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(54) **Title:** DIHYDROFUROPYRIDINE DERIVATIVES AS RHO- KINASE INHIBITORS

(57) **Abstract:** The invention relates to compounds of formula (I) inhibiting Rho Kinase that are dihydrofuropyridine 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).

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 ROKβ or ROCK1) and ROCK-II (ROKα 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.

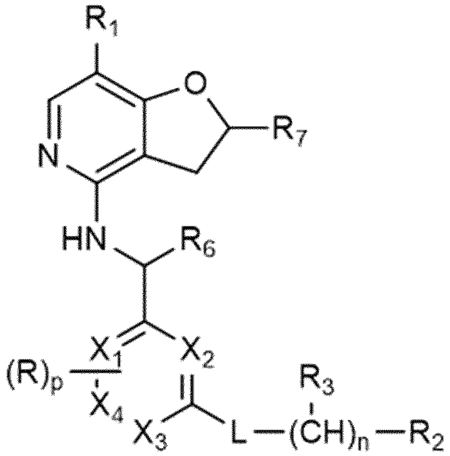
There remains a potential for developing novel and pharmacologically improved ROCK inhibitors in many therapeutic areas.

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 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, which are inhibitors of ROCK-I and ROCK-II, 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 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 administartion.

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_4 and R_5, R_6 and R_7 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 a pulmonary disease 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 “(C_1-C_6)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, and the like.

The expressions “(C_1-C_6)Haloalkyl” refer to the above defined “(C_1-C_6)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 “(C_1-C_6)Hydroxyalkyl” and “(C_1-C_6)aminoalkyl” refer to the above defined “(C_1-C_6)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. “(C_1-C_6)alkyl” groups) substituted by one or more amino group ($-NR_8R_9$). An example of aminoalkyl is a mono-aminoalkyl group such as $R_8R_9N-(C_1-C_6)$alkyl. The substituent R_8 and R_9 they are defined as R_4 and R_5 in the detailed description of the invention herebelow.

The term “(C_3-C_{10})cycloalkyl” likewise “(C_3-C_8)cycloalkyl” or “(C_3-C_6)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, benzothiopheneyl, 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 “(C_3-C_{10})heterocycloalkyl” likewise “(C_3-C_8)heterocycloalkyl” or “(C_3-C_6)heterocycloalkyl” refers to saturated or partially unsaturated monocyclic 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) 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(C_1-C_6)alkyl” refers to an aryl ring linked to a straight-chained or branched alkyl groups 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(C_1-C_6)alkyl” refers to an heteroaryl ring linked to a straight-chained or branched alkyl groups wherein the number of constituent carbon atoms is in the range from 1 to 6, e.g. furanylmethyl.

The term “alkanoyl”, refers to HC(O)- or to alkylcarbonyl groups (e.g. (C_1-C_6)alkylC(O)-) wherein the group “alkyl” has the meaning above defined. Examples include formyl, acetyl, propanoyl, butanoyl.

The term “(C_1-C_{10}) alkoxy” or “(C_1-C_{10}) alkoxyl”, likewise “(C_1-C_6) alkoxy” or “(C_1-C_6) alkoxyl” etc., refers to a straight or branched hydrocarbon of the indicated number of carbons, linked to the rest of the molecule through an oxygen bridge. “(C_1-C_6)Alkylthio” refers to the above hydrocarbon linked through a sulfur bridge.

The derived expression “(C_1-C_6)haloalkoxy” or “(C_1-C_6)haloalkoxyl” refers to the above defined haloalkyl, linked through an oxygen bridge. An example of (C_1-C_6)haloalkoxy is trifluoromethoxy.

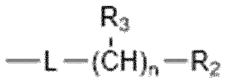
Likewise derived expression “(C_3-C_6)heterocycloalkyl-(C_1-C_6)alkyl” and “(C_3-C_6)cycloalkyl-(C_1-C_6) alkyl” refer to the above defined heterocycloalkyl and cycloalkyl groups linked to the rest of the molecule via an alkyl group of the indicated number of carbons, corresponding e.g. to linear formula (C_3-C_6)heterocycloalkyl-$(CH_2)_m$- or (C_3-C_6)cycloalkyl-$(CH_2)_m$- for example piperidin-4-yl-methyl, cyclohexylethyl.

The derived expression “(C_1-C_6)alkoxy-(C_1-C_6)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, for example methoxymethyl.

Likewise “(C_1-C_6)haloalkoxy (C_1-C_6)alkyl” refers to the above defined (C_1-C_6)haloalkoxy” group linked to the rest of the molecule via an alkyl group of the indicated number of carbons, for example difluoromethoxypropyl.

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 -SO_2- might be also represented as –$S(O)_2$– to disambiguate e.g. with respect to the sulfinic group –S(O)O–.

Likewise, the group –$(CHR_3)_n$-R_2 herein is a linear representation of the terminal part of the charachterizing group



$$-L-\overset{R_3}{(CH)_n}-R_2$$

found in formula (I), and (Ia).

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. $(CH_2)n$) 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 a 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.

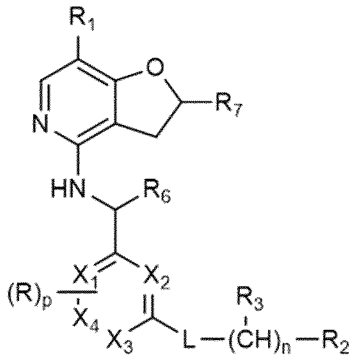
Racemic forms of compounds of formula (I) as well as the individual atropisomers (substantially free of its corresponding enantiomer) and stereoisomer-enriched atropisomers mixtures are included in the scope of the present invention.

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) as reported below, 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 carrier.

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



I

wherein

X_1, X_2, X_3 and **X_4** are all CH or one of X_1, X_2, X_3 and X_4 is N and the others are CH;

p is zero or an integer from 1 to 4;

each R, when present, is halogen in each occurrence independently selected from (C_1-C_6)alkyl and halogen selected from F, Cl, Br and I; wherein preferably R is F, Cl or methyl;

R_1 is pyrazolyl, preferably pyrazol-4-yl;

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

n is in each occurrence independently 0 (i.e. R_3 is absent) or an integer selected from 1, 2 or 3;

R_2 and R_3 are in each occurrence independently selected from the group consisting of

-H,

halogen,

-OH,

-$(CH_2)_mNR_4R_5$,

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6) alkoxy,

(C_1-C_6) alkoxy(C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)haloalkoxy,

(C_1-C_6)haloalkoxy(C_1-C_6)alkyl,

(C_3-C_{10})cycloalkyl,

aryl, heteroaryl and (C_3-C_6)heterocycloalkyl,

each of which cycloalkyl, aryl, heteroaryl and heterocycloalkyl

is in its turn optionally and independently substituted with one or more groups selected from

halogen,

-OH,

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6)alkoxy,

(C_1-C_6)alkoxy(C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)haloalkoxy,

$-(CH_2)_mNR_4R_5$,

$-O-(CH_2)_mNR_4R_5$,

alkanoyl,

aryl, heteroaryl, cycloalkyl,

aryl-(C_1-C_6)alkyl,

(C_3-C_6)heterocycloalkyl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl,

each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is still further optionally substituted by one or more group selected independently from halogen, -OH, (C_1-C_8)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl;

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

R_4 and R_5, the same or different, are selected from the group consisting of

-H,

(C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)hydroxyalkyl,

(C_3-C_6)heterocycloalkyl;

R_6 and R7 are independently selected from the group consisting of -H, (C_1-C_6)alkyl;

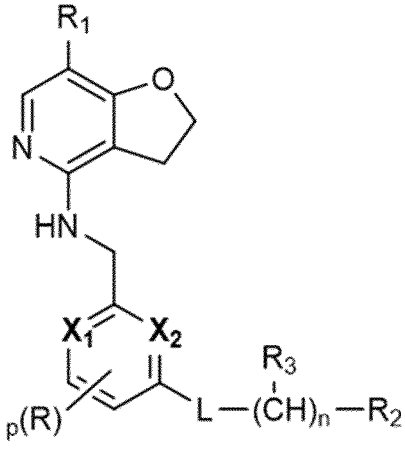
single enantiomers, diastereoisomers and mixtures thereof in any proportion and/or pharmaceutically acceptable salts and solvates thereof.

In a preferred embodiment the invention is directed to a compound of formula (I) wherein X_3 and X_4 are all CH groups and X_1 or X_2 are in the alternative independently a CH group or a nitrogen atom ;

R_1 is pyrazol-4-yl;

all the other variables being as defined above.

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



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Particularly preferred are compound of formula (I) as above defined,

wherein X_1 , X_2, X_3 , X_4 are all CH group;

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

R_1 is pyrazolyl, preferably pyrazol-4-yl;

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

n is 0 (i.e. R_3 is absent);

R_2 is in each occurrence independently selected from the group consisting of

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6)alkoxy(C_1-C_6)alkyl,

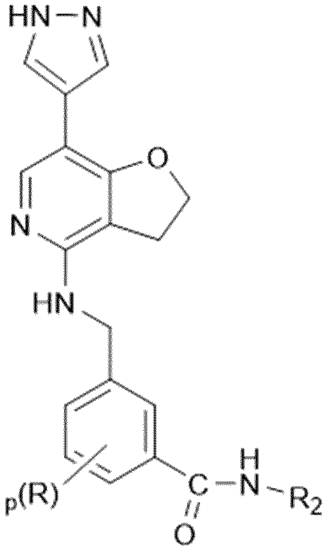
(C_1-C_6)haloalkyl,

(C_1-C_6)haloalkoxy (C_1-C_6)alkyl;

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 (Ib)



Ib

In another preferred embodiment the invention is directed to a compound of formula (I) wherein **X_1, X_2, X_3** and **X_4** are all CH;

p is zero or an integer from 1 to 4;

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

R_1 is pyrazolyl, preferably pyrazol-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;

R_3 when present is H, and

R_2 is selected from the group consisting of

aryl, heteroaryl and (C_3-C_6)heterocycloalkyl,

each of which aryl, heteroaryl and heterocycloalkyl

is in its turn optionally and independently substituted with one or more groups selected from

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6) alkoxy,

(C_1-C_6) alkoxy (C_1-C_6)alkyl,

$-(CH_2)_mNR_4R_5$,

$-O-(CH_2)_mNR_4R_5$,

aryl, heteroaryl, cycloalkyl,

aryl-(C_1-C_6)alkyl,

(C_3-C_6)heterocycloalkyl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl,

each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is still further optionally substituted by one or more group selected independently from halogen, -OH, (C_1-C_8)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl;

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

R_4 and R_5, the same or different, are selected from the group consisting of

-H,

(C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)hydroxyalkyl,

(C_3-C_6)heterocycloalkyl;

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

Particularly preferred in this last embodiment is a compound wherein R_2 is selected from (pyridinyl)methyl, (pyridinyl)ethyl, methoxypyridinyl, ((dimethylamino)ethoxy)pyridinyl, or from 1-(2-(dimethylamino)ethyl)-1H-indazole-5-yl, 1-(2-morpholinoethyl)-1H-indazole-5-yl, 1-(1-methylpiperidin-4-yl)-1H-indazole-5-yl;

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**
43	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxamide

