogenated alkyl groups wherein all of the hydrogen atoms are replaced by halogen atoms, e.g. trifluoromethyl or difluoro methyl groups.

By way of analogy, the terms “(C₁-C₆)Hydroxyalkyl” and “(C₁-C₆)aminoalkyl” refer to the above defined “(C₁-C₆)alkyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) or amino group respectively, examples being hydroxymethyl and aminomethyl and the like.

The definition of aminoalkyl encompasses alkyl groups (i.e. “(C₁-C₆)alkyl” groups) substituted by one or more amino groups (-NR₁₀R₉). An example of aminoalkyl is a mono-aminoalkyl group such as R₁₀R₉N-(C₁-C₆)alkyl. The substituents R₁₀ and R₉ are defined as R₄ and R₅ in the above detailed description of the invention.

Derived expression such as aminoalkoxyl thus refer to the above define aminoalkyl linked to the rest of the molecule from the alkyl side via an ether bridge, e.g. with linear representation -O-(CH₂)_mNR₄R₅.

The term “(C₃-C₁₀)cycloalkyl” likewise “(C₃-C₈)cycloalkyl” or “(C₃-C₆)cycloalkyl” refers to saturated cyclic hydrocarbon groups containing the indicated number of ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl and cycloheptyl, and polycyclic ring systems such as adamantan-yl.

The expression “Aryl” refers to mono, bi- or tri-cyclic carbon ring systems which have 6 to 20, preferably from 6 to 15 ring atoms, wherein at least one ring is aromatic.

The expression “heteroaryl” refers to mono-, bi- or tri-cyclic ring systems with 5 to 20, preferably from 5 to 15 ring atoms, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom (e.g. N, S or O).

Examples of aryl or heteroaryl monocyclic ring systems include, for instance, phenyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furanyl radicals and the like.

Examples of aryl or heteroaryl bicyclic ring systems include naphthalenyl, biphenylenyl, purinyl, pteridinyl, pyrazolopyrimidinyl, benzotriazolyl, benzoimidazole-yl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, indazolyl, benzothiophenyl, benzodioxinyl, dihydrobenzodioxinyl, indenyl, dihydro-indenyl, dihydrobenzo[1,4]dioxinyl, benzothiazole-2-yl, dihydrobenzodioxepinyl, benzooxazinyl, 1,2,3,4-tetrahydroisoquinoline-6-yl, 4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine, 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl, 5,6,7,8-tetrahydro-1,7-naphthyridine, radicals and the like.

Examples of aryl or heteroaryl tricyclic ring systems include fluorenyl radicals as well as benzocondensed derivatives of the aforementioned heteroaryl bicyclic ring systems.

The derived expression “(C₃-C₁₀)heterocycloalkyl” likewise “(C₃-C₈)heterocycloalkyl” or “(C₃-C₆)heterocycloalkyl” refers to saturated or partially unsaturated mono, bi- or tri- cycloalkyl groups of the indicated number of carbons, in which at least one ring carbon atom is replaced by at least one heteroatom (e.g. N, NH, S or O) and/or may bear an -oxo (=O) substituent group. Said heterocycloalkyl (i.e. heterocyclic radical or group) is further optionally substituted on the available points in the ring, namely on a carbon atom, or on an heteroatom available for substitution. Examples of heterocycloalkyl are represented by: oxetanyl, tetrahydro-furanyl, pyrrolidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro- or tetrahydro-pyridinyl, tetrahydropyranyl, pyranyl, 2H- or 4H-pyranyl, dihydro- or tetrahydrofuranyl, dihydroisoxazolyl, pyrrolidin-2-one-yl,

dihydropyrrolyl, 5-oxopyrrolidin-3-yl, (1R,5S,6R)-3-oxabicyclo[3.1.0]hexan-6-yl, octahydrocyclopenta[c]pyrrol-5-yl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl; 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl radicals and the like.

The term “Aryl(C₁-C₆)alkyl” refers to an aryl ring linked to a straight-chained or
5 branched alkyl group wherein the number of constituent carbon atoms is in the range from 1 to 6, e.g. phenylmethyl (i.e. benzyl), phenylethyl or phenylpropyl.

Likewise the term “Heteroaryl(C₁-C₆)alkyl” refers to an heteroaryl ring linked to a straight-chained or branched alkyl group wherein the number of constituent carbon atoms is in the range from 1 to 6, e.g. furanylmethyl.

10 The term “alkanoyl”, refers to HC(O)- or to alkylcarbonyl groups (e.g. (C₁-C₆)alkylC(O)-) wherein the group “alkyl” has the meaning above defined. Examples include formyl, acetyl, propanoyl, butanoyl.

The term “(C₁-C₁₀) alkoxy” or “(C₁-C₁₀) alkoxyl”, likewise “(C₁-C₆) alkoxy” or “(C₁-C₆) alkoxyl” etc., refers to a straight or branched hydrocarbon of the indicated
15 number of carbons, linked to the rest of the molecule through an oxygen bridge. “(C₁-C₆)Alkylthio” refers to the above hydrocarbon linked through a sulfur bridge.

The derived expression “(C₁-C₆)haloalkoxy” or “(C₁-C₆)haloalkoxyl” refers to the above defined haloalkyl, linked through an oxygen bridge. An example of (C₁-C₆)haloalkoxy is trifluoromethoxy.

20 Likewise derived expression “(C₃-C₆)heterocycloalkyl-(C₁-C₆)alkyl” and “(C₃-C₆)cycloalkyl-(C₁-C₆)alkyl” refer to the above defined heterocycloalkyl and cycloalkyl groups linked to the rest of the molecule via an alkyl group of the indicated number of carbons, corresponding e.g. to linear formula (C₃-C₆)heterocycloalkyl-(CH₂)_m- or (C₃-C₆)cycloalkyl-(CH₂)_m- for example piperidin-4-yl-methyl,
25 cyclohexylethyl.

The derived expression “(C₁-C₆)alkoxy-(C₁-C₆)alkyl” refers to the above defined alkoxy group linked to the rest of the molecule via an alkyl group of the indicated number of carbons, corresponding e.g. to linear formula (C₁-C₆)alkoxy-(CH₂)_m- for example methoxymethyl.

30 Likewise “(C₁-C₆)haloalkoxy (C₁-C₆)alkyl” refers to the above defined (C₁-C₆)haloalkoxy group linked to the rest of the molecule via an alkyl group of the indicated number of carbons, for example difluoromethoxypropyl.

Derived expression “(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkoxyl” or “(C₃-C₆)heterocycloalkyl-(C₁-C₆)alkoxyl” and “(C₃-C₈)cycloalkyl-(C₁-C₆)alkoxyl” or “(C₃-C₆)cycloalkyl-(C₁-C₆)alkoxyl” refer to the above defined heterocycloalkyl and cycloalkyl groups linked to the rest of the molecule via an alkoxyl group as above defined of the indicated number of carbons, corresponding e.g. to linear formula (C₃-C₈)cycloalkyl -(CH₂)_mO- (C₃-C₈)heterocycloalkyl -(CH₂)_mO- for example piperazin-1-yl-ethoxyl.

An oxo moiety is represented by (O) as an alternative to the other common representation, e.g. (=O). Thus, in terms of general formula, the carbonyl group is herein preferably represented as -C(O)- as an alternative to the other common representations such as -CO-, -(CO)- or -C(=O)-. In general the bracketed group is a lateral group, not included into the chain, and brackets are used, when deemed useful, to help disambiguating linear chemical formulas; e.g. the sulfonyl group -SO₂- might be also represented as -S(O)₂- to disambiguate e.g. with respect to the sulfinic group -S(O)O-.

When a numerical index the statement (value) “p is zero” or “p is 0” means that the substituent or group bearing the index p (e.g. (R)_p) is absent, that is to say no substituent, other than H when needed, is present. Likewise when the index is attached to a bridging divalent group (e.g. (CH₂)_n) the statement “n in each occurrence is zero...” or “n is 0” means that the bridging group is absent, that is to say it is a bond.

Whenever basic amino or quaternary ammonium groups are present in the compounds of formula (I), physiological acceptable anions, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, p-toluenesulfonate, pamoate and naphthalene disulfonate may be present. Likewise, in the presence of acidic groups such as COOH groups, corresponding physiological cation salts may be present as well, for instance including alkaline or alkaline earth metal ions.

Compounds of formula (I) when they contain one or more stereogenic center, may exist as optical stereoisomers.

Where the compounds of the invention have at least one stereogenic center, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more stereogenic centers, they may additionally exist as diastereoisomers. It is to be understood that all such single enantiomers, diastereoisomers and mixtures thereof in

any proportion are encompassed within the scope of the present invention. The absolute configuration (R) or (S) for carbon bearing a stereogenic center is assigned on the basis of Cahn-Ingold-Prelog nomenclature rules based on groups' priorities.

“Single stereoisomer”, “single diastereoisomer” or “single enantiomer”, when reported near the chemical name of a compound indicate that the isomer was isolated as single diastereoisomer or enantiomer (e.g via chiral chromatography) but the absolute configuration at the relevant stereogenic center was not determined/assigned.

Atropisomers result from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers (Bringmann G et al, *Angew. Chemie Int. Ed.* 44 (34), 5384-5427, 2005. doi:10.1002/anie.200462661).

Oki defined atropisomers as conformers that interconvert with a half-life of more than 1000 seconds at a given temperature (Oki M, *Topics in Stereochemistry* 14, 1-82, 1983).

Atropisomers differ from other chiral compounds in that in many cases they can be equilibrated thermally whereas in the other forms of chirality isomerization is usually only possible chemically.

Separation of atropisomers is possible by chiral resolution methods such as selective crystallization. In an atropo-enantioselective or atroposelective synthesis one atropisomer is formed at the expense of the other. Atroposelective synthesis may be carried out by use of chiral auxiliaries like a Corey Bakshi Shibata (CBS) catalyst, an asymmetric catalyst derived from proline, or by approaches based on thermodynamic equilibration when an isomerization reaction favors one atropisomer over the other.

Racemic forms of compounds of formula (I) as well as the individual atropisomers (substantially free of its corresponding enantiomer) and stereoisomer-enriched atropisomer mixtures are included in the scope of the present invention.

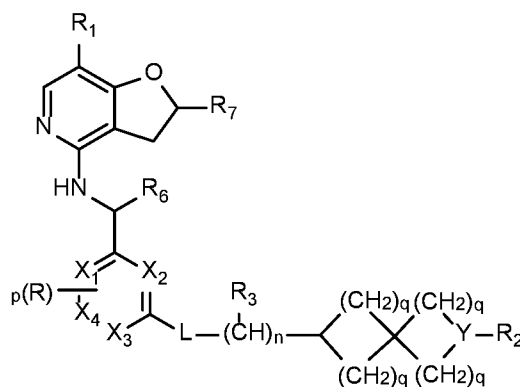
The invention further concerns the corresponding deuterated derivatives of compounds of formula (I). In the context of the present invention, deuterated derivative means that at least one position occupied by a hydrogen atom is occupied by deuterium in an amount above its natural abundance. Preferably, the percent of deuterium at that position is at least 90%, more preferably at least 95%, even more preferably 99%.

All preferred groups or embodiments described above and herebelow for

compounds of formula (I) may be combined among each other and apply as well *mutatis mutandis*.

As above mentioned, the present invention refers to compounds of general formula (I), acting as ROCK inhibitors, to processes for the preparation thereof, pharmaceutical compositions comprising them either alone or in combination with one or more active ingredient, in admixture with one or more pharmaceutically acceptable carriers.

In a first aspect the present invention is directed to a class of compounds of formula (I)



wherein

X₁, X₂, X₃ and X₄ are all CH or one of X₁, X₂, X₃ and X₄ is N and the others are CH;

preferably X₁, X₂, X₃ and X₄ are all CH;

Y is selected from N, or O;

q is in each occurrence independently selected from 1 or 2;

p is zero or an integer from 1 to 4;

each R, when present, is in each occurrence independently selected from (C₁-C₆)alkyl and halogen selected from F, Cl, Br and I; wherein preferably R is selected from F, Cl and methyl;

R₁ is pyrazolyl, preferably 1H-pyrazol-4-yl or pyridinyl, preferably pyridin-4-yl or pyrimidinyl, preferably pyrimidin-4-yl, substituted by one or more group selected from - (CH₂)_mNH₂; particularly preferably R₁ is 2-aminopyrimidin-4-yl;

L is -C(O)NH- or -NHC(O)- ;

n is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₃, when present, is in each occurrence independently H, or (C₁-C₆)alkyl,

R₂ is absent when Y is O, or when Y is N, R₂ is selected from the group consisting of

-H,

(C₁-C₆)alkyl,

5 (C₁-C₆)hydroxyalkyl,

(C₁-C₆)alkoxy (C₁-C₆)alkyl, preferably (C₁-C₆)alkoxy-(CH₂)_m-

ciano (C₁-C₆)alkyl, meaning NC-(C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

-(CH₂)_n-C(O)-(CH₂)_mNR₄R₅, preferably -C(O)(CH₂)_mNR₄R₅,

10 or -(CH₂)_nC(O)NR₄R₅,

alkanoyl, preferably (C₁-C₆)alkyl-carbonyl,

aryl, heteroaryl, (C₃-C₈)cycloalkyl,

(C₃-C₈)heterocycloalkyl, preferably (C₃-C₆)heterocycloalkyl, which is preferably oxethan-3-yl,

15 aryl-(C₁-C₆)alkyl,

heteroaryl-(C₁-C₆)alkyl which is preferably pyrimidin-5-ylmethyl;

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl, preferably (C₃-C₆)heterocycloalkyl-

(CH₂)_m-,

(C₃-C₈)cycloalkyl-(C₁-C₆)alkyl,

20 m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₄ and R₅, the same or different, are selected from the group consisting of

-H,

(C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

25 (C₁-C₆)hydroxyalkyl,

R₆ and R₇ are independently selected from the group consisting of -H, (C₁-C₆)alkyl;

single enantiomers, diastereoisomers and mixtures thereof in any proportion

and/or pharmaceutically acceptable salts and solvates thereof.

In a preferred embodiment the invention is directed to a compound of formula (I)

30 wherein X₁, X₂, X₃ and X₄ are all CH;

Y is -N-;

q is in each occurrence independently selected from 1 or 2;

p is zero or an integer from 1 to 4;

each R, when present, is an halogen in each occurrence independently selected from F, Cl, Br and I, wherein preferably R is F;

R₁ is pyrimidinyl substituted by -NH₂; particularly preferably R₁ is 2-aminopyrimidin-4-yl;

L is -C(O)NH-;

n is 0;

R₃ is absent

and

R₂ is selected from the group consisting of -H,

(C₁-C₆) alkoxy (C₁-C₆)alkyl, preferably (C₁-C₆)alkoxy-(CH₂)_m-,

ciano (C₁-C₆)alkyl, meaning NC-(C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

-(CH₂)_n-C(O)-(CH₂)_mNR₄R₅, preferably -C(O)(CH₂)_mNR₄R₅, or -

(CH₂)_nC(O)NR₄R₅,

alkanoyl, preferably (C₁-C₆)alkyl-carbonyl,

heteroaryl-(C₁-C₆)alkyl which is preferably pyrimidin-5-ylmethyl;

(C₃-C₈)heterocycloalkyl, preferably (C₃-C₆)heterocycloalkyl, which is preferably oxethan-3-yl,

m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₄ and R₅, the same or different, are selected from the group consisting of

-H,

(C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

(C₁-C₆)hydroxyalkyl,

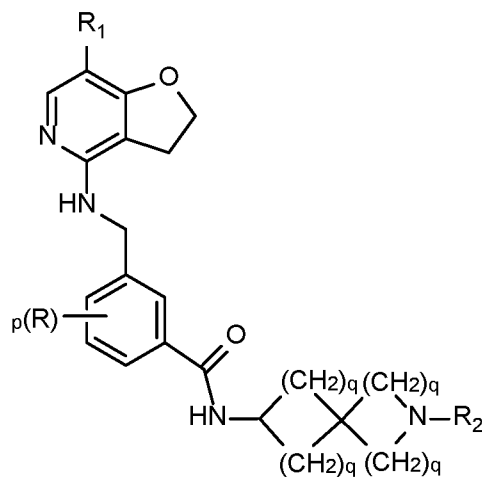
R₆ and R₇ are -H

all the other variables being as defined above,

single enantiomers, diastereoisomers and mixtures thereof in any proportion

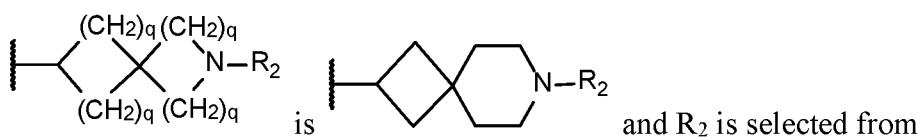
and/or pharmaceutically acceptable salts and solvates thereof.

Said preferred group of compounds is represented by the formula (Ia)



Ia

Particularly preferred is a compound of formula (I) or (Ia) wherein the group



- 5 2-methoxyethyl, 2-fluoroethyl, oxetan-3-yl, 2-(dimethylamino)-2-oxoethyl;
all the other variables and substitution being as defined above,
single enantiomers, diastereoisomers and mixtures thereof in any proportion
and/or pharmaceutically acceptable salts and solvates thereof.

Thus, a group of particularly preferred compounds are

Example	Chemical Name
10	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
9	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-fluoroethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
29	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide
20	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide
8	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-(dimethylamino)-2-oxoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
28	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide

A further preferred group of compounds according to the invention are those of formula (I) wherein

X₁, X₂, X₃ and X₄ are all CH;

p is zero or 1;

each R, when present, is F;

R₁ is selected from **1H-pyrazol-4-yl, pyridin-4-yl and 2-aminopyrimidin-4-yl**;

L is -C(O)NH-;

n is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₃, is H,

and

R₂ is absent when Y is O, or when Y is N, R₂ is selected from the group consisting of

-H,

(C₁-C₆) alkoxy (C₁-C₆)alkyl, which is 2-methoxyethyl,

ciano (C₁-C₆)alkyl which is 2-cyanoethyl,

(C₁-C₆) haloalkyl, which is 2-fluoroethyl,

-C(O)(CH₂)_m NR₄R₅, which is 2-(dimethylamino)-2-oxoethyl,

-(CH₂)_nC(O) NR₄R₅, which is dimethylglycyl,

alkanoyl, which is acetyl,

heteroaryl-(C₁-C₆)alkyl which is pyrimidin-5-ylmethyl;

(C₃-C₈)heterocycloalkyl, which is oxethan-3-yl,

m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₄ and R₅, are both (C₁-C₆)alkyl, which is methyl,

R₆ and R₇ are -H;

single enantiomers, diastereoisomers and mixtures thereof in any proportion, or pharmaceutically acceptable salts and solvates thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof in admixture with one or more pharmaceutically acceptable carriers or excipients, either alone or in combination with one or more further active ingredient as detailed below.

According to preferred embodiments, the invention provides the compounds listed in the table below and pharmaceutical acceptable salts thereof.

Example	Chemical Name
1	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-fluoroethyl)-2-azaspiro[3.3]heptan-6-yl)benzamide
2	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-oxaspiro[3.5]nonan-2-yl)benzamide
3	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-oxaspiro[3.3]heptan-6-yl)benzamide
4	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide
5	3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide
6	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide
7	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-cyanoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
8	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-(dimethylamino)-2-oxoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
9	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-fluoroethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
10	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
11	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide
12	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)benzamide
13	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide
14	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide
15	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide

Example	Chemical Name
16	N-(7-acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide
17	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(dimethylglycyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
18	N-(7-acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide
19	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(oxetan-3-yl)-3-azaspiro[5.5]undecan-9-yl)benzamide
20	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide
21	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(pyrimidin-5-ylmethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
22	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide
23	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(oxetan-3-yl)-2-azaspiro[3.5]nonan-7-yl)benzamide
24	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide
25	N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide
26	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide
27	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)benzamide
28	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide
29	3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide

The compounds of the invention, including all the compounds hereabove listed, can be prepared from readily available starting materials using the following general methods and procedures or by using slightly modified processes readily available to those of

ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present invention can be prepared using the methods described herein or by using other known methods, reagents and starting materials. When typical or preferred
5 process conditions (i.e. reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. While the optimum reaction conditions may vary depending on the particular reactants or solvent used, such conditions can be readily determined by those skilled in the art by routine optimization procedures.