44	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(1-methylpiperidin-4-yl)-1H-indazole-5-carboxamide
46	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-morpholinoethyl)-1H-indazole-5-carboxamide
17	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-4-yl)ethyl)benzamide
22	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-3-yl)ethyl)benzamide
31	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methoxypyridin-2-yl)benzamide
53	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-4-ylmethyl)benzamide
57	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-(2-(dimethylamino)ethoxy)pyridin-2-yl)benzamide

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

X_1, X_2, X_3 and **X_4** are all CH;

p is zero or 1;

each R, when present, is F;

R_1 is pyrazol 4-yl;

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

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

R_2 and R_3 are in each occurrence independently selected from the group consisting of

-H,

(C_1-C_6)alkyl which is methyl,

(C_1-C_6) alkoxy (C_1-C_6)alkyl which is 2-methoxyethyl,

(C_1-C_6)haloalkyl which is 3-fluoropropyl,

(C_3-C_{10})cycloalkyl which is cyclopropyl, cyclobutyl,

aryl which is phenyl;

heteroaryl which is pyridinyl, pyrazolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrimidinyl, 1,2,5-oxadiazol-3-yl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl, 1,2,3,4-tetrahydroisoquinoline-6yl, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 1H-indole-5yl, isoindolin-yl, 1H-indazole-5yl;

and

(C_3-C_6)heterocycloalkyl which is piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydro-2H-pyran-yl;

each of which cycloalkyl, aryl, heteroaryl and heterocycloalkyl

is in its turn optionally and independently substituted with one or more groups selected from

halogen which is Fluoro;

(C_1-C_6)alkyl which is methyl;

(C_1-C_6)hydroxyalkyl, which is hydroxyethyl;

(C_1-C_6) alkoxy, which is methoxy;

-$(CH_2)_mNR_4R_5$ which is (dimethylamino)methyl, 2-(dimethylamino)ethyl, dimethylamino wherein R_4 and R_5 are methyl and m is 0, 1or 2, oxetan-3-ylamino wherein R_4 is H, R_5 is oxetanyl and m is 0;

-O-$(CH_2)_mNR_4R_5$ which is ((dimethylamino)ethoxy)pyridinyl;

cycloalkyl which is cyclopropyl,

aryl-(C_1-C_6)alkyl, which is benzyl, phenethyl,

(C_3-C_6)heterocycloalkyl, which is oxetan-3-yl, piperidin-4-yl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl, which is morpholinoethyl, pyrrolidin-1-ylmethyl,

each of said heterocycloalkyl is still further optionally substituted by (C_1-C_8)alkyl which is methyl;

R_6 is -H, or methyl; and R_7 is -H

single enantiomers, diastereoisomers and mixtures thereof in any proportion and/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 carrier or excipient, either alone or in combination with one or more further active ingredient as detailed below.

According to specific embodiments, the invention provides the compounds listed in the table below single enantiomers, diastereoisomers and mixtures thereof in any proportion and/or pharmaceutically acceptable salts and solvates thereof.

Ex No.	Chemical Name
1	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-cyclopropylpiperidin-4-yl)benzamide
2	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)benzamide
3	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-fluoropropyl)benzamide
4	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-2-ylmethyl)benzamide
5	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(cyclopropylmethyl)benzamide
6	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5,5-dimethyltetrahydrofuran-3-yl)benzamide
7	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-methoxyethyl)benzamide
8	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((1-methyl-1H-imidazol-4-yl)methyl)benzamide
9	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyrimidin-5-ylmethyl)benzamide
10	N-((1,2,5-oxadiazol-3-yl)methyl)-3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide
11	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide
12	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3,3-difluorocyclobutyl)benzamide
13	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(isoxazol-3-ylmethyl)benzamide
14	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(thiazol-4-ylmethyl)benzamide
15	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)benzamide
16	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(1-methylpiperidin-4-yl)ethyl)benzamide
17	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-4-yl)ethyl)benzamide
18	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)phenyl)benzamide
19	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)benzyl)benzamide
20	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-morpholinoethyl)benzamide
21	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)benzamide
22	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-3-yl)ethyl)benzamide

Ex No.	Chemical Name
23	(S)-3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-hydroxy-1-phenylethyl)benzamide
24	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(4-((dimethylamino)methyl)benzyl)benzamide
25	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methylthiophen-2-yl)methyl)benzamide
26	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-phenethylpiperidin-4-yl)benzamide
27	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)benzamide
28	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(1-(oxetan-3-yl)piperidin-4-yl)ethyl)benzamide
29	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)methyl)benzamide
30	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((2-methylisoindolin-5-yl)methyl)benzamide
31	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methoxypyridin-2-yl)benzamide
32	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyrimidin-4-yl)benzamide
33	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(dimethylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide
34	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(oxetan-3-ylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide
35	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-4-((dimethylamino)methyl)benzamide
36	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxamide
37	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
38	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide
39	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-5-carboxamide
40	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide
41	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-3-carboxamide
42	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-4-carboxamide

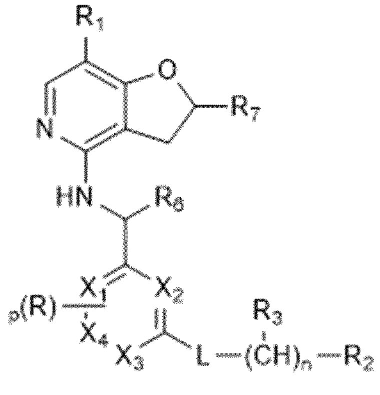
Ex No.	Chemical Name
43	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxamide
44	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(1-methylpiperidin-4-yl)-1H-indazole-5-carboxamide
45	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide
46	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-morpholinoethyl)-1H-indazole-5-carboxamide
47	N-(5-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide
48	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(pyrrolidin-1-ylmethyl)thiazole-2-carboxamide
49	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-3-((dimethylamino)methyl)benzamide
50	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-phenylacetamide
51	N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide
52	N-(3-(1-((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)ethyl)phenyl)acetamide
53	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-4-ylmethyl)benzamide
54	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-benzylpiperidin-4-yl)benzamide
55	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (Enantiomer 1)
56	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (Enantiomer 2)
57	3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-(2-(dimethylamino)ethoxy)pyridin-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 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.

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 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 PG_1) can be C_1-C_4 esters (PG_1: methyl, isopropyl, tert-butyl or ethyl), preferably methyl. A suitable protective group for intermediates requiring the amino group protection (herein reported as PG_2) can be carbamates such as tert-butylcarbamate (PG_2: tert-butoxycarbonyl or Boc), benzylcarbamate (PG_2: Benzyloxycarbonyl or Cbz), ethylcarbamate (PG_2: ethoxycarbonyl) or methylcarbamate (PG_2: methoxycarbonyl), preferably PG_2 is Boc. A suitable protective group PG_3 for intermediates requiring ring NH protection of five membered heterocycles can be a THP (2-tetrahydrofuranyl) or Boc.

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.



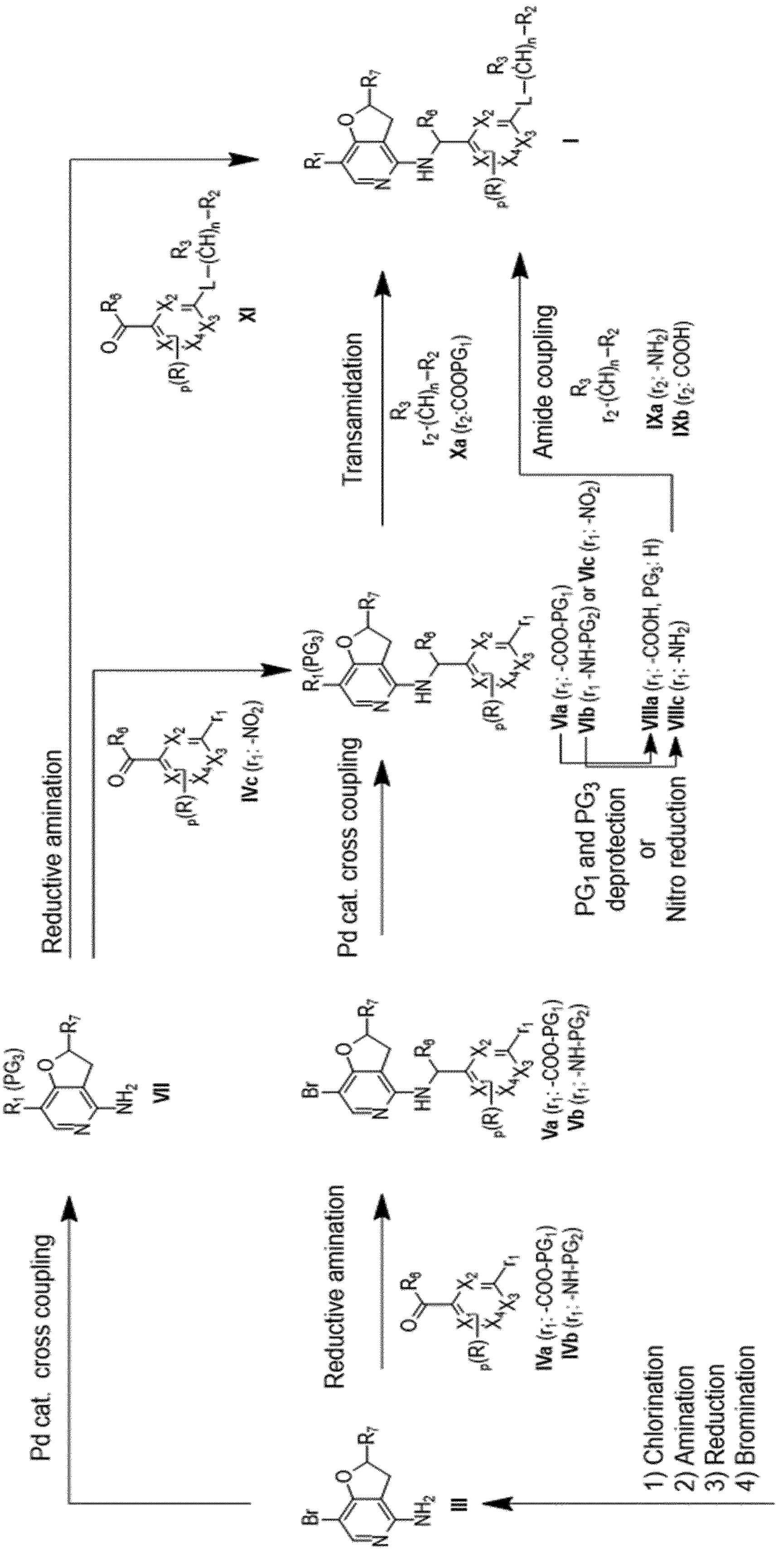
I

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 diastereoisomeric 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.

Examples 1 to 32, 35 to 48, 51 to 52 can be prepared according to *scheme 1* providing at least one non-limiting synthetic route for examples of the invention.

SCHEME 1


II
1) Chlorination
2) Amination
3) Reduction
4) Bromination
III
Pd cat. cross coupling
VII
Reductive amination
IVa (r1: -COO-PG1)
IVb (r1: -NH-PG2)
Va (r1: -COO-PG1)
Vb (r1: -NH-PG2)
Pd cat. cross coupling
Reductive amination
IVc (r1: -NO2)
VIa (r1: -COO-PG1)
VIb (r1: -NH-PG2) or VIc (r1: -NO2)
PG1 and PG3 deprotection
or
Nitro reduction
VIIIa (r1: -COOH, PG3: H)
VIIIc (r1: -NH2)
Transamidation
Xa (r2: COOPG1)
Amide coupling
IXa (r2: -NH2)
IXb (r2: COOH)
XI
I

Intermediate **II** can be converted into intermediate **III** by means of four consecutive 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 $POCl_3$ or $SOCl_2$.

The amination step can be carried out by introducing a masked ammonia such as benzophenone imine through a Buchwald type palladium catalyzed reaction using, for example, tris(dibenzylideneacetone)dipalladium(0)/BINAP catalytic system followed by reaction of the linked benzophenone imine with hydroxylamine to give the corresponding furo[3,2-c]pyridin-4-amine. 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 hydrogenating a solution of the furo[3,2-c]pyridin-4-amine in MeOH / acetic acid in the presence of a Pd/C catalyst under high H_2 pressure (e.g. 10 bar) and at a temperature of 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 for a few hours at low temperature (e.g. -10 – 0 °C).

Intermediate **III** and carbonyl intermediate **IVa** (or **IVb**) can be combined to give intermediate **Va** (or **Vb**) 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 acid.

Intermediate **Va** can be converted into intermediate **VIa** by a direct introduction of group R_1 through a metal catalyzed cross coupling reaction such as Suzuki coupling, Stille coupling or similar (Strategic application of named reactions in organic synthesis, L. Kurti, B. Czako, Ed. 2005). For example, a Suzuki coupling can be performed by reacting intermediate **Va** with the corresponding boronic acid or boron pinacolate ester of group R_1 (in some cases R_1 contains a ring NH moiety that needs to be masked to reduce reactivity or for synthetic convenience, it can be opportunely protected with a PG_3 group such as THP or Boc), in the presence of a Pd catalyst such as tris(dibenzylideneacetone)dipalladium(0), $PdCl_2(dppf)_2$.DCM adduct or tetrakistriphenylphosphinepalladium(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.

Intermediate **VIc** can be prepared from intermediate **VII** and **IVc** by reductive amination using a similar method to that described for the transformation of intermediate **III** into **Va**. Intermediate **VII** can be obtained from intermediate **III** using a similar process to that described above for transformation of intermediate **Va** into intermediate **VIa**.

Removal of PG_1 (when PG_1 is methyl) from intermediate **VIa** to give intermediate **VIIIa** (PG_3 is H) may be carried out by acidic or basic hydrolysis. For example, acidic hydrolysis of PG_1 (when PG_1 is methyl) can be carried out by heating (up to 100°C) **VIa** with a concentrated aqueous acid such as hydrochloric acid or sulfuric acid (if PG_3 is present, it is removed concurrently in the same reaction conditions).

Intermediate **VIc** can be converted into intermediate **VIIIc** by reduction of the nitro group by using a reducing system such as catalytic hydrogenation, redox with Fe/Sn in acidic condition or using hydrides. When PG_3 is THP, reduction of **VIc** to **VIIIc** is performed by catalytic hydrogenation with Pd/C in MeOH in order to retain the NH protecting group.

In another embodiment of the present invention intermediate **VIIIc** can be prepared reacting intermediate **Vb** as done for Va leading to intermediate **VIb** that can be easily converted into **VIIIc** by mean of a simple removal of the protecting group PG2 on the amine.

Reaction between acid intermediate **VIIIa** (PG_3 is H) and amino intermediate **IXa** (or alternatively acid **IXb** with amine **VIIIc**) to give a compound of formula **I** may be carried out under suitable amide coupling reaction conditions. For example, acid intermediate **VIIIa** may be reacted in the presence of an activating agent such as TBTU, HATU or COMU, with an organic base such as DIPEA or TEA, in a suitable organic solvent such as DCM or DMF, and at temperature generally around RT for a time ranging from a few hours to overnight. An alternative amide coupling condition that may be considered involves the reaction of intermediate **VIIIa** and **IXa** in the presence of 1-(methylsulfonyl)-1H-benzotriazole as a coupling agent, with an organic base such as TEA, at temperature up to 150°C for a few hours (for example 4 h). Wherein a compound of formula **I** contains in R_2 or R_3 a primary or secondary amine, this amino moiety needs to be masked during the amide coupling step by using suitably protected (generally Boc) intermediates **IXa** or **IXb**.

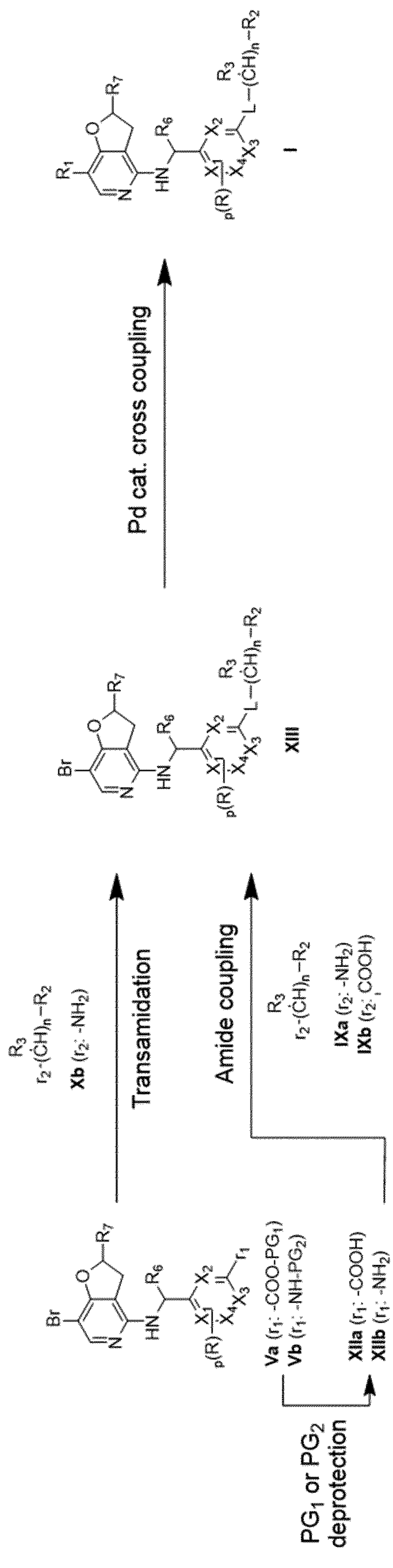
In another approach, a compound of formula **I** (wherein L is -NHC(O)-) can be synthesized from amino intermediate **VIIIc** and methyl ester intermediate **Xa** by means of a transamidation reaction. For example, this reaction can be carried out by reacting a methyl ester intermediate and an amino intermediate in a suitable organic solvent such as THF or DCM, in the presence of a suitable Lewis acid such as bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct or $InCl_3$ at temperatures up to 120°C.

In a different approach, a compound of formula **I** can be prepared from intermediate **VII** and intermediate **XI** by means of reductive amination using similar conditions to those described for the transformation of intermediate **III** into intermediate **Va**.

Wherein for convenience the PG_3 group (i.e. THP) on R_1 was kept throughout the synthetic sequence, it can be easily removed by heating (up to 100°C) the protected precursor with concentrated aqueous acid such as hydrochloric acid or sulfuric acid for a time up to 1 h or less.

In another approach, a compound of formula (**I**) can be prepared according to *scheme 2* providing at least one synthetic route for examples 49-50, 53-54 and 57.

SCHEME 2


Va (r1: -COO-PG1)
Vb (r1: -NH-PG2)
PG1 or PG2 deprotection
XIIa (r1: -COOH)
XIIb (r1: -NH2)
Xb (r2: -NH2)
Transamidation
Amide coupling
IXa (r2: -NH2)
IXb (r2: COOH)
XIII
Pd cat. cross coupling
I

Compounds of formula **I** can be obtained from intermediate **XIII** by a direct introduction of group R_1 through a metal catalyzed cross coupling reaction such as Suzuki coupling, Stille coupling or similar (Strategic application of named reactions in organic synthesis, L. Kurti, B. Czako, Ed. 2005) in the same way (*scheme 1*) as that described for transformation of intermediate **Va** into **VIa**. Wherein for synthetic convenience R_1 boronic acid or pinacolate needs to be protected with a PG_3 group (i.e. THP or Boc), PG_3 can be easily removed by heating (up to 100°C) the protected precursor with concentrated aqueous acid such as hydrochloric acid or sulfuric acid for a time up to 1 h or less.

Intermediate **XIII** can be obtained by an amide coupling between acid intermediate **XIIa** and amino intermediate **IXa** (or acid **IXb** and amine **XIIb**) using similar conditions to those described above (scheme 1) for the reaction of **VIIIa** and intermediate **IXa**. Intermediate **XIIa** and **XIIb** can be obtained from **Va** and **Vb** (described in *scheme 1*) by deprotection of PG_1 or PG_2, respectively.

Deprotection of PG_1 can be performed by basic or acid hydrolysis. Basic hydrolysis of **Va** (when PG_1 is Me or iPr) to give **XIIa** can be performed by means of 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.

Removal of PG_2 (when PG_2 is a Boc group) from intermediate **Vb** (for conveninency of description the preparation of **Vb** is reported into Scheme 1) to give the intermediate **XIIb** can be carried out by acidic deprotection. For example, an acidic Boc cleavage can be carried out by treatment with concentrated hydrochloric acid or trifluoroacetic acid.

Intermediate **XIII** (wherein L is -C(O)NH-) can be alternatively obtained from ester intermediate **Va** and amine intermediate **Xb** by a transamidation reaction in a similar manner (scheme 1) to that described for the reaction of intermediate **VIIIc** and amino intermediate **Xa**.

Where for convenience the PG_3 group (i.e. THP) on R_1 was kept throughout the synthetic sequence, it can be easily removed by heating (up to 100°C) the protected precursor with concentrated aqueous acid such as hydrochloric acid or sulfuric acid for a time up to 1 h or less.

Wherein a compound of formula **I** contains in R_2/R_3 a secondary or tertiary amine, or an amide, such compounds can be obtained by further elaboration of a compound of formula **I** (wherein R_2/R_3 contain a primary or secondary amine) by a reductive amination reaction or an amidation using generally accepted methods. Examples 33 and 34 were prepared by elaboration of a precursor of formula **I** containing a primary or secondary amine in R_2/R_3.

As herein described in details, the 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 enzymes mechanisms, 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 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 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 enzymes mechanisms.

In one embodiment, the disorders that can be treated by the compounds of the present invention include glaucoma, inflammatory bowel disease (IBD) 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 idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

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 injected, for example, 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.

Optimisation of drugs for inhaled delivery need certain characteristics that allow administered compound 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 absorpion, one or more features of the compounds need to be optimized such as, and not limited to, minimizing membrane permeability, reducing dissolution rate or introducing a degree of basicity into the compound to enhance binding to the phospholipid-rich lung tissue or through lysosomial trapping. In some embodiments, compounds of invention show one or more of the features above that are desirable for an inhaled compound.