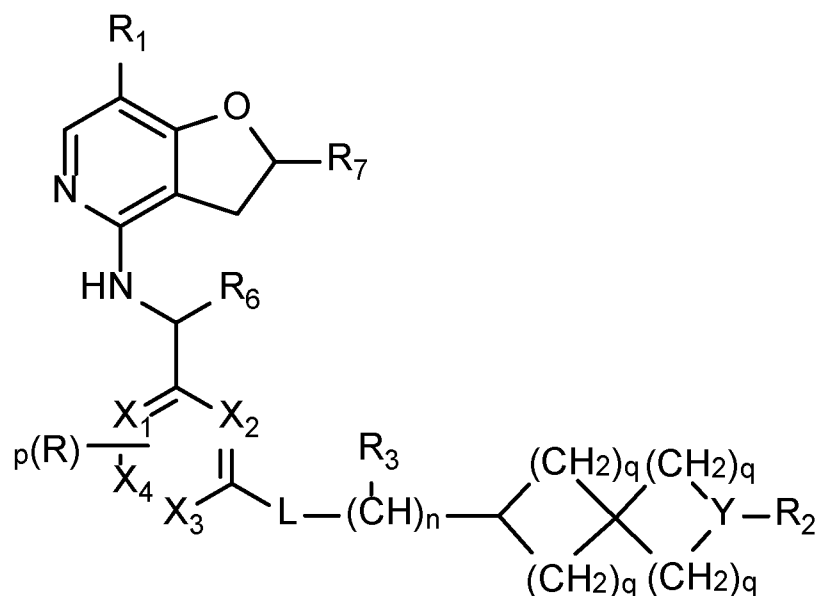
10 Thus, processes of preparation described below and reported in the following schemes should not be viewed as limiting the scope of the synthetic methods available for the preparation of the compounds of the invention.

In some cases a step is needed in order to mask or protect sensitive or reactive moieties, generally known protective groups (PG) could be employed, in accordance with
15 general principles of chemistry (Protective group in organic syntheses, 3rd ed. T. W. Greene, P. G. M. Wuts). A suitable protective group for intermediates requiring protection of a carboxylic acid (herein reported as PG₁) can be C₁-C₄ esters (PG₁: methyl, isopropyl, tert-butyl or ethyl), preferably methyl.

A suitable protective group for protecting NH of R₁ groups (herein reported as
20 PG₂) can be tert-butoxycarbonyl (Boc) or a tetrahydro-2H-pyran-2-yl (THP).

A suitable protective group for intermediates requiring the amino group protection (herein reported as PG₃) can be carbamates such as tert-butylcarbamate (tert-butoxycarbonyl or Boc), benzylcarbamate (Benzyloxycarbonyl or Cbz), ethylcarbamate (ethoxycarbonyl) or methylcarbamate (methoxycarbonyl), preferably PG₃ is Boc.

25 The compounds of formula (I), here reported again for clarity, including all the compounds here above listed, can be usually prepared according to the procedures shown in the schemes below. Where a specific detail or step differs from the general schemes it has been detailed in the specific examples, and/or in additional schemes.

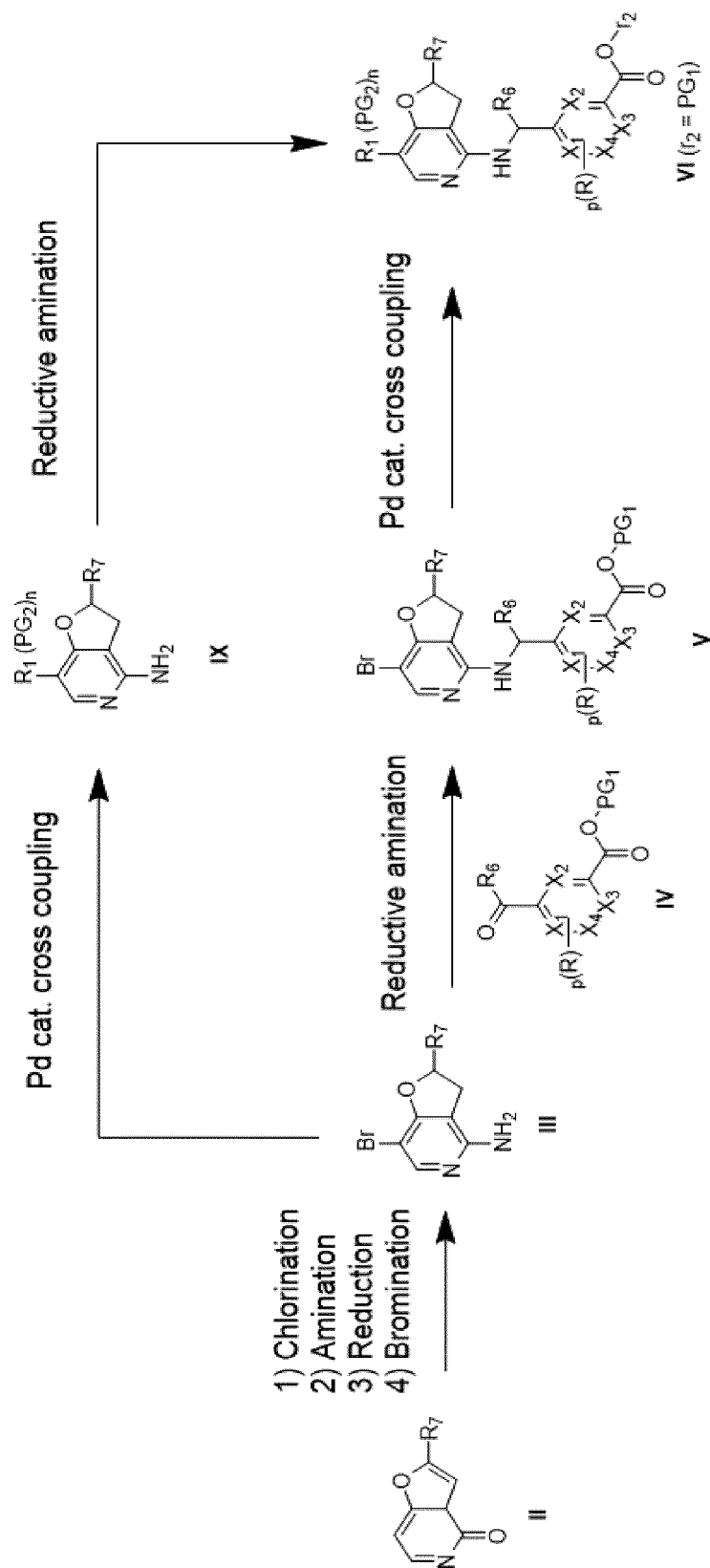


I

Compounds of formula (I) can contain one or more stereogenic centre. Enantiomerically pure compounds can be prepared according to generally known reactions, e.g. according to the reactions described below, by means of enantiomerically pure starting materials and intermediates. These intermediates may be commercially available or readily produced from commercial sources by those of ordinary skill in the art.

In another approach, enantiomerically pure compounds can be prepared from the corresponding racemates by means of chiral chromatography purification. Stereochemically pure compounds may be obtained by chiral separation from a stereoisomers mixture, or (whenever there are two or more stereogenic centres -i.e. chiral center- in compounds of formula (I)) stepwise by chromatographic separation of diastereoisomers followed by further chiral separation into single stereoisomers.

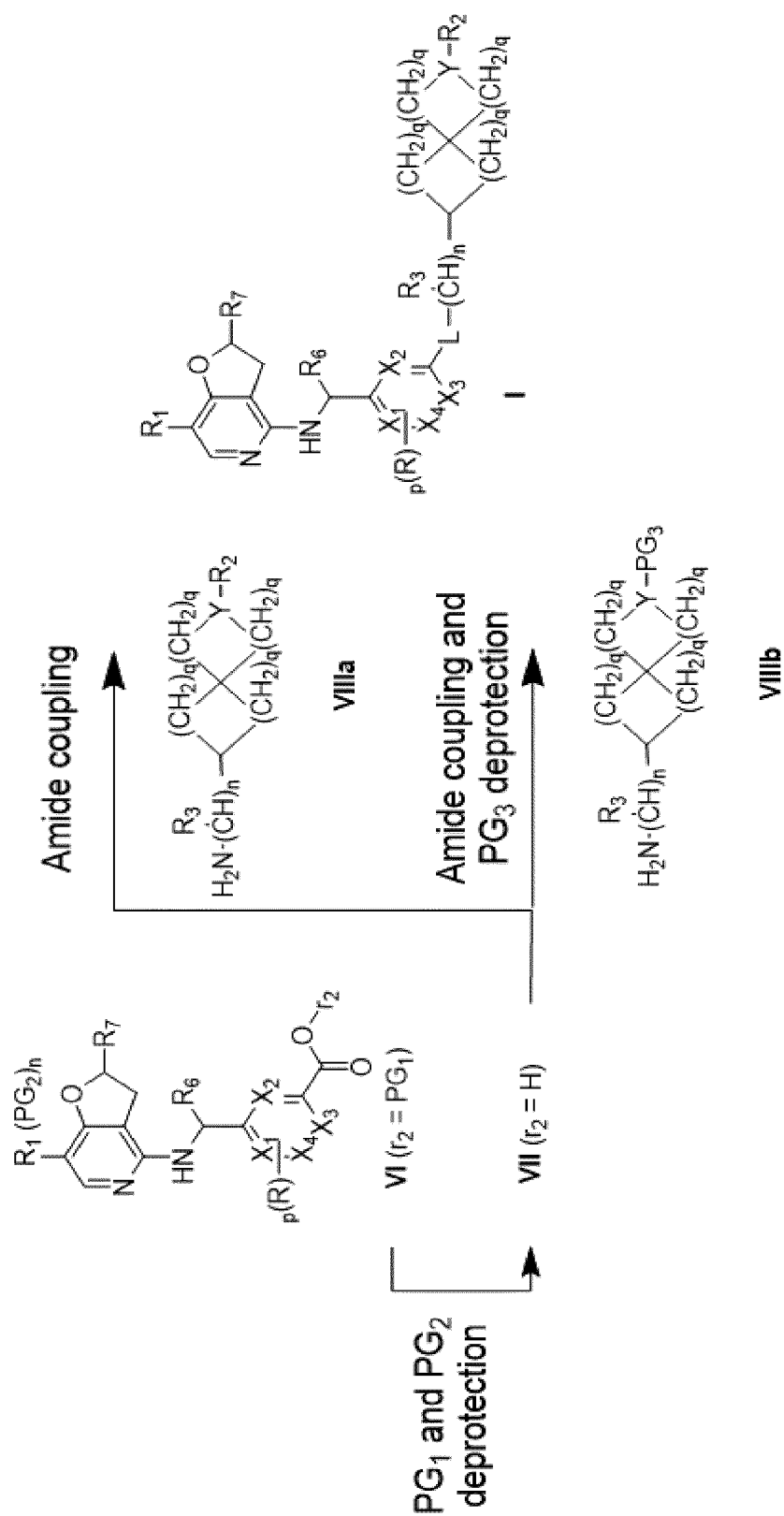
SCHEME 1 (part A)



(continue next page)

SCHEME 1 (part B)

(continue from last page)



Compounds of formula (I) can be prepared according to SCHEME 1 starting from intermediate **II** that is commercially available or easily obtainable by those skilled in the art.

Intermediate **II** can be converted into intermediate **III** by means of four consecutive
5 steps including 1) chlorination, 2) amination, 3) reduction and 4) bromination.

For example, the chlorination step may be carried out by refluxing intermediate **II** with an appropriate chlorinating agent (neat or in solution with an organic solvent such as DCM or dioxane) such as POCl₃ or SOCl₂.

The amination step can be carried out by introducing a masked ammonia such as
10 benzophenone imine through a Buchwald type palladium catalyzed reaction using, for example, tris(dibenzylideneacetone)dipalladium(0)/BINAP catalytic system followed by hydrolysis of the benzophenone imine by using hydroxylamine to give the corresponding furo[3,2-c]pyridin-4-amine. Alternatively, the amination step can be carried out by introducing 4-methoxybenzylamine by means of S_NAr reaction (nucleophilic aromatic
15 substitution) followed by deprotection with a strong acid such as trifluoroacetic acid or methanesulfonic acid. Reduction of furo[3,2-c]pyridin-4-amine to give 2,3-dihydrofuro[3,2-c]pyridin-4-amine (step 3) can be carried out, for example, by hydrogenation of a solution of furo[3,2-c]pyridin-4-amine in methanol / acetic acid in the presence of a Pd/C catalyst under high H₂ pressure (e.g. 10 bar) and at a temperature of
20 50°C or higher. Finally, intermediate **III** can be obtained by means of bromination of 2,3-dihydrofuro[3,2-c]pyridin-4-amine (step 4) by reaction with a brominating agent such as N-bromosuccinimide in a polar aprotic solvent such as acetonitrile or tetrahydrofuran for a few hours at low temperature (e.g. -10 – 0 °C).

Intermediate **III** and carbonyl intermediate **IV** can be combined to give
25 intermediate **V** through a reductive amination reaction that can be performed in an appropriate solvent such as DCM or THF, in the presence of a Lewis acid such as chloro(triisopropoxy)titanium(IV) or titanium tetraisopropoxide(IV) followed by addition of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of an organic acid such as acetic acid or trifluoroacetic
30 acid.

Intermediate **V** can be converted into intermediate **VI** by a direct introduction of group R₁ through a metal/palladium catalyzed cross coupling reaction such as Stille

coupling, Suzuki coupling or similar (Strategic application of named reactions in organic synthesis, L. Kurti, B. Czako, Ed. 2005).

For example a suitable palladium catalyzed cross coupling for introducing R_1 when it is an 2-aminopyrimidin-4-yl, is a Stille coupling. A Stille coupling can be performed by reacting intermediate **V** with the corresponding organostannane of group R_1 , in the presence of a Pd catalyst such as tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), or $PdCl_2(dppf)_2$, in an organic solvent such as dioxane or THF or DMF, in the presence of a copper(I) salt such as copper(I) thiophene-2-carboxylate, under heating (90-150°C). Organostannanes are generally commercially available or may be readily prepared by those skilled in the art starting from corresponding commercially available halides. Experimental procedures for the preparation of an organostannane not commercially available are reported in the experimental section. When R_1 is a 2-aminopyrimidin-4-yl, for synthetic convenience, the amino group needs to be masked/protected during the Stille coupling. Said amino group may be suitably protected (PG_2) by one or even two Boc groups and removed when convenient throughout the synthetic sequence.

For example a suitable palladium catalyzed cross coupling for introducing R_1 , when it is a pyrazolyl or pyridinyl, it is a Suzuki coupling. Suzuki coupling can be performed by reacting intermediate **V** with the corresponding boronic acid or boron pinacolate ester of group R_1 , in the presence of a Pd catalyst such as tris(dibenzylideneacetone)dipalladium(0), $PdCl_2(dppf)_2$.DCM adduct or tetrakis(triphenylphosphine)palladium(0), in an organic solvent such as dioxane, THF or DMF with or without water, with an inorganic base such as an alkaline carbonate (for example Cs_2CO_3) or an inorganic phosphate (for example K_3PO_4), under heating (90-150°C). Boronic acid and boronic pinacolate esters are generally commercially available or may be readily prepared by those skilled in the art starting from commercially available reagents. When R_1 is pyrazolyl, for synthetic convenience, the NH needs to be masked/protected during the Suzuki coupling. Said NH may be suitably protected (PG_2) by THP or Boc and removed when convenient throughout the synthetic sequence.

In another approach, intermediate **VI** can be obtained by inverting the order of reductive amination and Palladium cross coupling reaction. First, intermediate **III** can be converted into intermediate **IX** by Palladium catalyzed cross coupling in the same way as

described above for conversion of intermediate **V** in **VI**, then intermediate **IX** can be converted by a reductive amination reaction into intermediate **VI** in the same way as described above for conversion of intermediate **III** into **V**.

Removal of PG₁ (when PG₁ is methyl) from intermediate **VI** to give the
5 intermediate **VII** may be carried out by hydrolysis, using an inorganic base such as LiOH or NaOH in a mixture of an organic solvent such as THF and/or methanol with water, generally at RT and for a time ranging from 1 h to overnight. In the above mentioned reaction conditions, whether R₁ is a N-bis-Boc protected 2-aminopyrimidin-4-yl, one Boc group could undergo cleavage; then complete Boc removal could be performed by
10 treatment with a strong acid such as trifluoroacetic acid or concentrated hydrochloric acid. Where R₁ is a N-Boc protected pyrazolyl, the Boc group could undergo cleavage under PG₁ removal basic conditions.

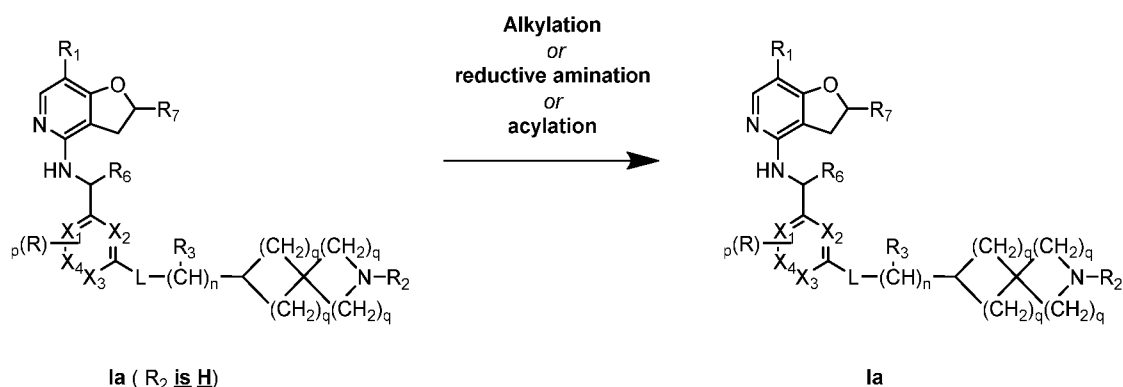
Removal of PG₂ (when PG₂ is Boc) from intermediate **VI** to give the intermediate **VII** may be carried out by acidic deprotection. For example, an acidic Boc cleavage may
15 be carried out by means of concentrated hydrochloric acid or trifluoroacetic acid. With these conditions Boc groups on bis-Boc protected 2-aminopyrimidin-4-yl can also be cleaved. Wherein R₁ is a pyrazolyl group protected by THP, said protective group can be easily removed by heating (up to 100°C) the protected precursor with concentrated aqueous acid such as 15 to 30% w/w aqueous hydrochloric acid or up to 30%w/w
20 aqueous sulfuric acid for a time up to 1 h or less. Under these condition also PG₁, when it is Me can be removed concomitantly.

Reaction between acid intermediate **VII** and amino intermediate **VIIIa** to give a compound of formula (**I**) may be carried out under suitable amide coupling reaction conditions. For example, acid intermediate **VII** may be reacted in the presence of an
25 activating agent such as TBTU, HATU or COMU, in the presence of an organic base such as DIPEA or TEA, in a suitable organic solvent such as DCM or DMF, and at a temperature generally around RT for a time ranging from a few hours to overnight.

A compound of formula (**I**) wherein Y equal to N and R₂ equal to H, this amino moiety needs to be masked during the amide coupling step by using suitably protected
30 (PG₃ generally Boc) intermediates **VIIIb**. The removal of PG₃, when PG₃ is a Boc group, it can be carried out by acidic deprotection by means of concentrated hydrochloric acid or trifluoroacetic acid.

Examples 1 to 5 can be prepared according *scheme 1*.

SCHEME 2



In another approach, a compound of formula (**Ia**) wherein R_2 is in each occurrence different from H, such compounds can be obtained by further elaboration of a compound of formula (**Ia**) (wherein R_2 is H) by means of an alkylation reaction, a reductive amination reaction or an amidation reaction by using generally known methods (*Scheme 2*). For example an alkylation can be carried out by reaction of the amine (compound of formula I wherein Y is N and R_2 is H) with an alkylating agent such as an alkylbromide, iodide, tosylate or similar reagents, in an organic solvent such as DMF or DCM, in the presence of an inorganic base such as K_2CO_3 at room temperature or higher. In the case of reductive amination on a compound of formula (**Ia**) (wherein R_2 is H), such reaction can be carried out by reacting said amine with the a suitable aldehyde or ketone in an organic solvent such as DMF, DCM or similar, in the presence of an acid such as acetic acid and a suitable reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride or similar well known methods to those skilled in the art. Amidation on a compound of formula (**Ia**) (wherein R_2 is H) can be carried out by reaction of the said amine with the a suitable carboxylic acid in the presence of a coupling agent such as HATU, TBTU or COMU, in an organic solvent such as DMF and/or DCM and in the presence of an organic base such as DIPEA. Examples from 6 to 27 were synthesized according *scheme 2*.

As herein described in details, compounds of the invention are inhibitors of kinase activity, in particular Rho-kinase activity.

In one aspect the invention provides a compound of formula (I) for use as a medicament, preferably for the prevention and /or treatment of pulmonary disease.

In a further aspect the invention provides the use of a compound (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of disorders associated with ROCK enzyme mechanisms, including immune system disorders and particularly for the treatment of disorders such as pulmonary diseases.

In particular the invention provides compounds of formula (I) for use in the prevention and /or treatment of immune system disorders including Graft-versus-host disease (GVHD), and for pulmonary disease selected from the group consisting of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).

Moreover the invention provides a method for the prevention and/or treatment of disorders associated with ROCK enzymes mechanisms, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

In particular the invention provides methods for the prevention and/or treatment wherein the disorder is an immune system disorder such as Graft-versus-host disease (GVHD), and/or a respiratory disease selected from asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), Pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).

Preferred is the use of the compounds of the invention for the prevention of the aforesaid disorders.

Equally preferred is the use of the compounds of the invention for the treatment of the aforesaid disorders.

Generally speaking, compounds which are ROCK inhibitors may be useful in the treatment of many disorders associated with ROCK enzyme mechanisms.

In one embodiment, the disorders that can be treated by the compounds of the present invention include glaucoma, inflammatory bowel disease (IBD), immune system disorders including Graft-versus-host disease (GVHD), and pulmonary diseases selected from asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease such as idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

In another embodiment, the disorder that can be treated by the compound of the

present invention is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease such as idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

In a further embodiment, the disorder is selected from asthma, chronic obstructive pulmonary disease (COPD).

The methods of treatment of the invention comprise administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof. As used herein, "safe and effective amount" in reference to a compound of formula (I) or a pharmaceutically acceptable salt thereof or other pharmaceutically-active agent means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects and it can nevertheless be routinely determined by the skilled artisan. The compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. Typical daily dosages may vary depending upon the particular route of administration chosen.

The invention also provides pharmaceutical compositions of compounds of formula (I) in admixture with one or more pharmaceutically acceptable carrier or excipient, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.

The present invention is also directed to use of the compounds of the invention and their pharmaceutical compositions for various route of administration

Administration of the compounds of the invention and their pharmaceutical compositions may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and known excipients, including suspending agents,

solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous.

Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable known inert diluents such as water and suitable known excipients such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be formulated as injectable composition, for example to be injected intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols.

Formulations for vaginal administration can be in the form of cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such as suitable carriers, are also known.

For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

Some preferred compounds of the invention exhibit profile suitable for inhalatory route administration.

Drugs optimized for inhaled delivery require certain characteristics that allow the compound, when administered to the lung to maintain a sufficient local concentration (lung retention) to exert a pharmacological effect of the desired duration, and non-relevant levels in unwanted compartments (i.e. plasma). To attenuate lung absorption, one or more features of a compounds need to be optimized such as, and not limited to, membrane permeability, dissolution rate and the degree of basicity. In this respect, to attain lung retention, permeability is low, dissolution rate is sufficiently slow, and a basic group is present to enhance binding to the phospholipid-rich lung tissue or to allow lysosomal trapping. In some embodiments, compounds of the invention show one or more of the

features above that are desirable for an inhaled compound.

Other preferred compounds of the invention exhibit a profile suitable for the oral route of administration. Drugs optimized for oral delivery require certain characteristics that allow the orally administered compound to be absorbed by the GI (gastrointestinal) tract and to be poorly cleared in order to give a good bioavailability (F%), thus to maintain a sufficient concentration in plasma and target tissues for a time adequate to sustain pharmacological effect. To enhance oral bioavailability, one or more features of the compounds need to be optimized such as, and not limited to, membrane permeability and in vivo clearance. In this respect, to attain high oral bioavailability membrane permeability is high and compounds have reduced metabolic hot spots to (optimized in-vitro clearance). In some embodiments, compounds of the invention show one or more of the features above for an oral compound.

For the treatment of the diseases of the respiratory tract, the compounds according to the invention, as above said, may be administered by inhalation.

Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized. In that case the powder may be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

A diluent or carrier, usually non-toxic and chemically inert to the compounds of the invention, e.g. lactose or any other additive suitable for improving the respirable fraction may be added to the powdered compounds of the invention.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

The propellant-free inhalable formulations comprising the compounds of the invention may be in the form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by soft-mist nebulizers such as Respimat®.

Further preferably the invention provides compounds of formula (I) and/or pharmaceutical compositions thereof, for use via inhalatory route of administration

particularly in the prevention and /or treatment of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH); preferably in the prevention and /or treatment of asthma, chronic obstructive pulmonary disease COPD.

5 Further preferably the invention provides compounds of formula (I) and/or pharmaceutical compositions thereof, for use via oral route of administration particularly in the prevention and /or treatment of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH), preferably in the prevention and /or
10 treatment of pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).

The compounds of the invention, regardless of the route of administration, can be administered as the sole active agent or in combination (i.e. as co-therapeutic agents administered in fixed dose combination or in combined therapy of separately formulated
15 active ingredients) with other pharmaceutical active ingredients selected from organic nitrates and NO donors; inhaled NO; stimulator of soluble guanylate cyclase (sGC); prostacyclin analogue PGI₂ and agonist of prostacyclin receptors; compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP), such as inhibitors of phosphodiesterases (PDE) 1, 2, 3, 4 and/or
20 5, especially PDE 5 inhibitors; human neutrophilic elastase inhibitors; compounds inhibiting the signal transduction cascade, such as tyrosine kinase and/or serine/threonine kinase inhibitors; antithrombotic agents, for example platelet aggregation inhibitors, anticoagulants or profibrinolytic substances; active substances for lowering blood pressure, for example calcium antagonists, angiotensin II antagonists, ACE inhibitors,
25 endothelin antagonists, renin inhibitors, aldosterone synthase inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists; neutral endopeptidase inhibitor; osmotic agents; ENaC blockers; anti-inflammatories including corticosteroids and antagonists of chemokine receptors; antihistamine drugs; anti-tussive drugs; antibiotics such as macrolide and DNase drug substance and selective cleavage
30 agents such as recombinant human deoxyribonuclease I (rhDNase); agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroxylase 1 (TPH1) inhibitors and multi-kinase inhibitors, beta2-agonists, corticosteroids,

anticholinergic or antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma and combinations thereof.

In a preferred embodiment, the compounds of the invention are dosed in combination with phosphodiesterase V such as sildenafil, vardenafil and tadalafil; organic nitrates and NO donors (for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhaled NO); synthetic prostacyclin analogue PGI₂ such as iloprost, treprostinil, epoprostenol and beraprost; agonist of prostacyclin receptors such as selexipag and compounds of WO 2012/007539; stimulators of soluble guanylate cyclase (sGC) like riociguat and tyrosine kinase like imatinib, sorafenib and nilotinib and endothelin antagonist (for example macitentan, bosentan, sitaxentan and ambrisentan).

In a further embodiment the compounds of the invention are dosed in combination with beta2-agonists such as salbutamol, salmeterol, and vilanterol, corticosteroids such as fluticasone propionate or furoate, flunisolide, mometasone furoate, rofleponide and ciclesonide, dexametasone, anticholinergic or antimuscarinic agents such as ipratropium bromide, oxytropium bromide, tiotropium bromide, oxybutynin, and combinations thereof.

In a further embodiment the compounds of the invention are dosed in combination with mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma.

The invention is also directed to a kit comprising the pharmaceutical compositions of compounds of the invention alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients and a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or a nebulizer.

The dosages of the compounds of the invention depend upon a variety of factors

including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, and pharmacokinetic profile of the compound.

Advantageously, the compounds of formula (I) can be administered for example, at
5 a dosage comprised between 0.001 and 10000 mg/day, preferably between 0.1 and 500 mg/day.

When the compounds of formula (I) are administered by inhalation route, they are preferably given at a dosage comprised between 0.001 and 500 mg/day, preferably between 0.1 and 100 mg/day.

10 A pharmaceutical composition comprising a compound of the invention suitable to be administered by inhalation is in various respirable forms, such as inhalable powders (DPI), propellant-containing metering aerosols (PMDI) or propellant-free inhalable formulations (e.g. UDV).

The invention is also directed to a device comprising the pharmaceutical
15 composition comprising a compound according to the invention, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a nebulizer particularly soft mist nebulizer.

Although for the treatment of the diseases of the respiratory tract, the compounds according to the invention can be administered by inhalation; they may be in some case
20 preferably be administered by the oral route.

When the compounds of formula (I) are administered by oral route, they are preferably given at a dosage comprised from 0.001 mg to 100 mg per kg body weight of a human, often 0.01 mg to about 50 mg per kg, for example 0.1 to 10 mg per kg, in single or multiple doses per day.

25 A pharmaceutical composition comprising a compound of the invention suitable to be administered by the oral route can be in various solid or liquid forms, such as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders or aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs formulations.

The following examples illustrate the invention in more detail.

PREPARATION OF INTERMEDIATES AND EXAMPLES

General Experimental details

Chemical Names of the compounds were generated with Structure To Name Enterprise 10.0 Cambridge Software or latest.

- 5 Purification by 'chromatography' or 'flash chromatography' refers to purification using the Biotage SPI purification system or equivalent MPLC system using a pre-packed polypropylene column containing unbounded activated silica with irregular particles with average size of 50 μm and nominal 60Å porosity. When 'NH-silica' or 'C18-silica' are specified, they refer respectively to aminopropyl chain bonded silica or octadecyl carbon chain (C18)-bonded silica. Fractions containing the required product (identified by TLC and/or LCMS analysis) were pooled and concentrated *in vacuo* or freeze-dried.
- 10

Where an Isolute® SCX-2 cartridge was used, 'Isolute® SCX-2 cartridge' refers to a pre-packed polypropylene column containing a non-end-capped propylsulfonic acid functionalised silica strong cation exchange sorbent.

15 **LCMS Methods**

Method 1

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	CSH C18 1.7 μm , 50 $\times$ 2.1mm at 40°C		
Mobile Phase A	0.1% Formic acid in water (v/v)		
Mobile Phase B	0.1% Formic acid in acetonitrile (v/v)		
Flow	1.0mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	97	03
	1.5	01	99
	1.9	01	99
	2.0	97	03
	2.5	97	03
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 2

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	CSH C ₁₈ 1.7µm, 50 × 2.1mm, at 40°C		
Mobile Phase A	0.05% Formic acid (v/v) in 95/5 water/acetonitrile		
Mobile Phase B	0.05% Formic acid (v/v) in 5/95 water/acetonitrile		
Flow	1.0 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	1.50	05	95
	1.90	05	95
	2.0	05	95
	2.3	05	95
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 3a and Method 3b

Instrumentation	Shimadzu LCMS-2020 Single Quadrupole Liquid Chromatograph Mass Spectrometer		
Column	Aquity HSS C ₁₈ 1.8µm, 50 × 2.1mm, at 25°C		
Mobile Phase A	0.1% formic acid (v/v) in water		
Mobile Phase B	0.1% formic acid (v/v) in acetonitrile		
Flow	0.5 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.00	95	05
	4.00	05	95
	5.00	05	95
	5.20	95	05
	6.00	95	05
Detectors	UV, 254 nm and 214 nm (Method 3a)		
	UV, 254 nm and 220 nm (Method 3b)		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 4

Instrumentation	Shimadzu LCMS-2020 Single Quadrupole Liquid Chromatograph Mass Spectrometer		
Column	Aquity HSS C ₁₈ 1.8µm, 50 × 2.1mm, at 25°C		
Mobile Phase A	0.1% Formic acid (v/v) in water		
Mobile Phase B	0.1% Formic acid (v/v) in acetonitrile		
Flow	0.5 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.00	95	05
	10.00	05	95
	10.50	05	95
	11.00	95	05
	12.00	95	05
Detectors	UV, 254 nm and 214 nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 5

Instrumentation	Agilent Technologies 1260 Infinity II with DAD detector / Agilent Technologies InfinityLab LC/MSD		
Column	BEH C ₁₈ 1.7µm, 50 × 2.1mm, at 25°C		
Mobile Phase A	0.05% Aqueous ammonia (v/v)		
Mobile Phase B	Acetonitrile		
Flow	0.5 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.00	80	20
	5.00	70	30
	5.60	70	30
	5.90	05	95
	7.10	05	95
	7.50	80	20
	9.00	80	20
Detectors	UV, Diode array 190 – 400 nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 6

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	Acquity UPLC CSH C18 1.7 μ m, 50 $\times$ 2.1mm at 40°C		
Mobile Phase A	0.1% Formic acid in water (v/v)		
Mobile Phase B	0.1% Formic acid in acetonitrile (v/v)		
Flow	1.0mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	97	03
	1.5	01	99
	1.9	01	99
	2.0	97	03
	2.5	97	03
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 7

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	Acquity BEH C18 1.7 μ m, 50 $\times$ 2.1mm at 40°C		
Mobile Phase C	0.03% Aqueous ammonia (v/v)		
Mobile Phase D	0.03% Ammonia in Acetonitrile (v/v)		
Flow	0.8 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	97	03
	1.5	03	97
	1.9	03	97
	2.0	97	03
	2.5	97	03
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 8

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	Acquity BEH C18 1.7 μ m, 50 $\times$ 2.1mm at 40°C		
Mobile Phase C	0.03% Aqueous ammonia (v/v)		
Mobile Phase D	0.03% Ammonia in acetonitrile (v/v)		
Flow	0.8 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	92	08
	1.5	03	97
	1.9	03	97
	2.0	92	08
	2.5	92	08
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 9

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	Acquity BEH C18 1.7 μ m, 50 $\times$ 2.1mm at 40°C		
Mobile Phase C	0.03% Aqueous ammonia (v/v)		
Mobile Phase D	0.03% Ammonia in Acetonitrile (v/v)		
Flow	0.8 mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	97	03
	4	03	97
	4.4	03	97
	4.5	97	03
	5	97	03
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 10

Instrumentation	UPLC + Waters DAD + Waters SQD2, single quadrupole UPLC-MS		
Column	HSS C18 1.8µm 100 x 2.1mm. (Plus guard cartridge), maintained at 40°C		
Mobile Phase A	0.1% Formic acid in water (v/v)		
Mobile Phase B	Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid		
Flow	0.4mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	0.4	95	05
	6.0	05	95
	6.8	05	95
	7.0	95	05
	8.0	95	05
Detectors	UV, diode array 210nm-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 11

Instrumentation	UPLC + Waters DAD + Waters SQD2, single quadrupole UPLC-MS		
Column	BEH Shield RP18 1.7µm 100 x 2.1mm. (Plus guard cartridge), maintained at 40°C		
Mobile Phase A	Aqueous 10mM ammonium hydrogen carbonate		
Mobile Phase B	Acetonitrile		
Flow	0.4mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	0.4	95	05
	6.0	05	95
	6.8	05	95
	7.0	95	05
	8.0	95	05
Detectors	UV, diode array 210nm-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 12

Instrumentation	Acquity i-Class (quaternary pump/PDA detector) + Quattro Micro Mass Spectrometer		
Column	BEH C ₁₈ 1.7µm, 100 × 2.1mm, maintained at 40°C		
Mobile Phase A	0.1% Aqueous formic acid (v/v)		
Mobile Phase B	0.1% Formic acid in acetonitrile (v/v)		
Flow	0.4mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	0.4	95	05
	6.0	05	95
	6.8	05	95
	7.0	95	05
	8.0	95	05
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 13

Instrumentation	Acquity UPLC (binary pump/PDA detector) + ZQ Mass Spectrometer		
Column	BEH C ₁₈ 1.7µm, 100 × 2.1mm, maintained at 40°C		
Mobile Phase A	0.1% Aqueous ammonia (v/v)		
Mobile Phase B	0.1% Ammonia in acetonitrile (v/v)		
Flow	0.4mL/min		
Gradient Program	Time (mins)	% A	%B
	0.0	95	05
	0.4	95	05
	6.0	05	95
	6.8	05	95
	7.0	95	05
	8.0	95	05
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

NMR Methods

NMR spectra were obtained on a Bruker Avance 400 MHz, 5mm QNP probe H, C, F, P, single Z gradient, two channel instrument running TopSpin 2.1, or on a Bruker Avance III 400 MHz, 5mm BBFO Plus probe, single Z gradient, two channel instrument running TopSpin 3.0, or on a Varian Unity Inova 400 spectrometer with a 5 mm inverse detection triple resonance probe operating at 400 MHz. Chemical shift are reported as δ values in ppm relative to tetramethylsilane. Coupling constants (J values) are given in hertz (Hz) and multiplicities are reported using the following abbreviation: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, nd=not determined.

MDAP Methods

Compounds were purified by reverse phase HPLC using a Waters Fractionlynx preparative HPLC system (2525 pump, 2996/2998 UV/VIS detector, 2767 liquid handler) or Gilson preparative HPLC system (322 pump, 155 UV/VIS detector, GX-281 liquid handler) or equivalent system. Collection was triggered by a threshold absorbance value at 260 nm and the presence of target molecular ion as observed under ESI conditions. The fractions that contained the desired product were lyophilized. The specific details of the conditions used, including the column, solvents, gradient and modifier (acidic or basic), are provided for some examples and merely provided for assistance. When specific conditions are not provided, they can be readily optimized by those skilled in the art.

In the procedures that follow, some of the starting materials are identified through an "Intermediate" or "Example" number with indications on step name. When reference is made to the use of a "similar" or "analogous" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variations, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

All solvents and commercial reagents were used as received. Where the preparation of starting materials is not described, these are commercially available, known in the literature, or readily obtainable by those skilled in the art using standard procedures.

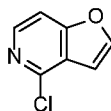
Abbreviations

ACN (acetonitrile), BINAP (2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene), COMU ((1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-

carbenium hexafluorophosphate), dba (Dibenzylideneacetone), DCM (dichloromethane), DIPEA or DIEA (*N*-Ethyl-diisopropylamine), DMF (*N,N*-Dimethylformamide), DMSO (Dimethylsulfoxide), dppf (1,1'-Ferrocenediyl-bis(diphenylphosphine)), EtOH (ethanol), EtOAc (ethyl acetate), FA (Formic acid), HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl]methylene]-N-methylmethanaminium hexafluorophosphate N-oxide), HPLC (High performance liquid chromatography), LCMS (Liquid chromatography – mass spectrometry), MDAP (Mass-directed auto-purification), MeOH (methanol), Me-THF (2-Methyltetrahydrofuran), MTBE (methyl tert-butyl ether), NMP (N-methylpyrrolidone), NMR (Nuclear magnetic resonance), Rt (Retention time), RT (Room temperature), SCX (Strong cation exchange), STAB (Sodium triacetoxyborohydride), TBTU (2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate), TEA (Triethylamine), TFA (Trifluoroacetic acid), THF (Tetrahydrofuran).