Other preferred compounds of the invention exhibit profile suitable for oral route administration.

Optimization of drugs for oral delivery need certain characteristics that allow orally administered compound to be absorbed by 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 bioavalability, one or more features of the compounds need to be optimized such as, and not limited to, maximizing membrane permeability and reducing metabolic hot spots (optimizing in-vitro clearance). In some embodiments, compounds of 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 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, idiopathic pulmonary fibrosis (IPF).

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 treatment of pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).

The compounds of the invention , regardless of the route of administration and desease to be treated, 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 active ingredients) with other pharmaceutical active ingredients selected from organic nitrates and NO donors; inhaled NO; stimulator of soluble guanylate cyclase (sGC); prostaciclin 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 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, 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 agents such as recombinant human deoxyribonuclease I (rhDNase); agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroylase 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; stimulator 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 mucolyticsinhibitors 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 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.

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 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 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.

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.

Purification by 'chromatography' or 'flash chromatography' refers to purification using the Biotage SPl 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' and 'C18-silica' are specified, they refer respectively to aminopropyl chain bonded silica and 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.

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

LCMS Methods

Method 1

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	CSH C18 1.7µm, 50 × 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	1.0 mL/min		
Gradient Program	Time (min)	% 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	Waters Acquity Classic + 996 PDA detector + Waters ZMD Mass Spectrometer		
Column	CSH C18 1.7µm, 50 × 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 (min)	% A	%B
	0.0	97	3
	0.15	97	3
	2.3	1	99
	2.4	1	99
	2.5	97	3
Detectors	UV, diode array 190-400nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 3

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	0.1% Formic acid in acetonitrile (v/v)		
Flow	0.4mL/min		
Gradient Program	Time (min)	% 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 4

<table>
<tr><td>Instrumentation</td><td colspan="3">UPLC + Waters DAD + Waters SQD2, single quadrupole UPLC-MS</td></tr>
<tr><td>Column</td><td colspan="3">BEH Shield RP18 1.7µm 100 x 2.1mm. (Plus guard cartridge), maintained at 40°C</td></tr>
<tr><td>Mobile Phase A</td><td colspan="3">Aqueous 10mM ammonium hydrogen carbonate</td></tr>
<tr><td>Mobile Phase B</td><td colspan="3">Acetonitrile</td></tr>
<tr><td>Flow</td><td colspan="3">0.4mL/min</td></tr>
<tr><td rowspan="7">Gradient Program</td><td>Time (min)</td><td>% A</td><td>%B</td></tr>
<tr><td>0.0</td><td>95</td><td>05</td></tr>
<tr><td>0.4</td><td>95</td><td>05</td></tr>
<tr><td>6.0</td><td>05</td><td>95</td></tr>
<tr><td>6.8</td><td>05</td><td>95</td></tr>
<tr><td>7.0</td><td>95</td><td>05</td></tr>
<tr><td>8.0</td><td>95</td><td>05</td></tr>
<tr><td rowspan="2">Detectors</td><td colspan="3">UV, diode array 210nm-400nm</td></tr>
<tr><td colspan="3">MS ionisation method - Electrospray (positive/negative ion)</td></tr>
</table>

Method 5

<table>
<tr><td>Instrumentation</td><td colspan="3">Acquity i-Class (quarternary pump/PDA detector) + Quattro Micro Mass Spectrometer</td></tr>
<tr><td>Column</td><td colspan="3">BEH C18 1.7µm, 100 × 2.1mm, maintained at 40°C</td></tr>
<tr><td>Mobile Phase A</td><td colspan="3">0.1% Formic acid in water (v/v)</td></tr>
<tr><td>Mobile Phase B</td><td colspan="3">0.1% Formic acid in acetonitrile (v/v)</td></tr>
<tr><td>Flow</td><td colspan="3">0.4mL/min</td></tr>
<tr><td rowspan="7">Gradient Program</td><td>Time (min)</td><td>% A</td><td>%B</td></tr>
<tr><td>0.0</td><td>95</td><td>05</td></tr>
<tr><td>0.4</td><td>95</td><td>05</td></tr>
<tr><td>6.0</td><td>05</td><td>95</td></tr>
<tr><td>6.8</td><td>05</td><td>95</td></tr>
<tr><td>7.0</td><td>95</td><td>05</td></tr>
<tr><td>8.0</td><td>95</td><td>05</td></tr>
<tr><td rowspan="2">Detectors</td><td colspan="3">UV, diode array 200-500nm</td></tr>
<tr><td colspan="3">MS ionisation method - Electrospray (positive/negative ion)</td></tr>
</table>

Method 6

<table>
<tr><td>Instrumentation</td><td colspan="3">Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer</td></tr>
<tr><td>Column</td><td colspan="3">CSH C18 1.7µm, 50 × 2.1mm, at 40°C</td></tr>
<tr><td>Mobile Phase A</td><td colspan="3">0.05% Formic acid (v/v) in 95/5 water/acetonitrile</td></tr>
<tr><td>Mobile Phase B</td><td colspan="3">0.05% Formic acid (v/v) in 5/95 water/acetonitrile</td></tr>
<tr><td>Flow</td><td colspan="3">1.0 mL/min</td></tr>
<tr><td rowspan="6">Gradient Program</td><td>Time (min)</td><td>% A</td><td>%B</td></tr>
<tr><td>0.0</td><td>95</td><td>05</td></tr>
<tr><td>1.50</td><td>05</td><td>95</td></tr>
<tr><td>1.90</td><td>05</td><td>95</td></tr>
<tr><td>2.0</td><td>05</td><td>95</td></tr>
<tr><td>2.3</td><td>05</td><td>95</td></tr>
<tr><td rowspan="2">Detectors</td><td colspan="3">UV, diode array 200-500nm</td></tr>
<tr><td colspan="3">MS ionisation method - Electrospray (positive/negative ion)</td></tr>
</table>

Method 7 and Method 8

<table>
<tr><td>Instrumentation</td><td colspan="3">Shimadzu LCMS-2020 Single Quadrupole Liquid Chromatograph Mass Spectromete</td></tr>
<tr><td>Column</td><td colspan="3">Aquity HSS C18 1.8µm, 50 × 2.1mm, at 25°C</td></tr>
<tr><td>Mobile Phase A</td><td colspan="3">0.1% Formic acid (v/v) in water</td></tr>
<tr><td>Mobile Phase B</td><td colspan="3">0.1% Formic acid (v/v) in acetonitrile</td></tr>
<tr><td>Flow</td><td colspan="3">0.5 mL/min</td></tr>
<tr><td rowspan="6">Gradient Program</td><td>Time (min)</td><td>% A</td><td>%B</td></tr>
<tr><td>0.00</td><td>95</td><td>05</td></tr>
<tr><td>4.00</td><td>05</td><td>95</td></tr>
<tr><td>5.00</td><td>05</td><td>95</td></tr>
<tr><td>5.20</td><td>95</td><td>05</td></tr>
<tr><td>6.00</td><td>95</td><td>05</td></tr>
<tr><td rowspan="2">Detectors</td><td colspan="3">UV, 254 nm and 214 nm (method 13)
UV, 254 nm and 220 nm (method 14)</td></tr>
<tr><td colspan="3">MS ionisation method - Electrospray (positive/negative ion)</td></tr>
</table>

Method 9

Instrumentation	Shimadzu LCMS-2020 Single Quadrupole Liquid Chromatograph Mass Spectrometer		
Column	Aquity HSS C18 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 (min)	% 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 10

Instrumentation	Agilent Technologies 1260 Infinity II with DAD detector / Agilent Technologies InfinityLab LC/MSD		
Column	BEH C18 1.7µm, 50 × 2.1mm, at 25°C		
Mobile Phase A	0.05% Aqueous ammonium hydroxide (v/v)		
Mobile Phase B	acetonitrile		
Flow	0.5 mL/min		
Gradient Program	Time (min)	% 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 11

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	CSH C18 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 (min)	% A	%B
	0.0	95	05
	3.50	05	95
	3.90	05	95
	4.00	05	95
	4.3	05	95
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 12

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	BEH C18 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 (min)	% 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 13

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	CSH C18 1.7µm, 50 × 2.1mm, at 50°C		
Mobile Phase A	Aqueous ammonmium formate (25mM) pH 3		
Mobile Phase B	0.1% Formic acid in acetonitrile		
Flow	0.35 mL/min		
Gradient Program	Time (min)	% A	%B
	0.00	99	01
	0.50	99	01
	3.00	70	30
	6.50	50	50
	7.50	20	80
	8.10	99	01
	10.00	99	01
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 14

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	Kinetex C8 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 in (v/v) 5/95 water/acetonitrile		
Flow	1.0 mL/min		
Gradient Program	Time (min)	% 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 15

Instrumentation	Acquity UPLC (binary pump/PDA detector) + QDa Mass Spectrometer		
Column	Kinetex C8 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 (min)	% A	%B
	0.0	95	05
	3.50	05	95
	3.90	05	95
	4.00	05	95
	4.3	05	95
Detectors	UV, diode array 200-500nm		
	MS ionisation method - Electrospray (positive/negative ion)		

Method 16

Instrumentation	Acquity H-Class (quaternary pump/PDA detector) + QDa Mass Spectrometer		
Column	Acquity BEH C18 1.7µm, 50 × 2.1mm at 40°C		
Mobile Phase A	0.03% Aqueous ammonia (v/v) (7.66mM)		
Mobile Phase B	0.03% ammonia in Acetonitrile (v/v) (7.66mM)		
Flow	0.8 mL/min		
Gradient Program	Time (min)	% A	%B
	0.0	97	3
	1.5	3	97
	2.3	3	97
	2.4	97	3
	2.5	97	3
Detectors	UV, diode array 190-400nm		
	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.

SFC Methods

Where compounds were purified using Supercritical Fluid Chromatography (SFC) either a Waters Thar Prep100 preparative SFC system (P200 CO_2 pump, 2545 modifier pump, 2998 UV/VIS detector, 2767 liquid handler with Stacked Injection Module) or a Waters Thar Investigator semi preparative system (Waters Fluid Delivery Module, 2998 UV/VIS detector, Waters Fraction Collection Module) was used. The compounds were purified using the column and conditions specified and fractions that contained the desired product were concentrated by vacuum centrifugation.

The modifier used under basic conditions was diethyl amine (0.1% V/V). Alternate modifiers such as formic acid (0.1% V/V), acetic acid (0.1% V/V), were used as an acidic modifier.

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.

The stereochemistry of the compounds in the Examples, where indicated, has been assigned on the assumption that absolute configuration at resolved stereogenic centers of starting materials is maintained throughout any subsequent reaction 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.

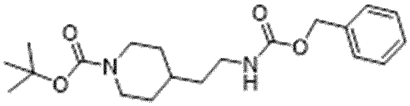
Abbreviations

ACN (acetonitrile), BINAP (2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene), COMU ((1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate), DCM (dichloromethane), DIPEA or DIEA (*N*-Ethyldiisopropylamine), 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-ylmethylene]-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), TBTU (2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate), TFA (Trifluoroacetic acid), THF (Tetrahydrofuran), XPhos Pd G2 Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II).