Intermediate 1

Step a

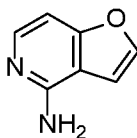


4-Chlorofuro[3,2-c]pyridine (Intermediate 1a)

A mixture of furo[3,2-c]pyridin-4-ol (70.4 g, 0.52 mol) in phosphoryl trichloride (430 mL) was heated at reflux for 1 h. Phosphoryl trichloride was distilled off, the residue poured into ice/water and neutralized to pH~6 with aqueous saturated NaHCO₃. The aqueous phase was extracted twice with DCM, then the organic layer was washed with saturated aqueous NaCl and evaporated to dryness. The crude material was purified by column chromatography on silica gel eluting with EtOAc-hexane to give the title compound (72.8 g).

LCMS (Method 3): Rt = 2.71 min, m/z 153.9 [M+H]⁺

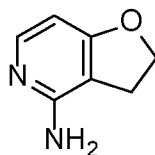
Step b



Furo[3,2-c]pyridin-4-amine (Intermediate 1b)

A solution of Intermediate 1a (72.8 g, 0.47 mol) in dry toluene (730 mL) was purged with argon over 20 min, then racemic BINAP (17.72 g, 0.028 mol), tris(dibenzylideneacetone)dipalladium(0) (8.69 g, 0.0095 mol) and potassium tert-butoxide (74.50 g, 0.66 mol) were added. After addition of benzophenone imine (95.5 mL, 0.57 mol), the mixture was heated at 90°C for 1.5 h. The reaction mixture was cooled to RT, diluted with THF and filtered through a pad of diatomaceous earth followed by washing with THF and diethyl ether. The combined filtrate was evaporated, and the residue taken into MeOH (260 mL) and added dropwise to a solution of hydroxylamine hydrochloride (98.87 g, 1.42 mol) in MeOH (1200 mL) which had previously been neutralized in an ice bath with NaOH (56.91 g, 1.42 mol). The reaction mixture was stirred at RT for 1 h and evaporated to dryness. The crude material was purified by chromatography on silica by eluting with 10-100% EtOAc in hexane to give a solid that was further purified by trituration and filtration in a mixture of MTBE and DCM. A second purification by chromatography on silica by eluting with 0-10% MeOH in DCM afforded the pure title compound (45.1 g).

LCMS (Method 3): Rt = 0.83 min, m/z 135.0 [M+H]⁺

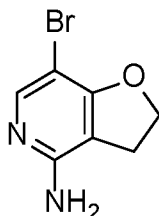
Step c**2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate 1c)**

Intermediate 1b (44.1 g, 0.33 mol) was dissolved in MeOH (530 mL) and acetic acid (56.4 mL), then 10% Pd/C (50% wet, 17.74 g) was added and the reaction mixture purged with argon before being hydrogenated at a pressure of 10 bar of H₂ at 50°C under vigorous stirring. After 20 h a further half equivalent of 10% Pd/C (50% wet) and further 3 h of hydrogenation were needed in order to achieve full conversion. The reaction mixture was filtered and washed with MeOH. The combined filtrate was evaporated, and the residue partitioned between EtOAc (500 mL) and water (500 mL). The aqueous layer was washed with further EtOAc (300 mL), neutralized with solid NaHCO₃ and saturated with NaCl. This aqueous mixture was extracted with DCM (8 x 300 mL) and the

combined organic layers washed with saturated aqueous NaCl (800 mL), dried over Na₂SO₄ and evaporated to afford the title compound (24.57 g).

LCMS (Method 4): Rt = 0.81 min, m/z 137.1 [M+H]⁺

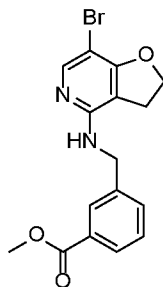
Step d



7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate 1d)

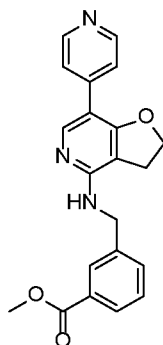
Intermediate 1c (24.57 g, 0.180 mol) was dissolved in MeCN (1230 mL) and then a solution of N-bromosuccinimide (35.33 g, 0.198 mol) in MeCN (490 mL) was added dropwise over 3 h at -10°C in darkness. The reaction was quenched with aqueous saturated NaHCO₃ (500 mL), water (500 mL), EtOAc (1000 mL) and aqueous 5% NaCl (500 mL). The resulting organic and aqueous phases were separated, and the aqueous layer further washed with EtOAc (1000 mL). The combined organic layers were washed with aqueous 5% NaCl (7 x 2000 mL) and concentrated to dryness. The residual solid was treated with a mixture of EtOAc (500 mL) and water (200 mL), placed in a sonic bath for some minutes and acidified with aqueous 10% KHSO₄ (300 mL). The solid that appeared was collected by filtration. The biphasic filtrate was partitioned, and the organic layer washed twice with aqueous 10% KHSO₄ (200 mL each). The combined aqueous layer was washed with EtOAc (3 x 500 mL) and mixed with the previous collected solid. The resulting aqueous mixture was neutralized to pH7 with NaHCO₃ and extracted with EtOAc (3 x 1000 mL). The combined organic phase was washed with saturated aqueous NaCl (500 mL), dried over anhydrous MgSO₄, and concentrated to give the title compound as a solid (27.1 g).

LCMS (Method 5): Rt = 1.69 min, m/z 215.0/217.0 [M+H]⁺

Step e**Methyl 3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoate (Intermediate 1e)**

- 5 Intermediate 1d (15.6 g, 0.074 mol) and methyl 3-formylbenzoate (18.1 g, 0.11 mol) were dissolved in anhydrous DCM (470 mL) with molecular sieves and kept under inert atmosphere. After 10 min, chloro(triisopropoxy)titanium(IV) (35.4 mL, 0.148 mol) was added dropwise and the resulting mixture stirred at RT over 2.5 h. Sodium triacetoxyborohydride (31.4 g, 0.148 mol) followed by acetic acid (8.5 mL, 0.148 mol)
- 10 were added and the mixture stirred at RT overnight. The reaction mixture was quenched with methanol and solvents were evaporated. The residue was dissolved in EtOAc and aqueous saturated NaHCO₃ solution. After being stirred for 15 min, the mixture was filtered through a thin pad of diatomaceous earth and washed with EtOAc. The combined filtrate was collected, and organic-aqueous phases were separated. The organic layer was
- 15 dried over Na₂SO₄ and evaporated. The crude material was purified by chromatography on silica by eluting with 20% - 40% EtOAc in hexane to give the title compound (19.3 g).

LCMS (Method 2): Rt = 0.85 min, m/z 362.9/364.9 [M+H]⁺

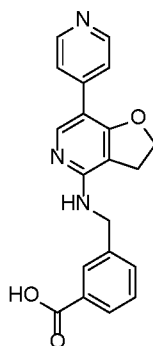
Step f

Methyl 3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)-methyl)benzoate (Intermediate 1f)

A solution of K_3PO_4 (19.6 g, 0.092 mol) in water (48 mL) was added to a solution of Intermediate 1e (11.97g, 0.033mol) and pyridin-4-ylboronic acid (8.9 g, 0.073 mol) in dioxane (204 mL). The resulting mixture was degassed with a stream of argon, then $Pd_2(dba)_3$ (3.0 g, 0.0033 mol) and tricyclohexylphosphine (2.3 g, 0.0083 mol) were added and the mixture stirred at 120°C overnight. The reaction mixture was concentrated and the residue taken into water and EtOAc. The layers were separated, and the aqueous phase was further extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica by eluting with 50%-100% EtOAc in hexane to give the title compound (6.4 g).

LCMS (Method 2): $R_t = 0.45$ min, m/z 362.0 $[M+H]^+$

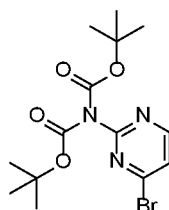
Step g



3-(((7-(Pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-benzoic acid (Intermediate 1)

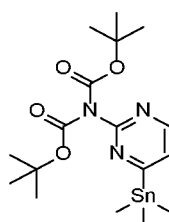
To a solution of Intermediate 1f (2.0 g, 5.5 mmol) in THF (34 mL) and methanol (34 mL), an aqueous solution of lithium hydroxide (1.15 g of $LiOH \cdot H_2O$ in 34 mL of water) was added and resulting mixture was stirred at RT over 5 h. The organic solvents were evaporated, and the residual aqueous solution neutralized with concentrated hydrochloric acid. After appearance of a precipitate, the mixture was sonicated for few minutes, then a small amount of NaCl was added and the mixture stirred for 10 min at RT. The resulting solid was collected by filtration, washed with water and dried to give the title compound (1.92 g).

LCMS (Method 2): $R_t = 0.35$ min, m/z 347.9 $[M+H]^+$

Intermediate 2**Step a****tert-Butyl (4-bromopyrimidin-2-yl)(tert-butoxycarbonyl)carbamate****(Intermediate 2a)**

A solution of 4-bromopyrimidin-2-amine (0.5 g, 2.87 mmol), di-tert-butyl dicarbonate (0.63 g, 2.87 mmol), potassium carbonate (0.79 g, 5.75 mmol) and a catalytic amount of DMAP in dioxane (4 mL) was stirred at ambient temperature for 18 h. Di-tert-butyl dicarbonate (0.94 g, 4.3 mmol) and potassium carbonate (1.58 g, 11.5 mmol) were added and the reaction mixture was stirred at 40°C for 4 h. The reaction mixture, diluted with EtOAc, was washed with saturated aqueous NaCl, the organic layer was dried with sodium sulphate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel by eluting with 0-40% EtOAc in cyclohexane, the relevant fractions were combined and concentrated to give the title product (416 mg).

LCMS (Method 12): $R_t = 3.69$ min, m/z 396.0/398.0 $[M+Na]^+$

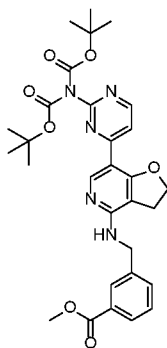
Step b**tert-Butyl (tert-butoxycarbonyl)(4-(trimethylstannyl)pyrimidin-2-yl)carbamate (Intermediate 2b)**

A degassed mixture of Intermediate 2a (310 mg, 0.828 mmol), hexamethylditin (0.19 mL, 0.911 mmol) and tetrakis(triphenylphosphine)palladium(0) (48 mg, 0.042 mmol) in THF (4 mL) was stirred at 80 °C for 6 h. The reaction mixture, diluted with EtOAc, was washed with saturated aqueous NaCl, the organic layer was dried with sodium sulphate and concentrated *in vacuo*. The solution was concentrated *in vacuo* and

the residue was purified by flash chromatography on silica gel by eluting with 0-50% EtOAc in cyclohexane, the relevant fractions were combined and concentrated to give the desired product (240 mg).

LCMS (Method 9): Rt = 3.30 min, m/z 458.3/460.3 [M+H]⁺

5 **Step c**

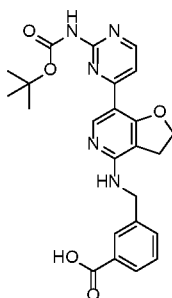


Methyl 3-(((7-(2-(bis(tert-butoxycarbonyl)amino)pyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoate (Intermediate 2c)

A degassed mixture of Intermediate 1e (1 g, 2.75 mmol), Intermediate 2b (1.39 g, 3.03 mmol), tetrakis(triphenylphosphine)palladium(0) (160 mg, 0.138 mmol) and copper(I) thiophene-2-carboxylate (53 mg, 0.275 mmol) in dioxane (15 mL) was heated at 130 °C under microwave irradiation for 1.5 h. The reaction mixture, diluted with ethyl acetate, was filtered through a pad of diatomaceous earth. The solution was concentrated *in vacuo* and the residue was purified by chromatography on a silica gel cartridge eluting with 0-100% ethyl acetate in cyclohexane to give the title product (929 mg)

LCMS (Method 9): Rt = 3.21 min, m/z 578.5 [M+H]⁺

Step d

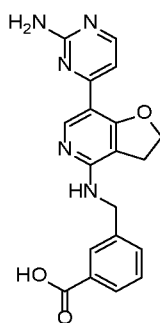


20 **3-(((7-(2-(bis(tert-butoxycarbonyl)amino)pyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (Intermediate 2d)**

A mixture of Intermediate 2c (929 mg, 1.62 mmol), lithium hydroxide monohydrate (0.075 g, 1.78 mmol) in THF (3 mL), methanol (3 mL) and water (6 mL) was stirred at ambient temperature for 18 h. Further lithium hydroxide monohydrate (0.15 g, 3.56 mmol) was added and the reaction mixture was stirred for a further 5 h. The resulting mixture was diluted with water and extracted with ethyl acetate. The pH of the aqueous phase was adjusted to pH ~6-7 with aqueous 1M HCl. The organic layer was dried with Na₂SO₄ and evaporated *in vacuo* to give the title product (750 mg).

LCMS (Method 9): Rt = 1.49 min, m/z 464.3 [M+H]⁺

Step e



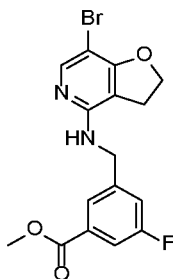
3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (Intermediate 2)

A mixture of Intermediate 2d (2 g, 4.32 mmol) in TFA (10 mL) and dichloromethane (40 mL) was stirred at ambient temperature for 2 h. The reaction mixture, diluted with MeOH, was purified by an SCX-2 cartridge by eluting with MeOH and then 2M methanolic ammonia. The ammonia solution was concentrated *in vacuo* to give the title product (1.5 g)

LCMS (Method 10): Rt = 2.15 min, m/z 364.0 [M+H]⁺

Intermediate 3

Step a

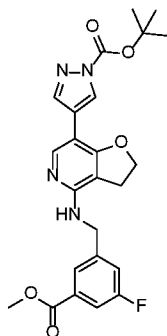


Methyl 3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzoate (Intermediate 3a)

Intermediate 3a was prepared similarly to Intermediate 1e from Intermediate 1d and methyl 3-fluoro-5-formyl-benzoate

5 LCMS (Method 6): Rt = 1.3 min, m/z 380.9/382.9 [M+H]⁺

Step b



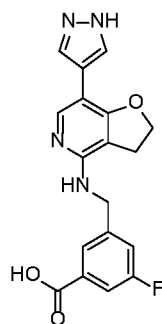
tert-Butyl 4-(4-(((3-fluoro-5-(methoxycarbonyl)benzyl)amino)-2,3-dihydrofuro-[3,2-c]pyridin-7-yl)-1H-pyrazole-1-carboxylate (Intermediate 3b)

10 A mixture of Intermediate 3a (220 mg, 0.577 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (187 mg, 0.635 mmol) and cesium carbonate (282 mg, 0.866 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was degassed and refilled with argon. To this was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM, (48 mg, 0.0577

15 mmol) and the reaction mixture was heated and stirred at 80°C for 2 h. The reaction mixture was cooled, filtered through a pad of diatomaceous earth and extracted with water. The organic layer was dried and evaporated to give the title compound (220 mg).

LCMS (Method 7): Rt = 1.62 min, m/z 469.3 [M+H]⁺

Step c



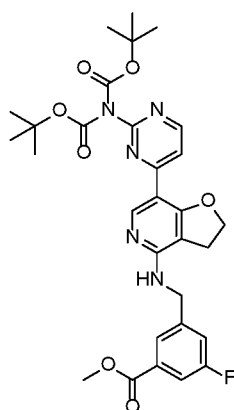
3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzoic acid (Intermediate 3)

To a solution of Intermediate 3b (220 mg, 0.470 mmol) in methanol (5 mL) was added a solution of lithium hydroxide (34 mg, 1.41 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated and neutralized with dilute aqueous HCl. The obtained precipitate was filtered, washed with water and dried to get the title compound (165 mg).

LCMS (Method 7): Rt = 0.8 min, m/z 355.3 [M+H]⁺

Intermediate 4

Step a

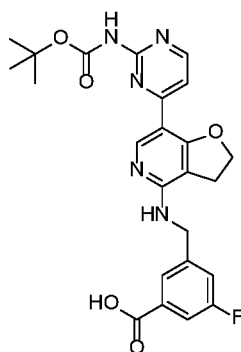


Methyl 3-(((7-(2-(bis(tert-butoxycarbonyl)amino)pyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzoate (Intermediate 4a)

Intermediate 4a was prepared from Intermediates 3a and intermediate 2b using a procedure analogous to that used in the preparation of Intermediate 2c.

LCMS (Method 7): Rt = 1.72 min, m/z 596.1 [M+H]⁺

Step b

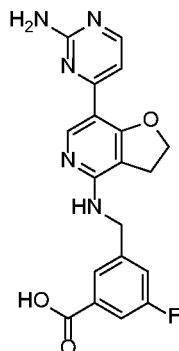


3-(((7-(2-((tert-Butoxycarbonyl)amino)pyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzoic acid (Intermediate 4b)

Intermediate 4b was prepared from Intermediate 4a using a procedure analogous to that used in the preparation of Intermediate 2d.

5 LCMS (Method 7): Rt = 0.94 min, m/z 482.4 [M+H]⁺

Step c



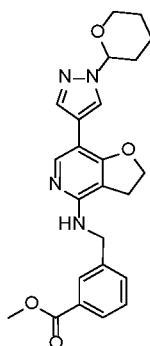
3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzoic acid (Intermediate 4)

10 Intermediate 4 was prepared from Intermediate 4b using a procedure analogous to that used in the preparation of Intermediate 2.

LCMS (Method 2): Rt = 0.82 min, m/z 382.3 [M+H]⁺

Intermediate 5

Step a



15

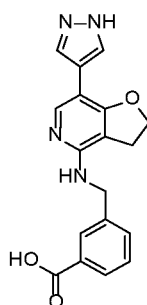
Methyl 3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoate (Intermediate 5a)

Intermediate 1e (0.9 g, 2,478 μmol), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.378 g, 4.96 μmol) and potassium

phosphate tribasic (1.578 g, 7.43 mmol) were dissolved in a mixture of THF (10 mL) and water (10 mL). The mixture was purged with argon for 10 min, then chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-iphenyl)]palladium(II) (0.292 g, 0.372 mmol) was added and the reaction stirred at RT for 6 h. The mixture was diluted with water (30 mL) and extracted with THF (3 x 25 mL). The organic phase was dried over Na₂SO₄ and concentrated to dryness. The crude was purified by flash chromatography on silica by eluting with 0-10% MeOH in DCM to afford the desired product (1.08 g).

LCMS (Method 2): Rt = 0.69 min, m/z 435.3 [M+H]⁺

Step b



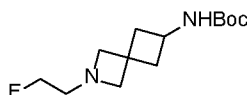
3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (Intermediate 5)

Intermediate 5a (1.26 g, 2.90 mmol) was suspended in aqueous 6M HCl (35 mL, 0.435 mmol). The mixture was heated at 90 °C for 30 min and then evaporated to dryness to afford the title compound (1.26 g) that was used in the next steps without further purifications.

LCMS (Method 2): Rt = 0.46 min, m/z 337.2 [M+H]⁺

Intermediate 6

Step a

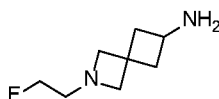


tert-Butyl (2-(2-fluoroethyl)-2-azaspiro[3.3]heptan-6-yl)carbamate (Intermediate 6a)

To a suspension of tert-butyl *N*-(2-azaspiro[3.3]heptan-6-yl)carbamate chloride (125 mg, 0.503 mmol) in dry DMF (mL) was added potassium carbonate (208 mg, 1.51 mmol). After sonication for 1 minute, 1-fluoro-2-iodo-ethane (0.088 mL, 1.01 mmol) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated, and the residue partitioned between water and EtOAc. The organic layer separated, dried over magnesium sulphate and the volatiles evaporated to give an oil which was purified by flash chromatography on silica eluting (with DCM to 2M NH₃ in MeOH from 0 to 5%) to give the title compound (42 mg).