PREPARATION OF INTERMEDIATES

Intermediate A1

Step A

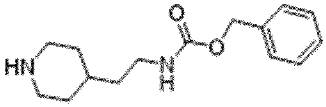


tert-Butyl 4-(2-(((benzyloxy)carbonyl)amino)ethyl)piperidine-1-carboxylate (Intermediate A1-a)

tert-Butyl 4-(2-aminoethyl)piperidine-1-carboxylate (0.3 g, 1.3 mmol) was dissolved in DCM (4.0 mL), then benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.33 g, 1.3 mmol) was added under stirring followed by triethylamine (0.18 mL, 1.3 mmol). The solution was stirred at RT for 3 h. The reaction mixture was diluted with DCM (30 mL) and the organic layer washed with saturated aqueous NH_4Cl (50 mL), then saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated to dryness to give the title compound (0.48g) that was used in the next step without further purification.

LCMS (Method 6): Rt = 1.22 min, m/z 385.1 $[M+Na]^+$

Step B

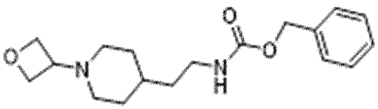


Benzyl (2-(piperidin-4-yl)ethyl)carbamate (Intermediate A1-b)

Intermediate A1-a (0.48 g, 1.313 mmol) was dissolved in a mixture of DCM (15 mL) / TFA (5 mL) at 0°C and the solution stirred at RT for 3 h. The reaction mixture was dried under reduced pressure and the crude purified on an Isolute® SCX-2 cartridge to give the title compound (0.36 g).

LCMS (Method 6): Rt = 0.41 min, m/z 263.0 $[M+H]^+$

Step C



Benzyl (2-(1-(oxetan-3-yl)piperidin-4-yl)ethyl)carbamate (Intermediate A1-c)

Intermediate A1-b (0.20 g, 0.76 mmol) and oxetan-3-one (0.055 g, 0.76 mmol) in

DCM (10 mL) was stirred at RT for 15 min, then sodium triacetoxyborohydride (0.24 g, 1.14 mmol) was added in one portion. The solution was stirred at RT for 4 h, then diluted with DCM, and the organic phase washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, concentrated to dryness and purified through an Isolute® SCX-2 cartridge to give the title compound (0.24 g).

LCMS (Method 6): Rt = 0.43 min, m/z 319.3 $[M+H]^+$

Step D

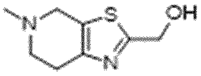
2-(1-(Oxetan-3-yl)piperidin-4-yl)ethan-1-amine (Intermediate A1)

Intermediate A1-c (0.10 g, 0.31 mmol), acetic acid (0.019 g, 0.31 mmol) and Pd/C (0.100 g, 0.942 mmol) in EtOH (5 mL) was degassed under vacuum/H_2 cycles (3 times), then hydrogenated at RT for 4 h. The reaction mixture was filtered and evaporated to dryness to give the title compound (0.058 g) that was used in the next step without further purification.

LCMS (Method 6): Rt = 0.12 min, m/z 185.3 $[M+H]^+$

Intermediate A2

Step A

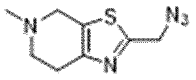


(5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)methanol (Intermediate A2-a)

To a 0°C cooled suspension of 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid hydrochloride (0.2 g, 0.85 mmol) in THF (5 mL), lithium aluminium hydride solution in THF (1.0 mL, 1.00 mmol) was added dropwise and stirring was continued at RT for 1 h. The reaction was quenched by the addition of saturated aqueous Na_2SO_4, the mixture filtered, dried over Na_2SO_4 and concentrated to dryness to give the title compound (0.125 g).

LCMS (Method 6): Rt = 0.13 min, m/z 185.0 $[M+H]^+$

Step B

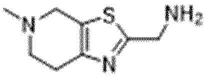


2-(Azidomethyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (Intermediate A2-b)

Intermediate A2-a (0.125 g, 0.68 mmol), diphenyl phosphorazidate (0.146 mL, 0.68 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.101 mL, 0.68 mmol) were dissolved in anhydrous THF (5 mL) and the resulting solution heated at 90°C under microwave irradiation for 1 h. The reaction mixture was evaporated to dryness and purified on NH-silica by elution with 0-10% MeOH in DCM to give the title compound (80 mg).

LCMS (Method 6): Rt = 0.14 min, m/z 210.0 $[M+H]^+$

Step C



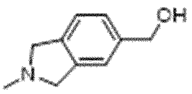
(5-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)methanamine (Intermediate A2)

Intermediate A2-b (0.08 g, 0.38 mmol) was dissolved in a mixture of THF (5 mL) and water (0.5 mL), then triphenylphosphine (0.301 g, 1.15 mmol) was added and the solution was refluxed for 2 h. The mixture was dried under reduced pressure and purified on an Isolute® SCX-2 cartridge to give the title compound (15 mg).

LCMS (Method 6): Rt = 0.10 min, m/z 184.0 $[M+H]^+$

Intermediate A3

Step A

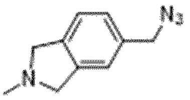


(2-Methylisoindolin-5-yl)methanol (Intermediate A3-a)

Intermediate A3-a was prepared using a procedure similar to that used for the synthesis of intermediate A2-a by replacing 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylic acid hydrochloride of *step a* with methyl 2-methylisoindoline-5-carboxylate.

LCMS (Method 6): Rt = 0.13 min, m/z 164.0 $[M+H]^+$

Step B

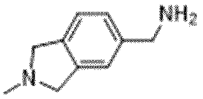


5-(Azidomethyl)-2-methylisoindoline (Intermediate A3-b)

Intermediate A3-b was prepared using a procedure similar to that used for the synthesis of intermediate A2-b by replacing intermediate A2-a of *step b* with intermediate A3-a.

LCMS (Method 6): Rt = 0.20 min, m/z 189.1 $[M+H]^+$

Step C



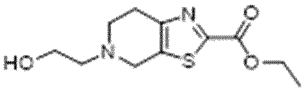
(2-Methylisoindolin-5-yl)methanamine (Intermediate A3)

Intermediate A3 was prepared using a procedure similar to that used for the synthesis of intermediate A2 by replacing intermediate A2-b of *step c* with intermediate A3-b.

LCMS (Method 6): Rt = 0.10 min, m/z 163.0 $[M+H]^+$

Intermediate A4

Step A

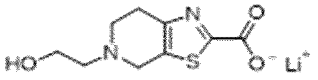


Ethyl 5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (Intermediate A4-a)

Ethyl 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (150 mg, 0.707 mmol) and cesium carbonate (691 mg, 2.120 mmol) were dissolved in acetonitrile (6 mL) and reacted for 10 min before addition of potassium iodide (58.7 mg, 0.353 mmol) and 2-bromoethanol (0.201 mL, 1.413 mmol). The reaction mixture was stirred for 7 h at 75°C, then filtered and evaporated to dryness. The resulting crude material was purified by flash chromatography on NH-silica by eluting with 0-10% MeOH in DCM. Appropriate fractions were evaporated to give the desired product (167 mg).

LCMS (Method 6): Rt = 0.16 min, m/z 257.0 $[M+H]^+$

Step B



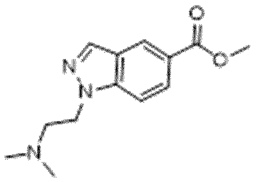
Lithium 5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxylate (Intermediate A4)

Intermediate A4-b was dissolved in THF (2.5 mL) and water (2.5 mL) then lithium hydroxide (78 mg) was added and the mixture stirred for 1 h at RT. The solvent was evaporated under vacuum to give the title compound (265 mg).

LCMS (Method 6): Rt = 0.14 min, m/z 228.8 $[M+H]^+$

Intermediate A5

Step A

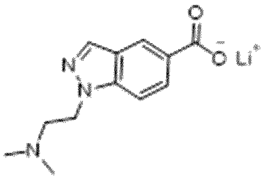


Methyl 1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxylate (Intermediate A5-a)

To a solution of methyl 1H-indazole-5-carboxylate (250 mg, 1.419 mmol) and N,N-dimethylethanolamine (0.289 mL, 2.84 mmol) in toluene (6 mL) was added 2-(trimethylphosphoranylidene)acetonitrile solution 0.5 M in THF (5.68 mL, 2.84 mmol). The reaction mixture was stirred at 110°C for 18 h. The solvent was evaporated under vacuum and then the crude was taken in EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was evaporated under vacuum and purified by flash chromatography on NH-silica by eluting with 1/1 heptane/EtOAc + 1% triethylamine. Appropriate fractions were pooled and dried to give the title compound (249 mg).

LCMS (Method 6): Rt = 0.36 min, m/z 248.2 $[M+H]^+$

Step B

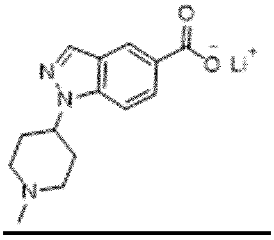


Lithium 1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxylate (Intermediate A5)

Intermediate A5-a (249 mg, 1.01 mmol) was dissolved in MeOH (2.5 mL) and water (2.5 mL) then lithium hydroxide (36.2 mg, 1.510 mmol) was added in one portion and the mixture stirred for 1 h at RT. Solvent was evaporated under vacuum to give the desired product (200 mg) that was used in the next step without further elaboration.

LCMS (Method 6): Rt = 0.16 min, m/z 234.2 $[M+H]^+$

Intermediate A6



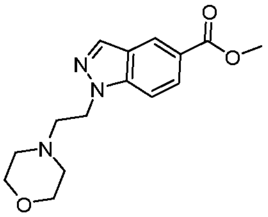
Lithium 1-(1-methylpiperidin-4-yl)-1H-indazole-5-carboxylate (Intermediate A6)

Intermediate A6 was prepared using a procedure similar to that used for the synthesis of intermediate A-5 by replacing N,N-dimethylethanolamine with 1-methylpiperidin-4-ol.

LCMS (Method 6): Rt = 0.39 min, m/z 260.0 $[M+H]^+$

Intermediate A7

Step A



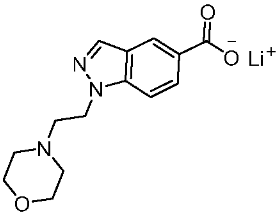
Methyl 1-(2-morpholinoethyl)-1H-indazole-5-carboxylate (Intermediate A7-

a)

Methyl 1H-indazole-5-carboxylate (500 mg, 2.84 mmol) and potassium carbonate (1.18 g, 8.51 mmol) were mixed in DMF (10 mL) and stirred at RT for 20 min, then 4-(2 chloroethyl)morpholine hydrochloride (1.205 mL, 5.68 mmol) was added. The reaction mixture was stirred at 70°C for 24 h. The mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were evaporated under vacuum. The resulting crude material was purified by flash chromatography on NH-silica by eluting with 0-50% EtOAc in hexane. Appropriate fractions were combined and dried to give the desired product (325 mg).