¹H NMR (CDCl₃) δ 4.60 (br s, 1H), 4.42 (td, J=4.9, 47.6 Hz, 2H), 3.98 (br s, 1H), 3.31 (s, 2H), 3.21 (s, 2H), 2.69 (td, J=5.0, 27.3 Hz, 2H), 2.58 - 2.50 (m, 2H), 1.97 - 1.90 (m, 2H), 1.42 (s, 9H).

Step b



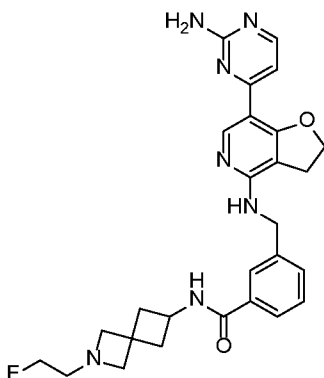
2-(2-Fluoroethyl)-2-azaspiro[3.3]heptan-6-amine; trifluoroacetic acid salt

(Intermediate 6)

To a solution of Intermediate 6a (42 mg, 0.163 mmol) in dry DCM (5 mL) was added trifluoroacetic acid (0.19 mL, 2.44 mmol). The reaction mixture was stirred at RT for 2h and then concentrated to give the title compound which was used in the next step without further purifications.

¹H NMR (d₆-DMSO) δ 8.0 (s, 3H), 5.1-4.3 (m, 4H), 4.27 - 4.12 (m, 4H), 3.63 - 3.56 (m, 2H), 2.67 - 2.60 (m, 1H), 2.38 - 2.25 (m, 2H).

Example 1



3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-fluoroethyl)-2-azaspiro[3.3]heptan-6-yl)benzamide

(Example 1)

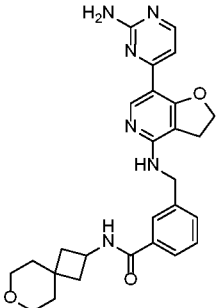
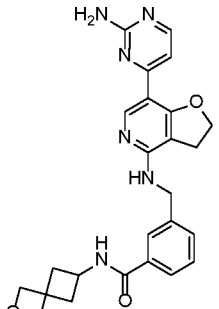
To a suspension of Intermediate 2 (59 mg, 0.163 mmol) and Intermediate 6 (44
5 mg, 0.163 mmol) in DMF (3 mL) was added DIPEA (0.085 mL, 0.488 mmol) and then
TBTU (57 mg, 0.179 mmol). The reaction mixture was stirred at room temperature for
18 h. The reaction mixture was concentrated and the residue purified by MDAP (Xbridge
Phenyl 3x50mm, 3um 5-95% MeOH / H₂O (10mM NH₄CO₃), 1.7ml/min, RT) then
further purified by reverse phase chromatography on C18 cartridge eluting with
10 water/acetonitrile (+ 0.1% NH₄OH) 10-95%). The relevant fractions were dried to give
the title compound (20 mg).

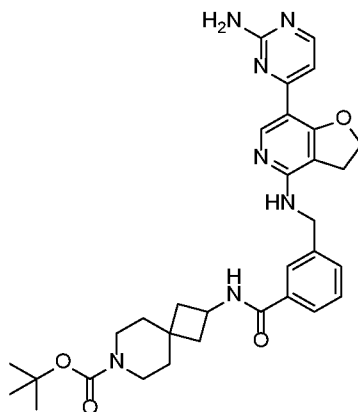
LCMS (Method 13): Rt = 3.36 min, m/z 504.2 [M+H]⁺

¹H NMR (d₆-DMSO) δ 8.66 (s, 1H), 8.53 (d, J=7.4 Hz, 1H), 8.15 (d, J=5.2 Hz, 1H),
7.81 (s, 1H), 7.66 (d, J=7.7 Hz, 1H), 7.46 (d, J=7.7 Hz, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.15
15 (t, J=6.0 Hz, 1H), 7.05 (d, J=5.4 Hz, 1H), 6.40 (s, 2H), 4.73 (t, J=9.8 Hz, 2H), 4.67 (d,
J=5.4 Hz, 2H), 4.41 (t, J=4.9 Hz, 1H), 4.31 - 4.21 (m, 2H), 3.23 (s, 2H), 3.11 (s, 2H), 3.03
(t, J=8.5 Hz, 2H), 2.64 (t, J=4.0 Hz, 1H), 2.59 - 2.54 (m, 1H), 2.43 - 2.35 (m, 2H), 2.19 -
2.12 (m, 2H).

Examples 2 to 3

20 The following examples were prepared in a similar manner of Example 1 by using
the intermediate and amine indicated in the table

Example	Structure	Starting materials	¹ H NMR	LCMS
2	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-oxaspiro[3.5]nonan-2-yl)benzamide	Intermediate 2 and 7-oxaspiro[3.5]nonan-2-amine	(400 MHz, d ₆ -DMSO) δ 8.75 (s, 1H), 8.65 (d, J=7.5 Hz, 1H), 8.24 (d, J=5.3 Hz, 1H), 7.91 (s, 1H), 7.78 (d, J=7.7 Hz, 1H), 7.58 - 7.54 (m, 1H), 7.46 (t, J=7.7 Hz, 1H), 7.25 (t, J=6.0 Hz, 1H), 7.14 (d, J=5.3 Hz, 1H), 6.50 (s, 2H), 4.82 (t, J=8.9 Hz, 2H), 4.76 (d, J=6.0 Hz, 2H), 4.49 (dd, J=8.2, 16.1 Hz, 1H), 3.62 (t, J=5.2 Hz, 2H), 3.54 (t, J=5.3 Hz, 2H), 3.12 (t, J=8.9 Hz, 2H), 2.34 - 2.27 (m, 2H), 1.97 - 1.90 (m, 2H), 1.67 (t, J=5.2 Hz, 2H), 1.60 (t, J=5.2 Hz, 2H).	R _t = 2.52 min, m/z 487.0 [M+H] ⁺ (Method 10)
3	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-oxaspiro[3.3]heptan-6-yl)benzamide	Intermediate 2 and 2-oxaspiro[3.3]heptan-6-amine	(400 MHz, d ₆ -DMSO) δ 8.67 (s, 1H), 8.56 (d, J=7.1 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.82 (dd, J=1.5, 1.5 Hz, 1H), 7.67 (ddd, J=1.4, 1.4, 7.6 Hz, 1H), 7.48 (ddd, J=1.5, 1.5, 7.6 Hz, 1H), 7.38 (dd, J=7.7, 7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.43 (s, 2H), 4.75 (t, J=9.1 Hz, 2H), 4.68 (d, J=6.1 Hz, 2H), 4.64 (s, 2H), 4.52 (s, 2H), 4.28 - 4.16 (m, 1H), 3.05 (t, J=8.8 Hz, 2H), 2.61 - 2.54 (m, 2H), 2.29 - 2.22 (m, 2H).	R _t = 2.24 min, m/z 459.0 [M+H] ⁺ (Method 10)

Intermediate 7a

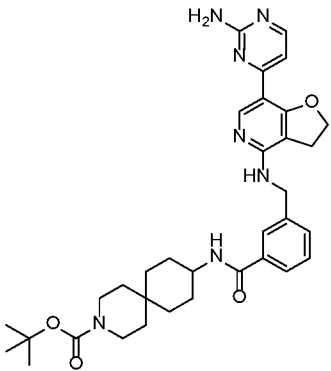
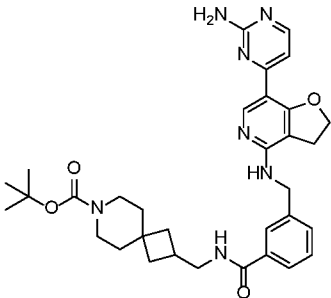
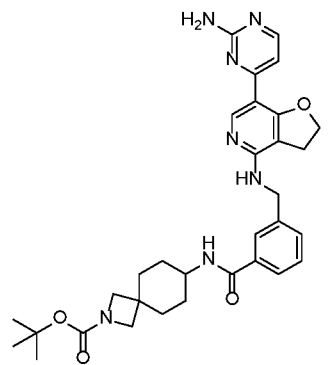
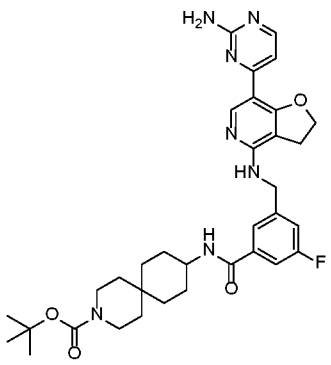
tert-Butyl 2-(3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamido)-7-azaspiro[3.5]nonane-7-carboxylate (Intermediate 7a)

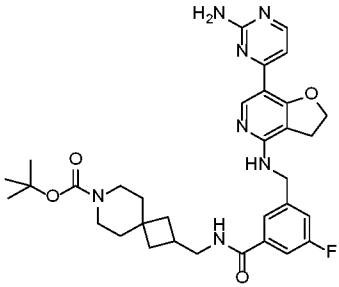
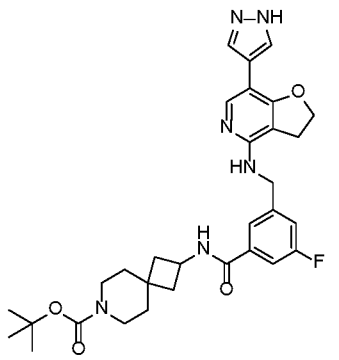
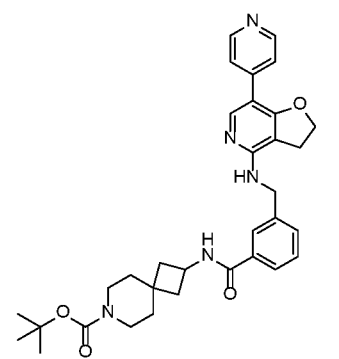
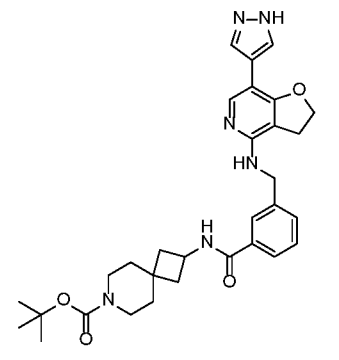
A mixture of Intermediate 2 (200 mg, 0.500 mmol), tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (132 mg, 0.550 mmol) and HATU (190 mg, 0.500 mmol) in DMF (3 mL) was stirred at RT and DIPEA (0.26 mL, 1.50 mmol) was added. The reaction mixture was stirred at RT for 1 h and then applied to a 5 g SCX-2 cartridge, which was subsequently washed with methanol and eluted using 2N ammonia in methanol. The ammonia fraction was evaporated to give the desired product (249 mg).

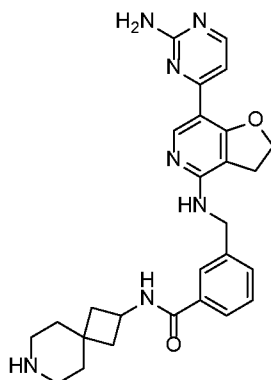
LCMS (Method 6): $R_t = 1.06$ min, m/z 586.3 $[M+H]^+$

Preparation of intermediate 7b to 7j

The following intermediates were prepared in a similar manner to Intermediate 7a from the acid and amine indicated. In some cases, TBTU was replaced with HATU, otherwise the conditions were the same.

Intermediate	Structure	Starting materials and coupling agent	LCMS
7b		Intermediate 2, tert-butyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate, TBTU	Rt = 1.46 min, m/z 614.5 [M+H] ⁺ (Method 7)
7c		Intermediate 2, tert-butyl 2-(aminomethyl)-7-azaspiro[3.5]nonane-7-carboxylate, HATU or TBTU	Rt = 1.50 min, m/z 600.0 [M+H] ⁺ (Method 7)
7d		Intermediate 2, tert-butyl 7-amino-2-azaspiro[3.5]nonane-2-carboxylate, HATU	Rt = 1.03 min, m/z 586.2 [M+H] ⁺ (Method 6)
7e		Intermediate 4, tert-butyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate, TBTU	Rt = 1.50 min, m/z 632.5 [M+H] ⁺ (Method 8)

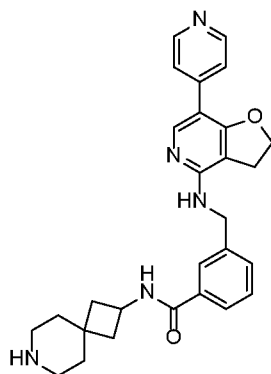
7f		Intermediate 4, tert-butyl 2-(aminomethyl)-7-azaspiro[3.5]nonane-7-carboxylate, TBTU	Rt = 1.46 min, m/z 618.5 [M+H] ⁺ (Method 8)
7g		Intermediate 3, tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate, TBTU	Rt = 1.46 min, m/z 577.5 [M+H] ⁺ (Method 7)
7i		Intermediate 1, tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate, TBTU	Rt = 1.50 min, m/z 570.6 [M+H] ⁺ (Method 7)
7j		Intermediate 5, tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate, TBTU	Rt = 1.06 min, m/z 559.3 [M+H] ⁺ (Method 1)

Example 4**3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide (Example 4)**

5 To a solution of Intermediate 7a (246 mg, 0.420 mmol) in DCM (3 mL) was added TFA (1.3 mL, 16.8 mmol) and the reaction mixture was left to stand overnight. The solution was diluted with methanol then applied to a 5 g SCX-2 cartridge, which was washed with methanol then eluted using 2N ammonia in methanol. The ammonia fraction was evaporated and the residue submitted to MDAP purification (Xbridge Phenyl
10 19x150mm, 10um 20-80% MeOH / H₂O (10mM NH₄CO₃), 20mL/min, RT) to give the pure title compound.

LCMS (Method 10): Rt = 1.91 min, m/z 486.4 [M+H]⁺

¹H NMR (d₆-DMSO) δ 8.68 (s, 1H), 8.55 (d, J=7.5 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.71 - 7.68 (m, 1H), 7.50 - 7.46 (m, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.78 - 4.66 (m, 4H), 4.42 - 4.35 (m, 1H), 3.04 (t, J=8.8 Hz, 2H), 2.67 - 2.62 (m, 2H), 2.59 - 2.54 (m, 2H), 2.19 - 2.12 (m, 2H), 1.83 - 1.76 (m, 2H), 1.53 - 1.42 (m, 4H).

Example 5

3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide (Example 5)

The example 5 was prepared in a similar way of example 4 by replacing intermediate 7a with intermediate 7i.

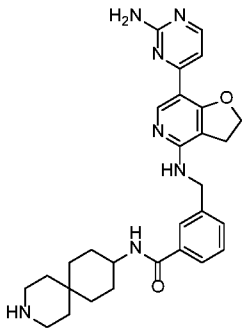
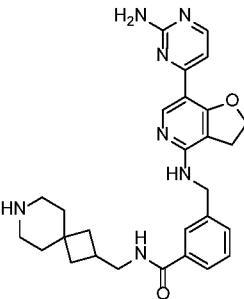
5 LCMS (Method 13): Rt = 3.06 min, m/z 470.3 [M+H]⁺

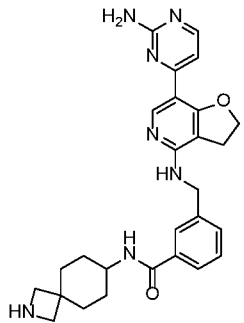
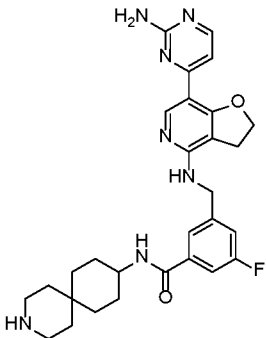
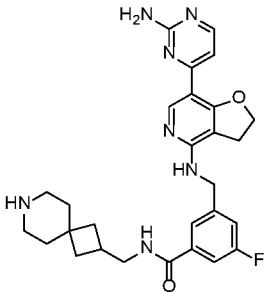
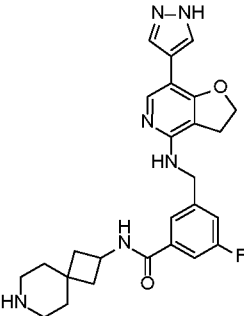
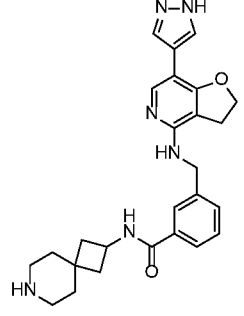
¹H NMR (d6-DMSO) δ 8.53 (d, J=7.5 Hz, 1H), 8.49 (dd, J=1.7, 4.5 Hz, 2H), 8.21 (b s, 1H), 7.81 (b s, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.65 (dd, J=1.87, 4.5 Hz, 2H), 7.46 (d, J=7.9 Hz, 1H), 7.37 (t, J=7.7 Hz, 1H), 7.12 (t, J=6.2 Hz, 1H), 4.73 (t, J=9.1 Hz, 2H), 4.67 (d, J=5.9 Hz, 2H), 4.37 (sext, J=8.4 Hz, 1H), 3.06 (t, J=8.7 Hz, 2H), 2.62 (t, J=5.17 Hz, 2H), 2.45-2.55 (m, 2H), 2.14 (t, J=9.9 Hz, 2H), 1.77 (t, J=9.9 Hz, 2H), 1.48 (t, J=5.21 Hz, 2H), 1.42 (t, J=5.4 Hz, 2H).

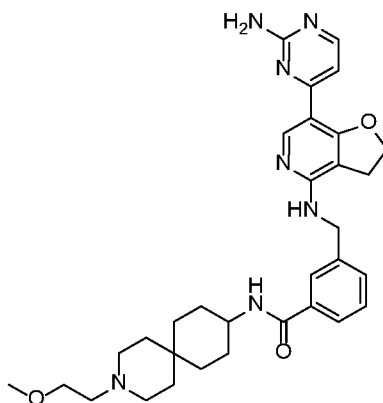
10

Intermediates 8a to 8h

The following intermediates were prepared similarly to Example 4 starting with the intermediate given.

Intermediate	Structure	Starting intermediate	LCMS
8a		7b	Rt = 1.25 min, m/z 514.5 [M+H] ⁺ (Method 7)
8b		7c	Rt = 1.27 min, m/z 500.0 [M+H] ⁺ (Method 7)

8c		7d	Rt = 0.73 min, m/z 486.1 [M+H] ⁺ (Method 6)
8d		7e	Rt = 1.32 min, m/z 532.5 [M+H] ⁺ (Method 8)
8e		7f	Rt = 1.28 min, m/z 518.4 [M+H] ⁺ (Method 8)
8f		7g	Rt = 1.27 min, m/z 477.5 [M+H] ⁺ (Method 7)
8h		7j	Rt = 0.63 min, m/z 459.3 [M+H] ⁺ (Method 1)

Example 6**3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide****(Example 6)**

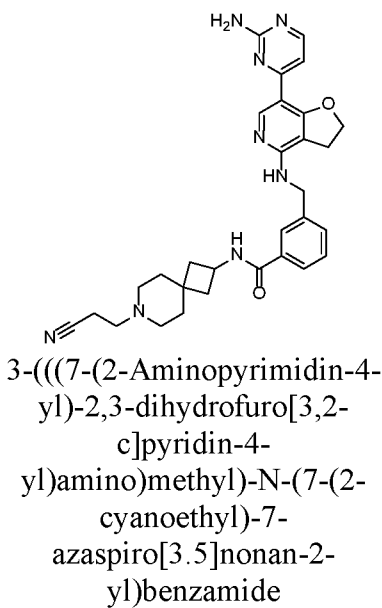
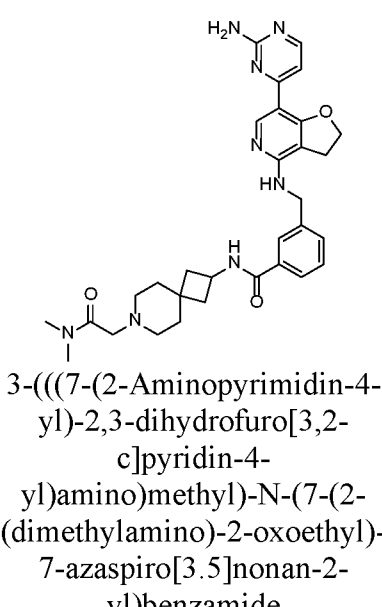
Intermediate 8a (140 mg, 0.273 mmol), 2-bromoethyl methyl ether (0.051 mL, 0.545 mmol) and potassium carbonate (75 mg, 0.545 mmol) were dissolved in DMF (3 mL) and stirred at RT for 20 h. Then the reaction mixture was diluted with methanol and loaded onto an Isolute® SCX-2 cartridge, washed with methanol and eluted with 2 N methanolic ammonia solution. Evaporation gave a residue that was purified by MDAP (Xbridge Phenyl 19x150mm, 10µm 40-100% MeOH / H₂O (10mM NH₄CO₃), 20mL/min, RT) to give the desired product (14.1 mg).

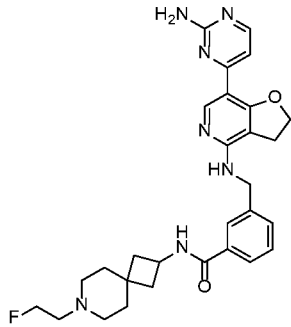
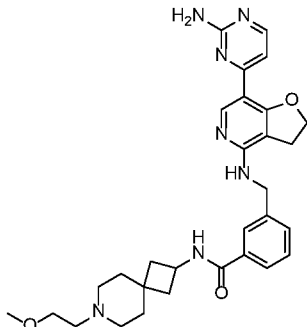
LCMS (Method 10) : Rt = 2.14 min, m/z 572.3 [M+H]⁺

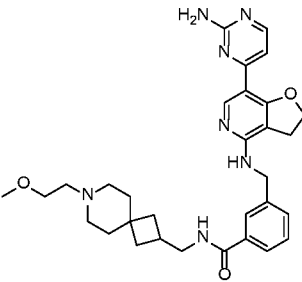
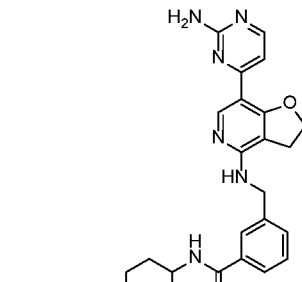
¹H NMR (400 MHz, DMSO-d₆) δ 8.67 (s, 1H), 8.17 - 8.14 (m, 2H), 7.83 (s, 1H), 7.69 (d, J=7.7 Hz, 1H), 7.48 (d, J=9.7 Hz, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.43 (s, 2H), 4.75 (t, J=8.4 Hz, 2H), 4.69 (d, J=6.6 Hz, 2H), 3.79 - 3.69 (m, 1H), 3.42 (t, J=6.0 Hz, 2H), 3.23 (s, 3H), 3.04 (t, J=9.0 Hz, 2H), 2.45 (t, J=6.0 Hz, 2H), 2.37 - 2.33 (m, 4H), 1.71 - 1.44 (m, 8H), 1.32 (t, J=5.3 Hz, 2H), 1.18 - 1.10 (m, 2H).

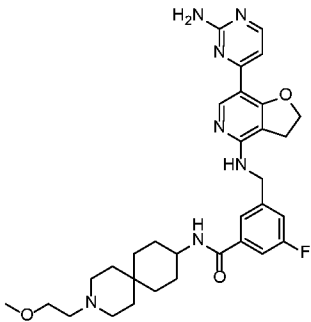
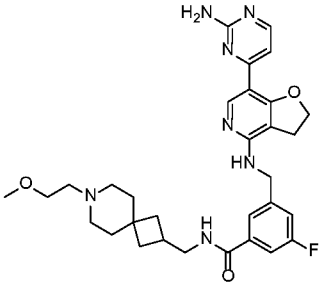
Examples 7 to 14

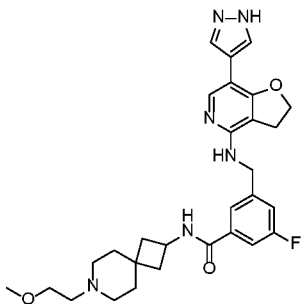
The following examples were prepared from the compounds given in the table using a similar method to Example 6.

Ex.	Structure	Starting materials	¹ H NMR	LCMS
7	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-cyanoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and 3-bromopropionitrile	(400 MHz, d6-DMSO) δ 8.68 (s, 1H), 8.55 (d, J=7.5 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=8.5 Hz, 2H), 4.69 (d, J=4.9 Hz, 2H), 4.43 - 4.36 (m, 1H), 3.04 (t, J=8.9 Hz, 2H), 2.66 (t, J=6.7 Hz, 2H), 2.54 - 2.52 (m, 2H), 2.38 (s, 2H), 2.29 (s, 2H), 2.19 - 2.13 (m, 2H), 1.85 - 1.78 (m, 2H), 1.62 - 1.51 (m, 4H).	Rt = 1.93 min, m/z 539 [M+H] ⁺ (Method 10)
8	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-(dimethylamino)-2-oxoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and 2-bromo-N,N-dimethylacetamide	(400 MHz, d6-DMSO) δ 8.66 (s, 1H), 8.53 (d, J=7.5 Hz, 1H), 8.15 (d, J=5.2 Hz, 1H), 7.82 (s, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.47 (d, J=7.5 Hz, 1H), 7.37 (t, J=7.7 Hz, 1H), 7.15 (t, J=6.0 Hz, 1H), 7.05 (d, J=5.3 Hz, 1H), 6.40 (s, 2H), 4.73 (t, J=7.8 Hz, 2H), 4.68 (d, J=4.9 Hz, 2H), 4.41 - 4.34 (m, 1H), 3.06 - 3.00 (m, 7H), 2.79 (s, 3H), 2.36 (br s, 2H), 2.27 (br s, 2H), 2.17 - 2.09 (m, 2H), 1.83 - 1.76 (m, 2H), 1.59 - 1.49 (m, 4H).	Rt = 1.92 min, m/z 571 [M+H] ⁺ (Method 12)

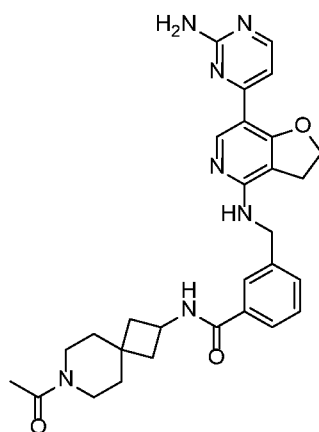
9	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-fluoroethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and 1-fluoro-2-iodoethane	(400 MHz, d6-DMSO) δ 8.68 (s, 1H), 8.55 (d, J=7.4 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.84 (s, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.48 (d, J=7.4 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.17 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.1 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=9.0 Hz, 2H), 4.69 (d, J=6.5 Hz, 2H), 4.51 (td, J=4.9, 47.7 Hz, 2H), 4.39 (q, J=8.1 Hz, 1H), 3.04 (t, J=8.9 Hz, 2H), 2.61 - 2.59 (m, 1H), 2.40 - 2.32 (m, 4H), 2.19 - 2.11 (m, 2H), 1.81 (dd, J=8.7, 11.8 Hz, 2H), 1.62 - 1.52 (m, 4H).	Rt = 3.36 min, m/z 532.4 [M+H] ⁺ (Method 11)
10	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and 2-bromoethyl methyl ether	(400 MHz, d6-DMSO) δ ¹H NMR (400 MHz, DMSO) d 8.68 (s, 1H), 8.55 (d, J=7.5 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.69 (d, J=7.9 Hz, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=8.9 Hz, 2H), 4.69 (d, J=5.6 Hz, 2H), 4.42 - 4.35 (m, 1H), 3.41 (t, J=6.0 Hz, 2H), 3.23 (s, 3H), 3.04 (t, J=8.9 Hz, 2H), 2.41 (t, J=6.5 Hz, 2H), 2.35 (s, 2H), 2.26 (s, 2H), 2.17 - 2.10 (m, 2H), 1.84 - 1.76 (m, 2H), 1.60 - 1.49 (m, 4H).	Rt = 1.98 min, m/z 544 [M+H] ⁺ (Method 10)

11	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide	Intermediate 8b and 2-bromoethyl methyl ether	(400 MHz, d6-DMSO) δ 8.68 (s, 1H), 8.41 (t, J=5.7 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.50 - 7.46 (m, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.76 (t, J=8.6 Hz, 2H), 4.69 (d, J=6.4 Hz, 2H), 3.40 (t, J=6.2 Hz, 2H), 3.32 - 3.23 (m, 2H), 3.22 (s, 3H), 3.04 (t, J=8.9 Hz, 2H), 2.49 - 2.41 (m, 1H), 2.38 (t, J=6.5 Hz, 2H), 2.34 - 2.17 (br m, 4H), 1.84 - 1.76 (m, 2H), 1.54 - 1.41 (m, 6H).	Rt = 2.1 min, m/z 558.3 [M+H]⁺ (Method 10)
12	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)methyl)benzamide	Intermediate 8c and 2-bromoethyl methyl ether	(400 MHz, d6-DMSO) δ 8.67 (s, 1H), 8.16 (d, J=5.1 Hz, 1H), 8.12 (d, J=7.8 Hz, 1H), 7.83 (s, 1H), 7.67 (d, J=8.0 Hz, 1H), 7.47 (d, J=6.6 Hz, 1H), 7.37 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.78 - 4.66 (m, 4H), 3.77 - 3.67 (m, 1H), 3.29 (t, J=5.6 Hz, 2H), 3.22 (s, 3H), 3.07 - 2.90 (m, 6H), 1.93 - 1.86 (m, 2H), 1.71 (dd, J=3.2, 12.2 Hz, 2H), 1.49 - 1.25 (m, 6H).	Rt = 1.86 min, m/z 544.4 [M+H]⁺ LCMS (Method 10)

13	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide	Intermediate 8d and 2-bromoethyl methyl ether	(400 MHz, d6-DMSO) δ 8.67 (s, 1H), 8.26 (d, J=8.2 Hz, 1H), 8.17 (d, J=5.3 Hz, 1H), 7.70 (s, 1H), 7.49 (td, J=1.7, 9.6 Hz, 1H), 7.29 (d, J=8.8 Hz, 1H), 7.21 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.43 (s, 2H), 4.76 (t, J=8.3 Hz, 2H), 4.67 (d, J=6.8 Hz, 2H), 3.78 - 3.68 (m, 1H), 3.42 (t, J=6.8 Hz, 2H), 3.23 (s, 3H), 3.06 (t, J=8.9 Hz, 2H), 2.45 (t, J=6.0 Hz, 2H), 2.36 (t, J=5.7 Hz, 4H), 1.70 - 1.58 (m, 4H), 1.53 - 1.47 (m, 4H), 1.32 (t, J=5.3 Hz, 2H), 1.18 - 1.09 (m, 2H).	Rt = 2.17 min, m/z 590.4 [M+H] ⁺ (Method 10)
14	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide	Intermediate 8e and 2-bromoethyl methyl ether	(400 MHz, d6-DMSO) δ 8.67 (s, 1H), 8.51 (t, J=6.0 Hz, 1H), 8.17 (d, J=5.3 Hz, 1H), 7.70 (s, 1H), 7.49 (d, J=8.9 Hz, 1H), 7.30 (d, J=9.7 Hz, 1H), 7.21 (t, J=6.1 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.43 (s, 2H), 4.79 - 4.66 (m, 4H), 3.39 (t, J=5.4 Hz, 2H), 3.28 (t, J=5.4 Hz, 2H), 3.22 - 3.22 (m, 3H), 3.06 (t, J=9.6 Hz, 2H), 2.48 - 2.41 (m, 1H), 2.38 (t, J=7.3 Hz, 2H), 2.32 - 2.16 (br m, 4H), 1.84 - 1.77 (m, 2H), 1.54 - 1.41 (m, 6H).	Rt = 2.2 min, m/z 576.5 [M+H] ⁺ (Method 10)

15	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Intermediate 8f and 2-bromoethyl methyl ether	(400 MHz, d₆-DMSO) δ 12.78 (s, 1H), 8.61 (d, J=7.5 Hz, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.82 (s, 1H), 7.67 (s, 1H), 7.48 (d, J=9.3 Hz, 1H), 7.26 (d, J=9.5 Hz, 1H), 6.74 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.60 (d, J=6.1 Hz, 2H), 4.36 (dd, J=8.1, 16.0 Hz, 1H), 3.39 (dd, J=6.0, 6.0 Hz, 2H), 3.22 (s, 3H), 3.06 (dd, J=8.8, 8.8 Hz, 2H), 2.39 (t, J=6.1 Hz, 2H), 2.35 (br s, 2H), 2.25 (br s, 2H), 2.17 - 2.09 (m, 2H), 1.78 (dd, J=8.6, 11.9 Hz, 2H), 1.58 - 1.48 (m, 4H).	R _t = 3.43 min, m/z 535.2 [M+H] ⁺ (Method 13)
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Example 16



N-(7-Acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide (Example 16)

- 5 To a stirring suspension of Example 4 (51 mg, 0.105 mmol), acetic acid (0.0072 mL, 0.126 mmol) and DIPEA (0.055 mL, 0.315 mmol) in DCM (3 mL) and DMF (1 mL) was added HATU (60 mg, 0.158 mmol). The reaction mixture was stirred overnight. The reaction mixture was diluted with methanol and applied to a SCX-2 cartridge, that was washed with methanol then eluted using 2N ammonia in methanol. The basic fraction was
- 10 evaporated to give a crude product that was purified by MDAP (Xbridge Phenyl

19x150mm, 10um 20-80% MeOH / H₂O (10mM NH₄CO₃), 20mL/min, RT) to give the title compound (28 mg).

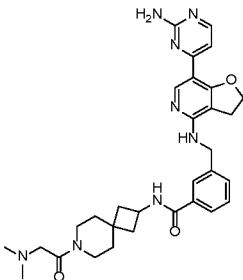
LCMS (Method 10) : Rt = 2.47 min, m/z 528.2 [M+H]⁺

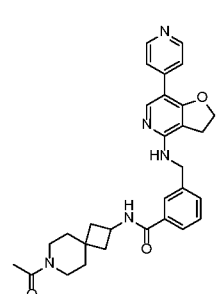
¹H NMR (400 MHz, DMSO) δ 8.68 (s, 1H), 8.59 (dd, J=4.5, 7.4 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.84 (s, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.49 (d, J=7.7 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.18 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=8.9 Hz, 2H), 4.69 (d, J=6.0 Hz, 2H), 4.43 (ddd, J=4.5, 8.0, 16.0 Hz, 1H), 3.43 - 3.38 (m, 3H), 3.31 - 3.27 (m, 1H), 3.04 (t, J=8.9 Hz, 2H), 2.24 - 2.19 (m, 2H), 1.99 (d, J=6.4 Hz, 3H), 1.91 - 1.84 (m, 2H), 1.63 - 1.43 (m, 4H).

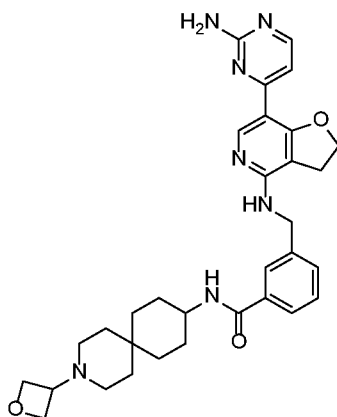
10

Examples 17 to 18

The following compounds were prepared in a similar manner substituting acetic acid and/or the carboxylic acid given and using the coupling reagent indicated.

Example	Structure	Starting materials/ reagent	¹ H NMR	LCMS
17	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(dimethylglycyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4, N,N-dimethylglycine, TBTU	(400 MHz, d6-DMSO) δ 8.68 (s, 1H), 8.59 (d, J=7.3 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.84 (s, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H), 7.39 (dd, J=7.7, 7.7 Hz, 1H), 7.18 (dd, J=6.0, 6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=9.0 Hz, 2H), 4.69 (d, J=6.2 Hz, 2H), 4.46 - 4.39 (m, 1H), 3.48 - 3.40 (m, 4H), 3.08 - 3.01 (m, 4H), 2.25 - 2.19 (m, 2H), 2.17 (d, J=3.3 Hz, 6H), 1.90 - 1.83 (m, 2H), 1.61 - 1.45 (m, 4H).	Rt = 2.03 min, m/z 571 [M+H] ⁺ (Method 10)

18	 N-(7-acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide	Example 5, acetic acid, HATU	(400 MHz, d6-DMSO) δ 8.59 (m, 1H), 8.51 (dd, J= 1.66, 4.62 Hz, 2H), 8.23 (bs, 1H), 7.83(bs, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.66 (dd, J= 1.7, 4.6 Hz, 2H), 7.49 (d, J=7.7 Hz, 1H), 7.40 (t, J=7.7 Hz, 1H), 7.15 (t, J=6.0 Hz, 1H), 4.75 (t, J=8.9 Hz, 2H), 4.69 (d, J=6.1 Hz, 2H), 4.38-4.48 (m, 1H), 3.25-3.45 (m, 4H), 3.08 (t, J=8.8 Hz, 2H), 2.56 (s, 2H), 2.21 (t, J=9.4 Hz, 2H), 1.87 (t, J=9.6 Hz, 2H), 1.60 (t, J=5.4 Hz, 1H), 1.53 (m, 2H), 1.45 (t, J=5.8 Hz, 1H).	Rt = 2.33 min, m/z 512.0 [M+H] ⁺ (Method 10)
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Example 19

3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(oxetan-3-yl)-3-azaspiro[5.5]undecan-9-yl)benzamide

(Example 19)

To a solution of Intermediate 8a (100 mg, 0.195 mmol, 1.00 eq) in DCM (5.00 mL) and DMF (1 mL) was added 3-oxetanone (0.015 mL, 0.234 mmol) and then acetic acid (0.011 mL, 0.195 mmol). The reaction mixture was sonicated for 10 minutes to aid dissolution. After 1 h at RT, sodium triacetoxyborohydride (83 mg, 0.389 mmol) was added and the reaction mixture was sonicated for a further 5 minutes and then allowed to stir at RT for 18h. The reaction was quenched with water (1 mL), diluted with DCM and

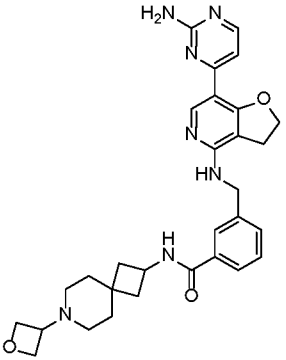
washed with aqueous saturated NaHCO₃. The organic layer was separated and washed with aqueous saturated NaCl, then dried over magnesium sulphate, filtered and the volatiles evaporated to give a residue that was purified by flash chromatography on C18 silica by gradient elution from 0 to 90% water/acetonitrile (+2.5% NH₄OH). Relevant fractions were dried to give the desired product (28.2 mg).