LCMS (Method 6): Rt = 0.38 min, m/z 290.0 $[M+H]^+$

Step B

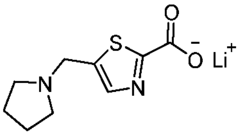


Lithium 1-(2-morpholinoethyl)-1H-indazole-5-carboxylate (Intermediate A7)

Intermediate A7 was prepared from intermediate A7-a using a procedure similar to that used in *step b* for the synthesis of intermediate A5 from intermediate A5-a.

LCMS (Method 6): Rt = 0.21 min, m/z 275.9 $[M+H]^+$

Intermediate A8



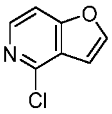
Lithium 5-(pyrrolidin-1-ylmethyl)thiazole-2-carboxylate (Intermediate A8)

Intermediate A8 was prepared using a procedure similar to that used for the synthesis of intermediate A7 by replacing in *step a* respectively the 4-(2-chloroethyl) morpholine hydrochloride with ethyl 5-(bromomethyl)thiazole-2-carboxylate and methyl 1H-indazole-5-carboxylate with pyrrolidine.

LCMS (Method 6): Rt = 0.14 min, m/z 213.0 $[M+H]^+$

Intermediate B

Step A

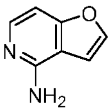


4-Chlorofuro[3,2-c]pyridine (Intermediate B-a)

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 $NaHCO_3$. 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 7): Rt = 2.71 min, m/z 153.9 $[M+H]^+$

Step B

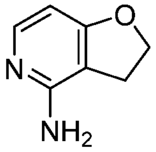


Furo[3,2-c]pyridin-4-amine (Intermediate B-b)

A solution of intermediate B-a (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 8): Rt = 0.83 min, m/z 135.0 $[M+H]^+$

Step C

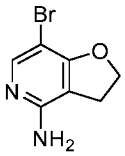


2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate B-c)

Intermediate B-b (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 H_2 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 $NaHCO_3$ 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 Na_2SO_4 and evaporated to afford the title compound (24.57 g).

LCMS (Method 9): Rt = 0.81 min, m/z 137.1 $[M+H]^+$

Step D

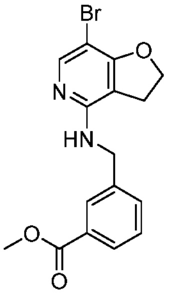


7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate B)

Intermediate B-c (24.57 g, 0.180 mol) was dissolved in ACN (1230 mL) and then a solution of N-bromosuccinimide (35.33 g, 0.198 mol) in ACN (490 mL) was added dropwise over 3 h at -10°C in darkness. The reaction was quenched with aqueous saturated $NaHCO_3$ (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% $KHSO_4$ (300 mL). The solid that appeared was collected by filtration. The biphasic filtrate was partitioned and the organic layer washed twice with aqueous 10% $KHSO_4$ (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 $NaHCO_3$ and extracted with EtOAc (3 x 1000 mL). The combined organic phase was washed with saturated aqueous NaCl (500 mL), dried over anhydrous $MgSO_4$, and concentrated to give the title compound as a solid (27.1 g).

LCMS (Method 10): Rt = 1.69 min, m/z 215.0/217.0 $[M+H]^+$

Intermediate C1



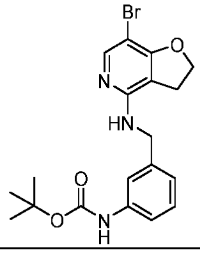
Methyl 3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoate (Intermediate C1)

Intermediate B (15.6 g, 0.074 mol) and methyl 3-formylbenzoate (18.1g, 0.11 mol) were dissolved in anhydrous DCM (470 mL) with molecular sieves and kept under an 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 (31.4g, 0.148 mol) followed by acetic acid (8.5 mL, 0.148 mol) were added and the mixture stirred at RT overnight. The reaction mixture was quenched with methanol and the solvents were evaporated. The residue was dissolved in EtOAc and aqueous saturated $NaHCO_3$ 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 dried over Na_2SO_4 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).

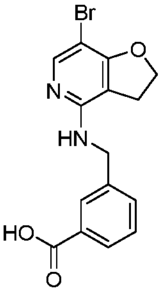
LCMS (Method 6): Rt = 0.85 min, m/z 362.9/364.9 $[M+H]^+$

Intermediate C2

The following intermediate was prepared using a procedure similar to that used for the synthesis of intermediate C1 by replacing methyl 3-formylbenzoate with the starting material given in the table.

	Structure	Starting material	LC-MS
C2		tert-butyl (3-formylphenyl)carbamate	Rt = 0.87 min, m/z 420.2 / 422.4 $[M+H]^+$ (Method 6)

Intermediate D1

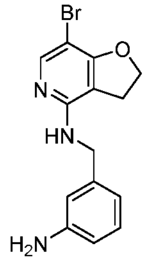


3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (Intermediate D1)

A solution of intermediate C1 (100 mg, 0.27 mmol), lithium hydroxide monohydrate (0.035 g, 0.83 mmol) in THF (1 mL), MeOH (1 mL) and water (2 mL) was stirred at RT for 1.5 h. The resulting mixture was diluted with water and extracted with EtOAc. The pH of the aqueous phase was adjusted to pH ~2-3 with aqueous 1M HCl. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give the product as a solid (89 mg).

LCMS (Method 1): Rt = 0.81 min, m/z 348.9/350.9 $[M+H]^+$

Intermediate D2

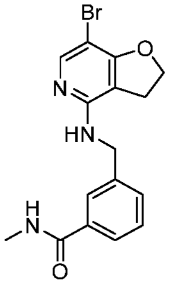


N-(3-Aminobenzyl)-7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate D2)

Intermediate C2 (800 mg) was dissolved in acetonitrile (6 mL) and then added with aqueous HCl 12 M. The solution was stirred at RT and after 1 h a precipitate appeared. The solid was collected by filtration to give the title compound (550 mg).

LCMS (Method 6): Rt = 0.38 min, m/z 320.0/322.0 $[M+H]^+$

Intermediate E1

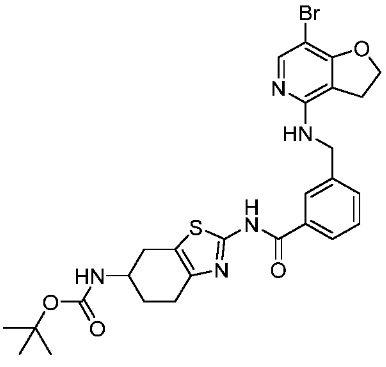


3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-methylbenzamide (Intermediate E1)

A mixture of Intermediate D1 (40 mg, 0.12 mmol), methylamine hydrochloride (23 mg, 0.35 mmol), TBTU (150 mg, 0.46 mmol) and N,N-diisopropylethylamine (0.12 mL, 0.69 mmol) in DCM (4 mL) was stirred at RT for 18 h. The resulting mixture was diluted with water and extracted with DCM. The organic layer was dried over sodium sulphate and evaporated *in vacuo*. The residue, diluted with MeOH, was passed down an Isolute® SCX-2 cartridge eluting with MeOH and then 2M methanolic ammonia. The solution was concentrated in *vacuo* to give the desired product (29 mg).

LCMS (Method 1): Rt = 0.73 min, m/z 362.0/364.0 $[M+H]^+$

Intermediate E2

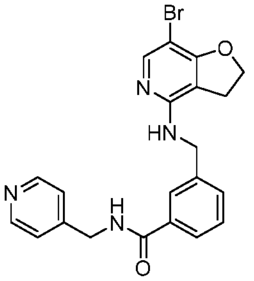


tert-Butyl (2-(3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)-methyl)benzamido)-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)carbamate (Intermediate E2)

Diisopropylethylamine (1.0 mL, 6.0 mmol) was added to a stirred solution of 3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (700 mg, 2.0 mmol), tert-butyl (2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)carbamate (540 mg, 2.0 mmol) and TBTU (837 mg, 2.61 mmol) in DMF (12 mL). The mixture was stirred at RT for 6 h then allowed to stand for 16 h. The mixture was diluted with EtOAc (25 mL) and the solution was washed with water (25 mL). The aqueous phase was extracted with EtOAc (25 mL). The combined organic phase was washed with aqueous saturated NaCl (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was taken into DCM and loaded onto an Isolute® SCX-2 column, washed with DCM then 2:1 DCM:MeOH, after eluted with 2:1 DCM:2M methanolic ammonia and concentrated under reduced pressure. The residue was taken into DCM and purified by flash chromatography on a Si column eluting with 0-50% EtOAc in DCM then with 100% EtOAc to afford the desired product as a fawn foam (775 mg).

LCMS (Method 2): Rt =1.46 min, m/z 600.0/601.9 $[M+H]^+$

Intermediate E3

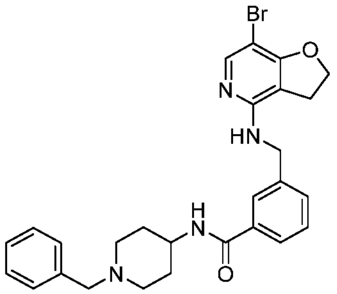


3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-4-ylmethyl)benzamide (Intermediate E3)

Intermediate C1 (250 mg, 0.688 mmol), pyridin-4-ylmethanamine (0.210 mL, 2.065 mmol) and bis(trimethylaluminum) 1,4 diazabicyclo[2.2.2]octane adduct (529 mg, 2.065 mmol) were dissolved in THF (6 mL) and the mixture purged with nitrogen. The resulting mixture was heated under microwave irradiation at 120°C for 30 min. The reaction mixture was quenched with water, extracted with DCM and the organic phase evaporated under vacuum. The resulting crude was purified by flash chromatography on C18-silica by eluting with 0-20% B in A (A: water/acetonitrile 95/5 + 0.1% HCOOH, B: acetonitrile/water 95/5 + 0.1% HCOOH). The appropriate fractions were pooled and evaporated to afford the title compound (164 mg).

LCMS (Method 6): Rt =0.39 min, m/z 439.1/441.1 $[M+H]^+$

Intermediate E4

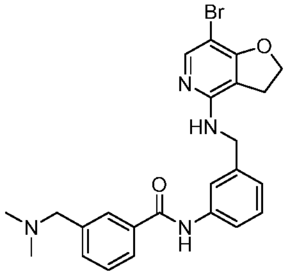


N-(1-Benzylpiperidin-4-yl)-3-(((7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide (Intermediate E4)

Intermediate E4 was prepared using a similar procedure to that previously described for intermediate E3 by replacing pyridin-4-ylmethanamine with 1-benzylpiperidin-4-amine.

LCMS (Method 6): Rt =0.51 min, m/z 521.2/523.1 $[M+H]^+$

Intermediate E5

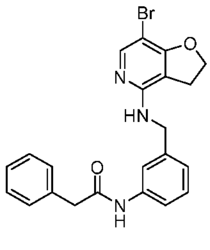


N-(3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-3-((dimethylamino)methyl)benzamide (Intermediate E5)

3-((Dimethylamino)methyl)benzoic acid hydrochloride (98 mg, 0.454 mmol) and COMU (0.133 mL, 0.273 mmol) were dissolved in anhydrous DCM (5 mL) and stirred for 10 min, then intermediate D2 (81mg, 0.23 mmol) and DIEA (0.158 mL, 0.908 mmol) were added and the mixture stirred for 2 h at RT. The reaction mixture was diluted with DCM and the organic phase washed twice with saturated aqueous $NaHCO_3$ and evaporated under vacuum. The crude product was purified by flash chromatography on silica by eluting with 0-30% of 80/20 DCM/MeOH (+ 1% triethylamine) in DCM. Appropriate fractions were combined and evaporated under vacuum to give the desired product (115 mg).