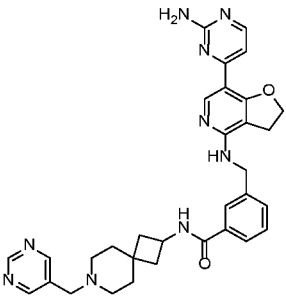
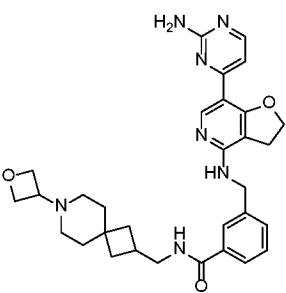
LCMS (Method 12): Rt = 1.97 min, m/z 570 [M+H]⁺

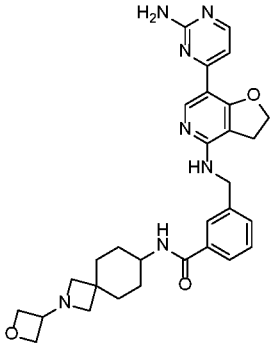
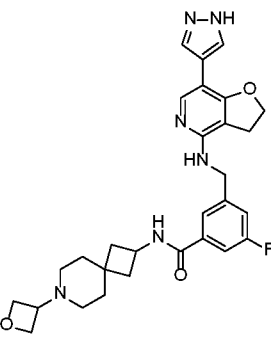
¹H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 8.16 - 8.12 (m, 2H), 7.81 (s, 1H), 7.66 (d, J=7.6 Hz, 1H), 7.46 (d, J=7.6 Hz, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.17 - 7.13 (m, 1H), 7.05 (d, J=5.2 Hz, 1H), 6.40 (s, 2H), 4.76 - 4.64 (m, 4H), 4.50 (t, J=6.3 Hz, 2H), 4.39 (t, J=5.9 Hz, 2H), 3.77 - 3.69 (m, 1H), 3.41 - 3.36 (m, 1H), 3.06 - 2.99 (m, 2H), 2.16 (s, 4H), 1.67 - 1.43 (m, 8H), 1.35 - 1.30 (m, 2H), 1.16 - 1.05 (m, 2H).

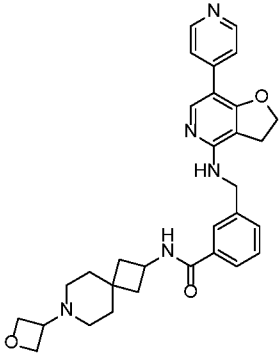
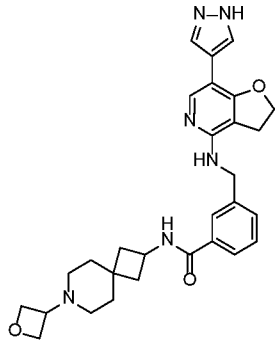
Examples 20 to 26

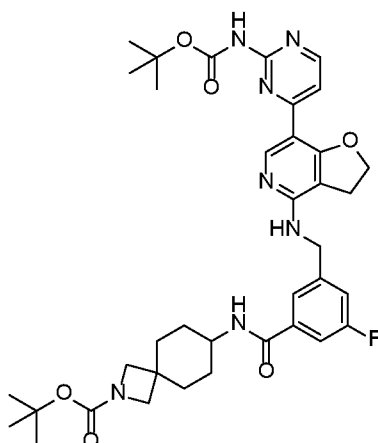
The following examples were prepared from the intermediates given in the table using a similar method to Example 19.

Ex.	Structure	Starting materials	¹ H NMR	LCMS
20	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and 3-oxetanone	(400 MHz, d ₆ -DMSO) δ 8.67 (s, 1H), 8.55 (d, J=7.5 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.19 - 7.14 (m, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=9.5 Hz, 2H), 4.68 (d, J=5.9 Hz, 2H), 4.51 (t, J=6.5 Hz, 2H), 4.43 - 4.37 (m, 3H), 3.35-3.27 (m, 1H), 3.04 (t, J=8.9 Hz, 2H), 2.19 - 2.08 (m, 6H), 1.85 - 1.78 (m, 2H), 1.63 - 1.52 (m, 4H).	Rt = 1.89 min, m/z 542 [M+H] ⁺ (Method 10)

21	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(pyrimidin-5-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Example 4 and pyrimidine-5-carbaldehyde	(400 MHz, d₆-DMSO) δ 9.10 (s, 1H), 8.72 (s, 2H), 8.67 (s, 1H), 8.55 (d, J=7.5 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.69 (d, J=7.9 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.2 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.74 (t, J=8.9 Hz, 2H), 4.68 (d, J=6.0 Hz, 2H), 4.39 (dd, J=8.0, 16.1 Hz, 1H), 3.49 (s, 2H), 3.04 (t, J=8.9 Hz, 2H), 2.35 (br s, 2H), 2.26 (br s, 2H), 2.18 - 2.11 (m, 2H), 1.82 (dd, J=8.5, 11.9 Hz, 2H), 1.63 - 1.53 (m, 4H).	Rt = 1.94 min, m/z 578.2 [M+H] ⁺ (Method 10)
22	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide	Intermediate 8b and 3-oxetanone	(400 MHz, d₆-DMSO) δ 8.68 (s, 1H), 8.41 (t, J=5.8 Hz, 1H), 8.16 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 7.67 (d, J=7.7 Hz, 1H), 7.48 (d, J=7.7 Hz, 1H), 7.38 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=9.1 Hz, 2H), 4.68 (d, J=7.7 Hz, 2H), 4.50 (t, J=6.5 Hz, 2H), 4.38 (t, J=6.1 Hz, 2H), 3.28 (t, J=6.4 Hz, 3H), 3.04 (t, J=8.8 Hz, 2H), 2.48 - 2.42 (m, 1H), 2.15 - 2.02 (m, 4H), 1.81 (dd, J=8.8, 12.4 Hz, 2H), 1.57 - 1.44 (m, 6H).	Rt = 1.96 min, m/z 556.0 [M+H] ⁺ (Method 10)

23	 3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(oxetan-3-yl)-2-azaspiro[3.5]nonan-7-yl)benzamide	Intermediate 8c and 3-oxetanone	(400 MHz, d6-DMSO) δ 8.67 (s, 1H), 8.17 - 8.13 (m, 2H), 7.83 (s, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.37 (t, J=7.7 Hz, 1H), 7.17 (t, J=6.0 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 6.42 (s, 2H), 4.75 (t, J=9.3 Hz, 2H), 4.68 (d, J=6.1 Hz, 2H), 4.55 (t, J=6.6 Hz, 2H), 4.37 (t, J=5.8 Hz, 2H), 3.77 - 3.70 (m, 2H), 3.07 - 3.00 (m, 4H), 2.94 (s, 2H), 1.91 (d, J=12.7 Hz, 2H), 1.72 (dd, J=3.5, 12.5 Hz, 2H), 1.53 - 1.32 (m, 4H).	Rt = 3.16 min, m/z 542.0 [M+H] ⁺ (Method 11)
24	 3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Intermediate 8f and 3-oxetanone	(400 MHz, d6-DMSO) δ 12.80 (s, 1H), 8.63 (d, J=7.5 Hz, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.69 (s, 1H), 7.50 - 7.47 (m, 1H), 7.28 (d, J=9.3 Hz, 1H), 6.76 (t, J=6.1 Hz, 1H), 4.71 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 4.51 (t, J=6.5 Hz, 2H), 4.43 - 4.36 (m, 3H), 3.31 (d, J=6.4 Hz, 1H), 3.08 (t, J=8.8 Hz, 2H), 2.19 - 2.09 (m, 6H), 1.81 (dd, J=8.5, 11.9 Hz, 2H), 1.63 - 1.53 (m, 4H).	Rt = 1.98 min, m/z 533.4 [M+H] ⁺ (Method 10)

25	 N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide	Example 5 and 3-oxetanone	(400 MHz, d₆-DMSO) δ 8.56 (d, J=7.41 Hz, 1H) 8.51 (dd, J=1.5, 4.6 Hz, 2H), 8.23 (bs, 1H), 7.82 (bs, 1H), 7.69 (d, J=7.7 Hz, 1H), 7.66 (dd, J=1.7, 4.6 Hz, 2H), 7.48 (d, J=7.5 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.14 (t, J=6.1 Hz, 1H), 4.75 (t, J=8.9 Hz, 2H), 4.68 (d, J=5.9 Hz, 2H), 4.51 (t, J=6.4 Hz, 2H), 4.36-4.44 (m, 3H), 3.26-3.34 (m, 1H), 3.08 (t, J=9.3 Hz, 2H), 2.56 (s, 1H), 2.15 (t, J=9.5 Hz, 4H), 2-2.1 (bs, 1H), 1.82 (t, J=9.5 Hz, 2H), 1.60 (t, J=5.3 Hz, 2H), 1.55 (t, J=5.3 Hz, 2H).	R_t = 1.7 min, m/z 526.2 [M+H]⁺ (Method 10)
26	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide	Intermediate 8h and 3-oxetanone	(400 MHz, d₆-DMSO) δ 8.54 (1H, d, J=7.5 Hz), 8.18 (1H, s), 8.08 (1H, s), 7.87 (1H, s), 7.81 (1H, s), 7.69-7.66 (1H, m), 7.48 (1H, d, J=7.9 Hz), 7.37 (1H, dd, J=7.7, 7.7 Hz), 6.70 (1H, t, J=6.0 Hz), 4.70 (2H, t, J=8.8 Hz), 4.62 (2H, d, J=6.1 Hz), 4.51 (2H, t, J=6.5 Hz), 4.41 (4H, m), 3.06 (2H, t, J=8.8 Hz), 2.19-2.08 (4H, m), 1.85-1.78 (2H, m), 1.60 (2H, t, J=5.2 Hz),	R_t = 1.82 min, m/z 515.0 [M+H]⁺ (Method 10)

Intermediate 9a

tert-Butyl 7-(3-(((7-(2-((tert-butoxycarbonyl)amino)pyrimidin-4-yl)-2,3-dihydro-furo[3,2-c]pyridin-4-yl)amino)methyl)-5-fluorobenzamido)-2-azaspiro[3.5]nonane-2-carboxylate (Intermediate 9a)

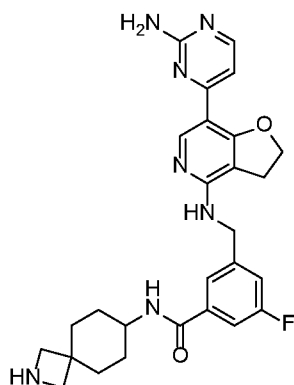
To a solution of Intermediate 4b (150 mg, 0.312 mmol), HATU (150 mg, 0.467 mmol) and DIPEA (0.16 mL, 0.935 mmol) in DMF (4 mL) was added tert-butyl 7-amino-2-azaspiro[3.5]nonane-2-carboxylate (82 mg, 0.343 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was further washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give the desired product (235 mg).

LCMS (Method 8) : Rt = 1.60 min, m/z 704.5 [M+H]⁺

Intermediate 9b

The following intermediate was prepared in a similar manner from Intermediate 4b using the amine and coupling reagent indicated.

Intermediate	Structure	Starting materials	LCMS
8b		tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate, TBTU	Rt = 1.66 min, m/z 704.6 [M+H] ⁺ (Method 7)

Intermediate 10a

3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(2-azaspiro[3.5]nonan-7-yl)benzamide (Intermediate 9a)

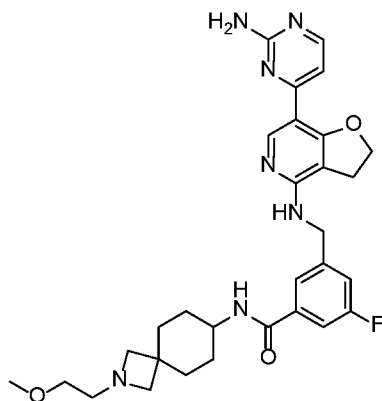
To a solution of Intermediate 9a (230 mg, 0.327 mmol) in DCM (10 mL) was added TFA (0.63 mL, 8.17 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the crude compound was loaded onto an SCX-2 cartridge, which was washed with methanol. The compound was eluted using 2N ammonia solution in methanol and the eluents were collected and concentrated to give the desired product (150 mg).

LCMS (Method 8): $R_t = 1.08$ min, m/z 504.4 $[M+H]^+$

Intermediate 10b

The following intermediate was prepared in a similar manner of intermediate 10a from the intermediate indicated.

Intermediate	Structure	Starting material	LCMS
10b		Intermediate 9b	$R_t = 1.14$ min, m/z 504.5 $[M+H]^+$ (Method 7)

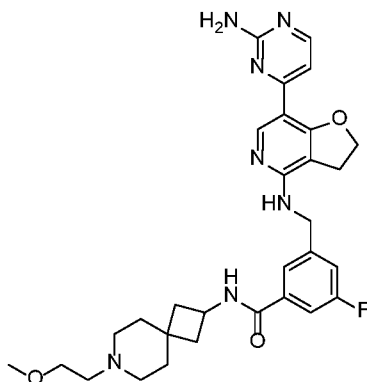
Example 27

3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)benzamide (Example 27)

Example 27 was prepared from Intermediate 10a and 2-bromoethylmethyl ether using a procedure analogous to that used in the preparation of Example 6.

LCMS (Method 10): $R_t = 2.13$ min, m/z 562.5 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 8.22 (d, $J=7.8$ Hz, 1H), 8.17 (d, $J=5.3$ Hz, 1H), 7.71 - 7.69 (m, 1H), 7.50 (dd, $J=1.9, 9.3$ Hz, 1H), 7.29 (d, $J=9.5$ Hz, 1H), 7.20 (t, $J=6.1$ Hz, 1H), 7.07 (d, $J=5.3$ Hz, 1H), 6.44 - 6.42 (m, 2H), 4.76 (t, $J=9.0$ Hz, 2H), 4.68 (d, $J=6.0$ Hz, 2H), 3.76 - 3.66 (m, 1H), 3.28 (t, $J=6.0$ Hz, 2H), 3.22 - 3.22 (m, 3H), 3.09 - 3.02 (m, 2H), 2.96 - 2.95 (m, 2H), 2.87 (s, 2H), 2.57 - 2.53 (m, 2H), 1.87 (d, $J=12.7$ Hz, 2H), 1.70 (dd, $J=3.1, 12.2$ Hz, 2H), 1.49 - 1.29 (m, 4H).

Example 28

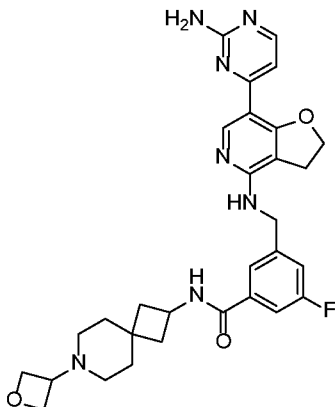
3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide (Example 28)

Example 28 was prepared from Intermediate 10b and 2-bromoethylmethyl ether using a procedure analogous to that used in the preparation of Example 6.

LCMS (Method 10): $R_t = 2.18$ min, m/z 562.5 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 8.67 (s, 1H), 8.65 - 8.61 (m, 1H), 8.17 (d, $J=5.3$ Hz, 1H), 7.70 (s, 1H), 7.52 (dd, $J=1.4, 7.2$ Hz, 1H), 7.30 (d, $J=9.4$ Hz, 1H), 7.21 (t, $J=6.0$ Hz, 1H), 7.07 (d, $J=5.3$ Hz, 1H), 6.44 - 6.42 (m, 2H), 4.79 - 4.73 (m, 2H), 4.70 - 4.66 (m, 2H), 4.37 (dd, $J=8.0, 16.2$ Hz, 1H), 3.41 (t, $J=6.0$ Hz, 2H), 3.23 (s, 3H), 3.06 (t, $J=8.9$ Hz, 2H), 2.43 - 2.39 (m, 2H), 2.35 - 2.33 (m, 4H), 2.18 - 2.11 (m, 2H), 1.80 (dd, $J=8.5, 11.9$ Hz, 2H), 1.58 - 1.55 (m, 2H), 1.54 - 1.50 (m, 2H).

Example 29



3-(((7-(2-Aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide (Example 29)

Example 29 was prepared from Intermediate 10b and 3-oxetanone using a procedure analogous to that used in the preparation of Example 19.

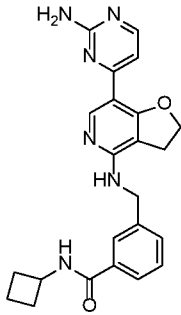
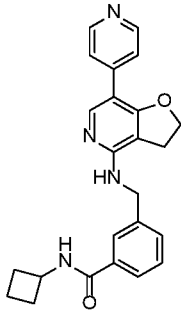
LCMS (Method 11) : $R_t = 3.36$ min, m/z 560.5 $[M+H]^+$

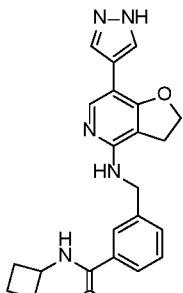
1H NMR (400 MHz, DMSO) δ 8.67 - 8.62 (m, 2H), 8.20 (s, 1H), 8.17 (d, $J=5.3$ Hz, 1H), 7.70 (s, 1H), 7.51 (d, $J=9.2$ Hz, 1H), 7.30 (d, $J=9.4$ Hz, 1H), 7.21 (t, $J=6.0$ Hz, 1H), 7.07 (d, $J=5.3$ Hz, 1H), 6.43 (s, 2H), 4.76 (t, $J=8.5$ Hz, 2H), 4.69 (d, $J=6.0$ Hz, 2H), 4.51

(t, J=6.5 Hz, 2H), 4.43 - 4.36 (m, 3H), 3.06 (t, J=9.0 Hz, 3H), 2.19 - 2.09 (m, 6H), 1.81 (dd, J=8.5, 11.9 Hz, 2H), 1.63 - 1.53 (m, 4H).

Preparation of comparative compounds

The comparative examples were prepared in a similar way to example 1 from the starting material indicated in the table below.

Ex.	Structure	Starting materials	¹ H NMR	LCMS
A	 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-cyclobutylbenzamide	Intermediate 2, cyclobutylamine	(400 MHz, d6-DMSO) δ 8.66 (s, 1H), 8.58 (d, J=7.5 Hz, 1H), 8.15 (d, J=5.2 Hz, 1H), 7.82 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.39-7.35 (m, 1H), 7.18-7.14 (m, 1H), 7.06 (d, J=5.2 Hz, 1H), 6.41 (s, 2H), 4.74 (t, J=8.9 Hz, 2H), 4.67 (d, J=5.8 Hz, 2H), 4.40 (dt, J=8.4, 16.4 Hz, 1H), 3.03 (t, J=8.9 Hz, 2H), 2.24-2.17 (m, 2H), 2.11-2.01 (m, 2H), 1.70-1.61 (m, 2H).	Rt = 2.40 min, m/z 417.1 [M+H] ⁺ (Method 6)
B	 N-cyclobutyl-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide	Intermediate 1, cyclobutylamine	(400 MHz, d6-DMSO) δ 8.61-8.57 (m, 1H), 8.52-8.50 (m, 2H), 8.23 (s, 1H), 7.82 (s, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.66 (q, J=2.0 Hz, 2H), 7.50-7.46 (m, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.17-7.12 (m, 1H), 4.75 (t, J=9.0 Hz, 2H), 4.68 (d, J=6.0 Hz, 2H), 4.42 (qt, J=8.1, 8.2 Hz, 1H), 3.08 (dd, J=8.4, 9.4 Hz, 2H), 2.26-2.18 (m, 2H), 2.13-2.02 (m, 2H), 1.72-1.62 (m, 2H).	Rt = 2.33 min, m/z 401.0 [M+H] ⁺ (Method 10)

C	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-cyclobutylbenzamide	Intermediate 5, cyclobutylamine	(400 MHz, d6-DMSO) δ 12.57 (s, 1H), 8.27-8.25 (m, 1H), 8.08 (s, 1H), 7.92-7.76 (m, 3H), 7.68 (d, J=7.7 Hz, 1H), 7.50 (d, J=7.5 Hz, 1H), 7.39-7.34 (m, 1H), 6.31 (t, J=6.0 Hz, 1H), 4.70 (t, J=8.7 Hz, 2H), 4.66 (d, J=5.6 Hz, 2H), 4.46-4.39 (m, 1H), 3.08 (t, J=8.8 Hz, 2H), 2.31-2.22 (m, 2H), 2.16-2.05 (m, 2H), 1.77-1.66 (m, 2H).	Rt = 2.60 min, m/z 390.0 [M+H] ⁺ (Method 10)
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PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION.