LCMS (Method 6): Rt =0.42 min, m/z 481.0/483.0 $[M+H]^+$

Intermediate E6



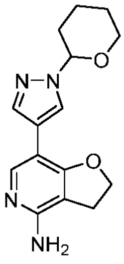
N-(3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-phenylacetamide (Intermediate E6)

2-Phenylacetic acid (112 mg, 0.82 mmol) and COMU (0.240 mg, 0.49 mmol) were dissolved in DCM (4 mL) and reacted for 10 min at RT, then intermediate D2 (150 mg, 0.41mmol) and DIEA (0.143 mL, 0.819 mmol) were added. The reaction was stirred for 2 h at RT. The reaction mixture diluted with DCM, washed twice with saturated aqueous $NaHCO_3$ and evaporated. The resulting crude was purified by flash chromatography on

C18-silica by eluting with 0-10% B in A (A: water/acetonitrile 95/5 + 0.1% HCOOH, B: acetonitrile/water 95/5 + 0.1% HCOOH) to give the desired product (126 mg).

LCMS (Method 6): Rt =0.81 min, m/z 438.0/440.0 $[M+H]^+$

Intermediate F



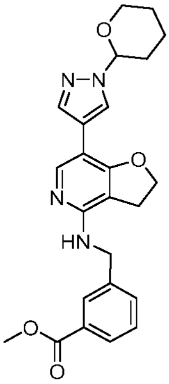
7-(1-(Tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate F)

Intermediate B (1.80 g, 8.4 mmol), 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-boronic acid (3.03 g, 11 mmol), and cesium carbonate (8.18 g, 25 mmol) were mixed in DMF (72 mL) and water (36 mL). The reaction was purged with argon for 10 min, then tetrakis(triphenylphosphine)palladium(0) (0.97 g, 0.8 mmol) was added and the reaction mixture heated at 70°C overnight. The reaction was allowed to cool to RT, diluted with water (72 mL) and extracted with EtOAc (5 x 250 mL). The combined organic layers were washed with saturated aqueous NaCl (505 mL) and concentrated to dryness. The crude was purified on silica by eluting with 0-8% MeOH in DCM to afford the title compound (1.13 g).

LCMS (Method 6): Rt =0.41 min, m/z 287.2 $[M+H]^+$

Intermediate G

Step A

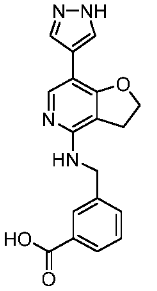


Methyl 3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoate (Intermediate G-a)

Intermediate C1 (0.9 g, 2,478 mmol), 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 mmol) 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 Na_2SO_4 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 6): Rt =0.69 min, m/z 435.3 $[M+H]^+$

Step B



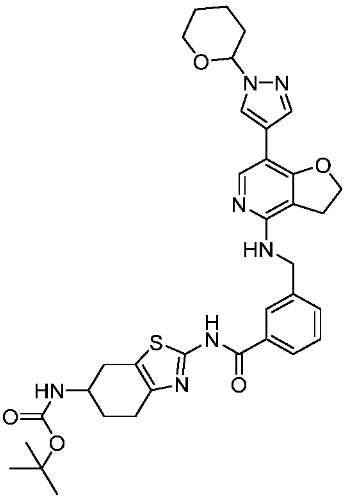
3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzoic acid (Intermediate G)

Intermediate G-a (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 6): Rt =0.46 min, m/z 337.2 $[M+H]^+$

Intermediate H1

Step A

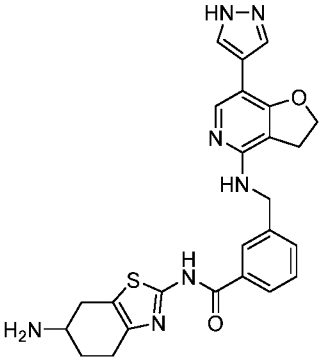


tert-Butyl (2-(3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamido)-4,5,6,7-tetrahydrobenzo[d]-thiazol-6-yl)carbamate (Intermediate H1-a)

Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-diphenyl)]palladium(II) (59 mg, 0.075 mmol) was added to a mixture of intermediate E2 (300 mg 0.5 mmol), potassium phosphate tribasic (318 mg, 1.5 mmol), 1-(tetrahydropyran-2-yl)-1H-pyrazole-4-boronic acid pinacol ester (278 mg, 1.0 mmol) in THF (2.0 mL) and water (2 mL) which had been degassed with argon. The mixture was heated at 80°C for 1 h in a microwave reactor. The cold mixture was diluted with EtOAc (15 mL) and washed with water (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica by eluting sequentially with DCM, 20% EtOAc in DCM, 50% EtOAc in DCM and EtOAc to afford the desired product (307 mg).

LCMS (Method 2): Rt =1.26 min, m/z 672.3 $[M+H]^+$

Step B



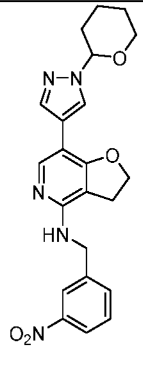
3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (Intermediate H1)

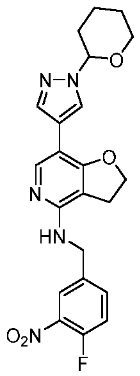
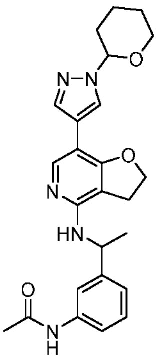
A solution of intermediate H1-a (305 mg, 0.45 mmol), in 1.25M hydrogen chloride solution in MeOH (10 mL), was stirred for 1.25 h, then treated with 12M aqueous hydrochloric acid (2.0 mL). The resulting mixture was stirred for 2.5 h then a further aliquot of 12M aqueous hydrochloric acid (1.0 mL) was added. The mixture was stirred for a further 3 h then concentrated *in vacuo*. The residue was taken into MeOH (30 mL) and the solution was filtered through an Isolute® SCX-2 cartridge. The cartridge was washed with MeOH then eluted with 20% 2M methanolic ammonia in DCM. Concentration of the basic fractions afforded the desired product (150 mg).

LCMS (Method 2): Rt = 0.63 min, m/z 488.0 $[M+H]^+$

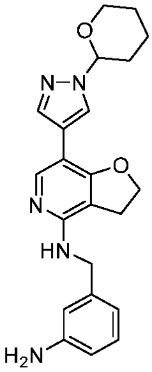
Intermediate I1 to I3

The following intermediates were prepared using a procedure similar to that used for the synthesis of intermediate C1 by replacing respectively intermediate B with intermediate F and methyl 3-formylbenzoate with starting material given into the table.

	Structure	Starting material	LC-MS
I1		3-nitrobenzaldehyde	Rt = 0.44 min, m/z 422.2 $[M+H]^+$ (Method 6)

I2		4-fluoro-3-nitrobenzaldehyde	Rt = 0.63 min, m/z 439.7 $[M+H]^+$ (Method 6)
I3		N-(3-acetylphenyl)acetamide	Rt = 0.56 min, m/z 448.3 $[M+H]^+$ (Method 6)

Intermediate J1

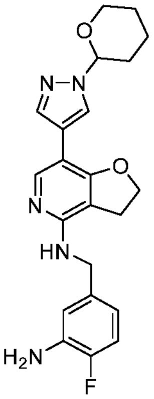


N-(3-Aminobenzyl)-7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate J1)

Intermediate I1 (330 mg, 0.783 mmol) was dissolved in ethanol (7.5 mL) then Pd/C 5% wet (667 mg, 0.313 mmol) was added and the reaction stirred under a blanket of hydrogen for 1 h. The reaction mixture was filtered and the solvent evaporated under vacuum to give the title compound (178 mg) which was used in next steps without further purifications.

LCMS (Method 6): Rt = 0.44 min, m/z 392.0 $[M+H]^+$

Intermediate J2

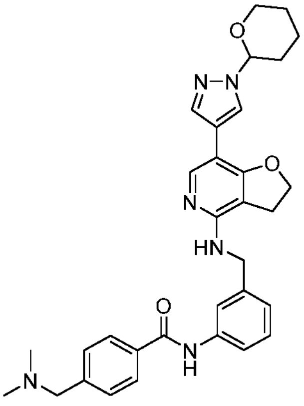


N-(3-Amino-4-fluorobenzyl)-7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate J2)

Intermediate J2 was prepared from intermediate I2 using a procedure similar to that used for the synthesis of intermediate J1 from intermediate I1.

LCMS (Method 6): Rt = 0.55 min, m/z 410.0 $[M+H]^+$

Intermediate K1



4-((Dimethylamino)methyl)-N-(3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)benzamide (Intermediate K1)

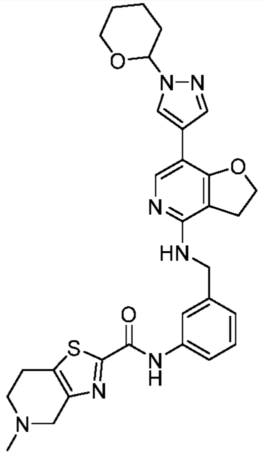
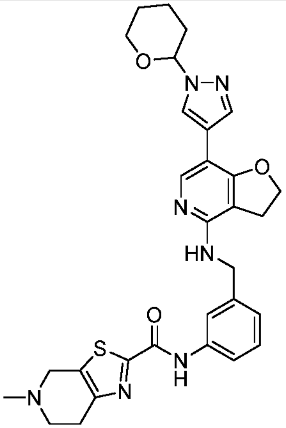
4-((Dimethylamino)methyl)benzoic acid hydrochloride (55.1 mg, 0.26 mmol), DIEA (0.140 mL, 0.51 mmol) and HATU (116 mg, 0.31 mmol) were dissolved in anhydrous DCM (4 mL) and reacted for 10 min, then intermediate J1 (50 mg, 0.128 mmol) was added and the reaction mixture stirred for 1 h at RT. The reaction mixture was diluted with DCM and washed with water (2 x 2.5 mL). The organic layer was dried under vacuum and the residue purified by flash chromatography on NH-silica by eluting with

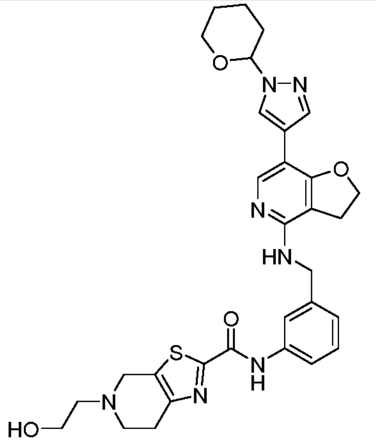
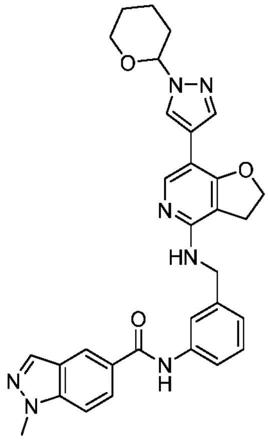
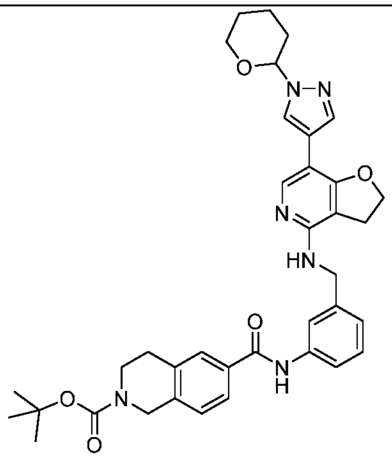
0-10% MeOH in DCM. Appropriate fractions were combined and evaporated under vacuum to give the desired compound (16 mg).