In vitro inhibitory activity assay description ROCK1 and ROCK2

The effectiveness of compounds of the present invention to inhibit Rho kinase activity can be determined in a 10μl assay containing 40mM Tris pH7.5, 20mM MgCl₂ 0.1mg/mL BSA, 50μM DTT and 2.5μM peptide substrate (Myelin Basic Protein) using an ADP-Glo kit (Promega). Compounds were dissolved in DMSO such that the final concentration of DMSO was 1% in the assay. All reactions/incubations are performed at 25°C. Compound (2μl) and either Rho kinase 1 or 2 (4μl) were mixed and incubated for 30 mins. Reactions were initiated by addition of ATP (4μl) such that the final concentration of ATP in the assay was 200μM. After a 1 hour incubation 10μl of ADP-Glo Reagent was added and after a further 1 hour incubation 20μl of Kinase Detection Buffer was added and the mixture incubated for a further 45 minutes. The luminescent signal was measured on a luminometer. Controls consisted of assay wells that did not contain compound with background determined using assay wells with no enzyme added. Compounds were tested in dose-response format and the inhibition of kinase activity was calculated at each concentration of compound. To determine the IC₅₀ (concentration of compound required to inhibit 50% of the enzyme activity) data were fit to a plot of % inhibition vs Log₁₀ compound concentration using a sigmoidal fit with a variable slope and fixing the maximum to 100% and the minimum to 0%. To determine the K_i values the Cheng-Prusoff equation was utilized ($K_i = IC_{50} / (1 + [S]/K_m)$).

Compounds according to the invention showed K_i values lower than 500 nM on both isoforms.

The results for individual compounds are provided below in following table and are expressed as range of activity.

5 **In vitro inhibitory activity assay description for PKA**

The effectiveness of compounds of the present invention to inhibit PKA activity can be determined in a 10 μ l assay containing 40mM Tris pH7.5, 20mM MgCl₂ 0.1mg/ml BSA, 50 μ M DTT and 260 μ M peptide substrate (kemptide) using an ADP-Glo kit (Promega). Compounds were dissolved in DMSO such that the final concentration of DMSO was 1% in the assay. All reactions/incubations are performed at 25°C. Compound and PKA enzyme (6 μ l) were mixed and incubated for 30 mins. Reactions were initiated by addition of ATP (4 μ l) such that the final concentration of ATP in the assay was 10 μ M. After a 30 minute incubation 10 μ l of ADP-Glo Reagent was added and after a further 1 hour incubation 20 μ l of Kinase Detection Buffer was added and the mixture incubated for a further 45 minutes. The luminescent signal was measured on a luminometer. Controls consisted of assay wells that did not contain compound with background determined using assay wells with no enzyme added. Compounds were tested in dose-response format and the inhibition of kinase activity was calculated at each concentration of compound. To determine the IC_{50} (concentration of compound required to inhibit 50% of the enzyme activity) data were fit to a plot of % inhibition vs Log₁₀ compound concentration using a sigmoidal fit with a variable slope and fixing the maximum to 100% and the minimum to 0%. To determine the K_i values the Cheng-Prusoff equation was utilized ($K_i = IC_{50} / (1 + [S] / K_m)$).

In vitro inhibitory activities for PKA were reported as selectivity ratio vs. ROCK-2. Selectivity ratio PKA/ROCK2 was calculated by dividing the K_i value for PKA by the K_i value of ROCK2 and reported in the following table.

Table 1

Ex No.	ROCK 1	ROCK2	Ratio (PKA/ROCK2)	Corresponding Comparative example
1	++++	++++	***	A
2	++++	++++	***	A
3	++++	++++	**	A
4	++++	++++	***	A
5	++++	++++	***	B
6	++++	++++	***	A
7	++++	++++	***	A
8	++++	++++	***	A
9	++++	++++	***	A
10	++++	++++	***	A
11	++++	++++	***	A
12	++++	++++	***	A
13	++++	++++	***	A
14	++++	++++	***	A
15	++++	++++	***	A
16	++++	++++	***	A
17	++++	++++	***	A
18	+++	+++	***	B
19	++++	++++	***	A
20	++++	++++	***	A
21	++++	++++	**	A
22	+++	++++	***	A
23	+++	++++	***	A
24	++++	++++	***	C
25	++++	++++	***	B
26	++++	++++	***	C
27	++++	++++	***	A
28	++++	++++	**	A
29	++++	++++	***	A
A	+++	+++	*	
B	++	++	*	
C	++	++	**	

wherein the compounds are classified in term of potency with respect to their

inhibitory activity on ROCK1 and ROCK2 isoforms according to the following classification criterion:

++++: $K_i \leq 0,3 \text{ nM}$

+++ : $0.3 < K_i \leq 3 \text{ nM}$

5 ++ : $K_i 3 < K_i \leq 30 \text{ nM}$

+ : $K_i > 30 \text{ nM}$

The Compounds according to the invention showed advantageously K_i values equal to or lower than 3 nM , preferably even equal to or lower than 0,3 nM, at least on ROCK2; further preferably lower than 3 nM, preferably even equal to or lower than 0,3 nM on both
10 isoforms. The compounds according to the invention are more potent than the respective *comparative example A, B and C*.

Moreover, preferred compounds according to the invention exhibit marked selectivity versus PKA. The compounds according to the invention are at least 30 fold, preferably equal to or more than 100 fold, more selective in terms of ROCK2 selectivity
15 vs PKA, than the respective *comparative example A,B,C*

In the table the compounds are classified in term of selectivity with respect to their ratio of inhibitory activity (K_i) of PKA on ROCK2 isoform according to the following classification criterion:

*** : $\text{ratio} \geq 100$

20 ** : $30 \leq \text{ratio} < 100$

* : $\text{ratio} < 30$

Experimental bronchospasm

Animals

Male CD Sprague Dawley rats (220-250 g) were purchased from Charles River
25 Laboratories Italy (Calco, Lecco). Prior to use animals were acclimated for at least 5 days to the local vivarium conditions (room temperature: 20-24°C; relative humidity: 40-70%), having free access to standard rat chow and softened tap water. All the procedures were performed in animal operating rooms according to ethical guidelines for the conduct of animal research (D. L.vo 116/92).

30 Rats were anaesthetized with a combination of anesthetics (Zoletil 20 mg/kg + Xylazine 5 mg/kg, ip) for the i.t. administration. A laryngoscope was moved forward into

the mouth to visualize the trachea and guide the insertion of the tip of a custom-made small diameter cannula directly into the trachea and located 1-2 mm above the bifurcation.

Protocol

In order to assess the residual inhibitory activity of test compounds 1 hour after
5 their administration, rats were surgically prepared. Body temperature was kept constant at 37° C by a heated blanket.

The trachea was cannulated and the lungs were ventilated artificially with a constant volume ventilator (rodent ventilator mod. 7025, Ugo Basile, Comerio, Varese, Italy) at a frequency of 80 strokes/min and at a tidal volume of 10 ml/kg. To avoid spontaneous
10 breathing, the animals were injected intravenously (i.v.) with pancuronium bromide (2 mg/kg).

Bronchoconstriction was induced by the i.v. injection of carbachol (cch) 80 µg/kg. In control experiments, repeated injections of this dose produced reproducible short-lasting (1-2 min duration) bronchospasms. Bronchoconstriction, quantified as a reduction
15 of tidal volume, was evaluated according to the method described by Konzett & Roessler (1). Systemic blood pressure and changes in airway resistance were monitored with a digital pressure transducer.

After stabilisation of artificial breathing and blood pressure, animals were injected (i.v.) with cch every 3 min, until 3 stable and reproducible basal responses were obtained.
20 Challenges did not ever exceed the number of 10. The effect of test compounds was expressed as % inhibition of cch-evoked bronchoconstriction in time-matched, vehicle-treated, animals (controls).

Tested compounds were dissolved in dH₂O and 1% Tween-80 or 0,001% HCl and further diluted to target concentrations. Tested compounds were instilled locally into the
25 trachea in a volume of 125 µl.

All data are presented as mean ± s.e.mean. The % inhibition of experimental bronchospasm was calculated comparing the drug-treated with the vehicle-treated control animals. Data analysis was performed using GraphPad Prism software.

(1) Konzett H and Roessler R (1940). Versuchsanordnung zu untersuchungen an der
30 bronchialmuskulatur. Arch. Exp. Path. Pharmac.; 195: 71-74.

Ex No.	Dose ($\mu\text{g/Kg}$)	Inhibition % ($\pm$ s.e.mean)
8	10 $\mu\text{g/Kg}$	56.3 $\pm$ 2.1
9	10 $\mu\text{g/Kg}$	75.5 $\pm$ 9
10	10 $\mu\text{g/Kg}$	61.5 $\pm$ 2.5
20	10 $\mu\text{g/Kg}$	58.5 $\pm$ 2.1
28	10 $\mu\text{g/Kg}$	65.2 $\pm$ 3.5
29	3 $\mu\text{g/Kg}$	74.3 $\pm$ 6.9
A	10 $\mu\text{g/Kg}$	30.0 $\pm$ 3.9

From the above data it is evident that compounds according to the present invention, further to high inhibitory activity on ROCK1 and ROCK2 and marked selectivity versus PKA, can exhibit additional improved properties that are preferred and make them particularly suitable for development and administration by inhalation route.

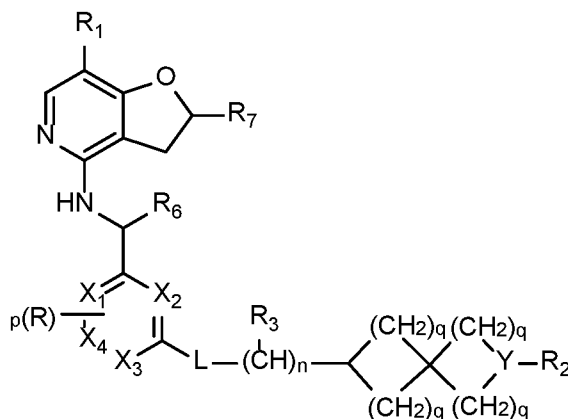
- 5 Specifically at least they were potent broncodilators, exhibiting anti-bronchospastic activity, in the bronchospasm in vivo test above reported. The compounds reported showed inhibition of CCH bronchoconstriction higher than 30%, Particularly preferred compounds showed inhibition of CCH bronchoconstriction higher than 50%, at a dose of 10 ($\mu\text{g/Kg}$), some even more potent compounds exhibit inhibition of CCH bronchoconstriction higher
- 10 than 70% at a dose level of 3 ($\mu\text{g/Kg}$).

The above is particularly evident when comparing inhibition of bronchoconstriction brought about by compound of the invention characterized by a

spiro-moiety , vs compound A (used as comparator), the compounds of the invention showing superior activity as broncodilators.

CLAIMS

1. A compound of formula (I)



I

- 5 wherein
- X₁, X₂, X₃ and X₄** are all CH or one of X₁, X₂, X₃ and X₄ is N and the others are CH;
- Y is selected from N, or O;
- q is in each occurrence independently selected from 1 or 2;
- 10 p is zero or an integer from 1 to 4;
- each R, when present, is in each occurrence independently selected from (C₁-C₆)alkyl and halogen selected from F, Cl, Br and I;
- R₁ is pyrazolyl, pyridinyl or pyrimidinyl substituted by one or more group selected from -(CH₂)_mNH₂; particularly preferably R₁ is 2-aminopyrimidin-4-yl;
- 15 L is -C(O)NH- or -NHC(O)- ;
- n is in each occurrence independently 0 or an integer selected from 1, 2 or 3;
- R₃, when present, is in each occurrence independently H, or (C₁-C₆)alkyl,
- R₂ is absent when Y is O, or when Y is N, R₂ is selected from the group consisting of
- 20 -H,
- (C₁-C₆)alkyl,
- (C₁-C₆)hydroxyalkyl,
- (C₁-C₆)alkoxy (C₁-C₆)alkyl,
- ciano (C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,
 -(CH₂)_n-C(O)-(CH₂)_mNR₄R₅,
 alkanoyl,
 aryl, heteroaryl, (C₃-C₈)cycloalkyl,
 5 (C₃-C₈)heterocycloalkyl,
 aryl-(C₁-C₆)alkyl,
 heteroaryl-(C₁-C₆)alkyl,
 (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl,
 (C₃-C₈)cycloalkyl-(C₁-C₆)alkyl,

10 m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₄ and R₅, the same or different, are selected from the group consisting of

-H,

(C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

15 (C₁-C₆)hydroxyalkyl,

R₆ and R₇ are independently selected from the group consisting of -H, (C₁-C₆)alkyl;
 single enantiomers, diastereoisomers and mixtures thereof in any proportion
 and/or pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1

20 wherein **X₁**, **X₂**, **X₃** and **X₄** are all CH;

Y is -N-;

q is in each occurrence independently selected from 1 or 2;

p is zero or an integer from 1 to 4;

each R, when present, is an halogen in each occurrence independently selected from

25 F, Cl, Br and I, wherein preferably R is F;

R₁ is pyrimidinyl substituted by -NH₂;

L is -C(O)NH-;

n is 0;

R₃ is absent

30 and

R₂ is selected from the group consisting of

-H,

(C₁-C₆) alkoxy (C₁-C₆)alkyl,

ciano (C₁-C₆)alkyl,

(C₁-C₆)haloalkyl,

-(CH₂)_n-C(O)-(CH₂)_mNR₄R₅,

alkanoyl,

heteroaryl-(C₁-C₆)alkyl,

(C₃-C₈)heterocycloalkyl,

m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₄ and R₅, the same or different, are selected from the group consisting of

-H,

(C₁-C₆)alkyl,

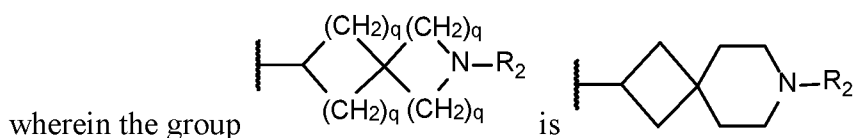
(C₁-C₆)haloalkyl,

(C₁-C₆)hydroxyalkyl,

R₆ and R₇ are -H

single enantiomers, diastereoisomers and mixtures thereof in any proportion and/or pharmaceutically acceptable salts and solvates thereof

3. A compound according to claim 1 or 2,



and R₂ is selected from

2-methoxyethyl, 2-fluoroethyl, oxetan-3-yl, 2-(dimethylamino)-2-oxoethyl.

4. A compound according to claim 1

wherein

X₁, X₂, X₃ and X₄ are all CH;

p is zero or 1;

each R, when present, is F;

R₁ is selected from 1H-pyrazol-4-yl, pyridin-4-yl and 2-aminopyrimidin-4-yl;

L is -C(O)NH-;

n is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R₃, is H,

and

R_2 is absent when Y is O, or when Y is N, R_2 is selected from the group consisting of

-H,

(C₁-C₆) alkoxy (C₁-C₆)alkyl, which is 2-methoxyethyl,

ciano (C₁-C₆)alkyl which is 2-cyanoethyl,

(C₁-C₆) haloalkyl, which is 2-fluoroethyl,

-C(O)(CH₂)_m NR₄R₅, which is 2-(dimethylamino)-2-oxoethyl,

-(CH₂)_nC(O) NR₄R₅, which is dimethylglycyl,

alkanoyl, which is acetyl,

heteroaryl-(C₁-C₆)alkyl which is pyrimidin-5-ylmethyl;

(C₃-C₈)heterocycloalkyl, which is oxethan-3-yl,

m is in each occurrence independently 0 or an integer selected from 1, 2 or 3;

R_4 and R_5 , are an (C₁-C₆)alkyl, which is methyl,

R_6 and R_7 are -H;

single enantiomers, diastereoisomers and mixtures thereof in any proportion, or pharmaceutically acceptable salts and solvates thereof.

5. A compound according to claim 1 selected from

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-fluoroethyl)-2-azaspiro[3.3]heptan-6-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-oxaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-oxaspiro[3.3]heptan-6-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-

yl)amino)methyl)-N-(7-(2-cyanoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-(dimethylamino)-2-oxoethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

5 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-fluoroethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

10 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)benzamide;

15 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(3-(2-methoxyethyl)-3-azaspiro[5.5]undecan-9-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-((7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)methyl)benzamide;

20 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

N-(7-acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide;

25 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(dimethylglycyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

N-(7-acetyl-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-(oxetan-3-yl)-3-azaspiro[5.5]undecan-9-yl)benzamide;

30 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-

yl)amino)methyl)-N-(7-(pyrimidin-5-ylmethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-

5 yl)methyl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(oxetan-3-yl)-2-azaspiro[3.5]nonan-7-yl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

10 N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)-3-(((7-(pyridin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

15 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(2-(2-methoxyethyl)-2-azaspiro[3.5]nonan-7-yl)benzamide;

3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(2-methoxyethyl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

20 3-(((7-(2-aminopyrimidin-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-5-fluoro-N-(7-(oxetan-3-yl)-7-azaspiro[3.5]nonan-2-yl)benzamide;

single enantiomers, diastereoisomers and mixtures thereof in any proportion, or pharmaceutically acceptable salts and solvates thereof

25 6. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, in admixture with one or more pharmaceutically acceptable carrier or excipient.

7. A pharmaceutical composition according to claim 6 suitable to be administered by inhalation, selected from inhalable powders, propellant-containing metering
30 aerosols or propellant-free inhalable formulations.

8. A device comprising the pharmaceutical composition according to claim 7, which

may be a single- or multi-dose dry powder inhaler, a metered dose inhaler or a soft mist nebulizer.

9. A pharmaceutical composition according to claim 6 suitable to be administered by oral route, selected from, gelcaps, capsules, caplets, granules, lozenges and bulk powders or aqueous and non-aqueous solutions, emulsions, suspensions, syrups, or elixirs formulations.
10. A compound or a pharmaceutical composition according to any one of claims 1 to 5 or 6 for use as a medicament.
11. A compound or a pharmaceutical composition for use according to claim 10, in the prevention and /or treatment of immune system disorders including Graft-versus-host disease (GVHD), and pulmonary diseases selected from the group consisting of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).
12. A compound or a pharmaceutical composition according to claim 11 for use via inhalatory route of administration particularly in the prevention and /or treatment of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).
13. A combination of a compound as defined in any one of the claims 1 to 5 with one or more active ingredients selected from the classes consisting of organic nitrates and NO donors; inhaled NO; stimulator of soluble guanylate cyclase (sGC); prostacilin analogue PGI₂ and agonist of prostacyclin receptors; compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP); human neutrophilic elastase inhibitors; compounds inhibiting the signal transduction cascade; active substances for lowering blood pressure; neutral endopeptidase inhibitor; osmotic agents; ENaC blockers; anti-inflammatories including corticosteroids and antagonists of chemokine receptors; antihistamine drugs; anti-tussive drugs; antibiotics and DNase drug substance and

- 5 selective cleavage agents; agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroxylase 1 (TPH1) inhibitors and multi-kinase inhibitors, beta2-agonists, corticosteroids, anticholinergic or antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/085286

A. CLASSIFICATION OF SUBJECT MATTER INV. A61P11/06 A61P11/08 A61P37/06 C07D491/048 A61K31/4355 ADD. 		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/016129 A1 (CHIESI FARM SPA [IT]) 23 January 2020 (2020-01-23) cited in the application claims; examples -----	1-13
A	US 2006/241127 A1 (BAYER HEALTHCARE AG [DE]; FEURER ACHIM [DE] ET AL.) 26 October 2006 (2006-10-26) cited in the application claims; examples ----- -/--	1-13
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 27 March 2023		Date of mailing of the international search report 05/04/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Bedel, Christian

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2022/085286

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DUONG-QUY SY ET AL: "Role of Rho-kinase and its inhibitors in pulmonary hypertension", PHARMACOLOGY & THERAPEUTICS, ELSEVIER, GB, vol. 137, no. 3, 20 December 2012 (2012-12-20), pages 352-364, XP028980355, ISSN: 0163-7258, DOI: 10.1016/J.PHARMTHERA.2012.12.003 cited in the application the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2022/085286

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