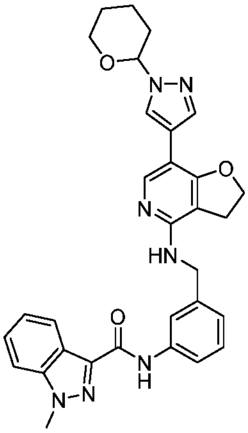
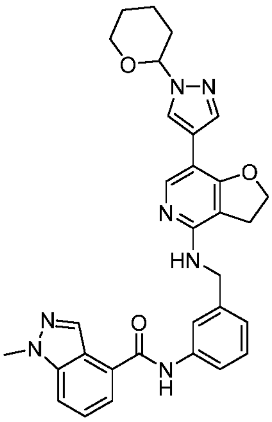
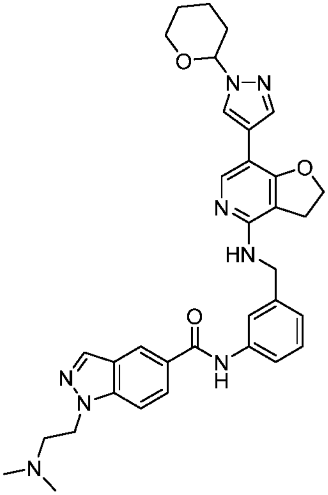
LCMS (Method 6): Rt = 0.41 min, m/z 553.0 $[M+H]^+$

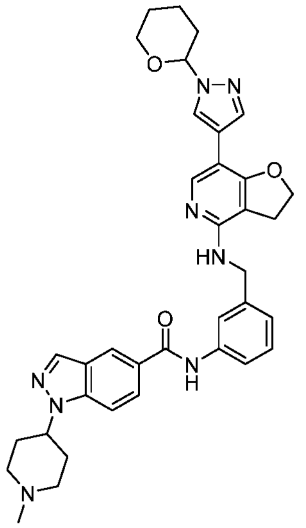
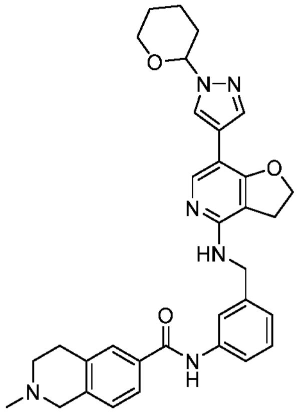
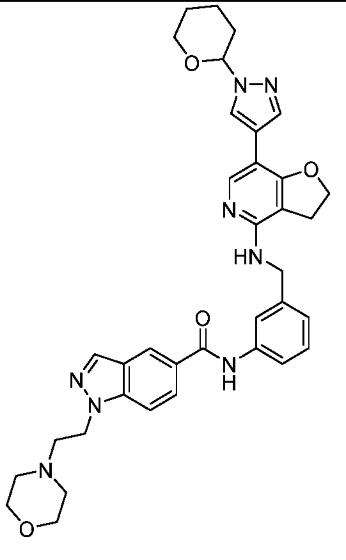
Intermediate K2 to K14

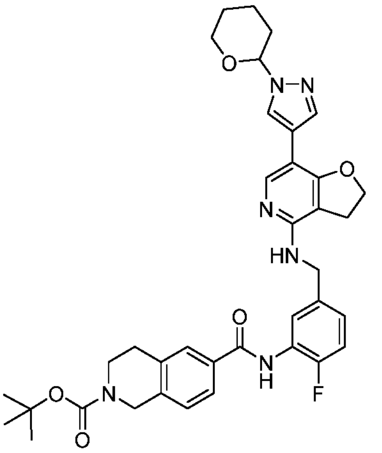
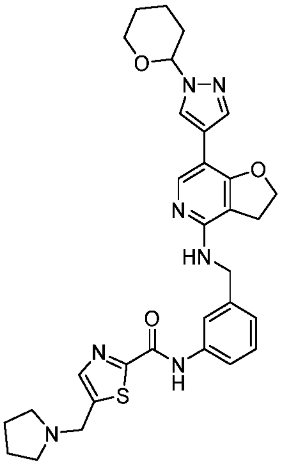
The following intermediates were prepared using a procedure similar to that used for the synthesis of intermediate K1 by replacing intermediate J1 and 4-((dimethylamino)methyl)benzoic acid hydrochloride with the starting materials given the table below.

	Structure	Starting material	LC-MS
K2		Intermediate J1 and 5-methyl-4,5,6,7-tetrahydrothiazolo [4,5-c]pyridine-2-carboxylic acid	Rt = 0.76 min, m/z 572.3 $[M+H]^+$ (Method 15)
K3		Intermediate J1 and 5-methyl-4,5,6,7-tetrahydrothiazolo [5,4-c]pyridine-2-carboxylic acid	Rt = 0.72 min, m/z 572.3 $[M+H]^+$ (Method 15)

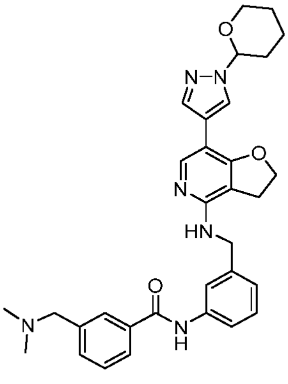
K4		Intermediate J1 and Intermediate A4	Rt = 0.67 min, m/z 602.1 $[M+H]^+$ (Method 15)
K5		Intermediate J1 and 1-methyl-1H-indazole-5-carboxylic acid	Rt = 1.09 min, m/z 550.1 $[M+H]^+$ (Method 15)
K6		Intermediate J1 and 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid	Rt = 0.87 min, m/z 651.8 $[M+H]^+$ (Method 6)

K7		Intermediate J1 and 1-methyl-1H-indazole-3-carboxylic acid	Rt = 0.74 min, m/z 550.1 $[M+H]^+$ (Method 6)
K8		Intermediate J1 and 1-methyl-1H-indazole-4-carboxylic acid	Rt = 1.09 min, m/z 550.1 $[M+H]^+$ (Method 6)
K9		Intermediate J1 and Intermediate A5	Rt = 0.43 min, m/z 606.8 $[M+H]^+$ (Method 6)

K10		Intermediate J1 and Intermediate A6	Rt = 0.44 min, m/z 633.2 [M+H]$^+$ (Method 6)
K11		Intermediate J1 and 2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid	Rt = 0.45 min, m/z 564.9 [M+H]$^+$ (Method 6)
K12		Intermediate J1 and Intermediate A7	Rt = 0.52 min, m/z 648.9 [M+H]$^+$ (Method 14)

K13		Intermediate J2 and 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid	Rt = 0.52 min, m/z 668.9[M+H]$^+$ (Method 6)
K14		Intermediate J1 and Intermediate A8	Rt = 0.46 min, m/z 585.9 [M+H]$^+$ (Method 6)

Intermediate K15

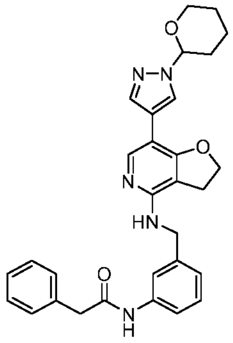


3-((Dimethylamino)methyl)-N-(3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)benzamide (Intermediate K15)

1-(Tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (48.8 mg, 0.176 mmol), intermediate E6 (65 mg, 0.135 mmol) and cesium carbonate (132 mg, 0.405 mmol) were mixed into DMF (2 mL) and water (1 mL) and purged with argon for 10 min. Tetrakis(triphenylphosphine)palladium(0) (0.018 mL, 0.014 mmol) was added and the reaction heated to 70°C for 2 h. The reaction mixture was concentrated and the crude purified by flash chromatography on C18-silica by eluting with 0-30% B in A (A: water/acetonitrile 95:5 + 0.1% HCOOH, B: acetonitrile/water 95:5 + 0.1% HCOOH). Appropriate fractions were pooled and evaporated to dryness to give the title compound (37.5 mg).

LCMS (Method 6): Rt = 0.41 min, m/z 553.3 $[M+H]^+$

Intermediate K16

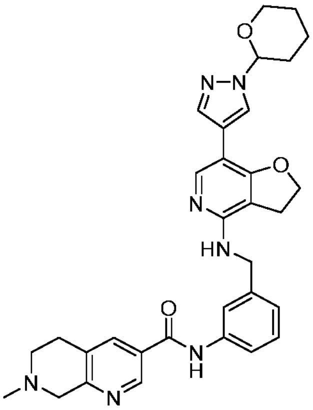


2-Phenyl-N-(3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)acetamide (Intermediate K16)

Intermediate K16 was prepared from intermediate E7 using a procedure similar to that used for the synthesis of intermediate K15 from intermediate E6.

LCMS (Method 11): Rt = 1.2 min, m/z 510.1 $[M+H]^+$

Intermediate K17



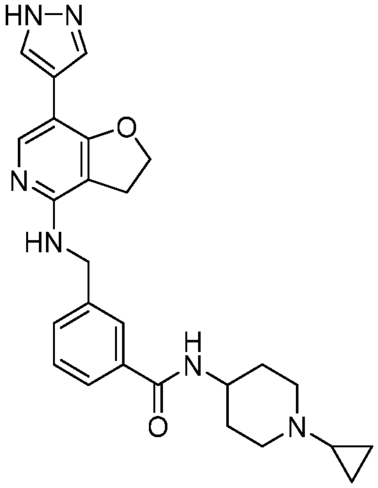
7-Methyl-N-(3-(((7-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide (Intermediate K17)

Intermediate J1 (102 mg, 0.261 mmol), bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (134 mg, 0.523 mmol), ethyl 7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxylate (115 mg, 0.523 mmol) and THF (3 mL) were charged in a closed vessel and heated at 110°C for 1 h under microwave irradiation. The reaction was quenched by the addition of water and then diluted with DCM. The organic phase was separated and evaporated under vacuum. The crude material was purified by flash chromatography on C18-silica by eluting with 0-60% B in A (A: water/acetonitrile 95:5 + 0.1% HCOOH, B: acetonitrile/water 95:5 + 0.1% HCOOH) to afford the title compound (11 mg).

LCMS (Method 6): Rt = 0.39 min, m/z 565.9 $[M+H]^+$

PREPARATION OF EXAMPLES

Example 1



3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-cyclopropylpiperidin-4-yl)benzamide (Example 1)

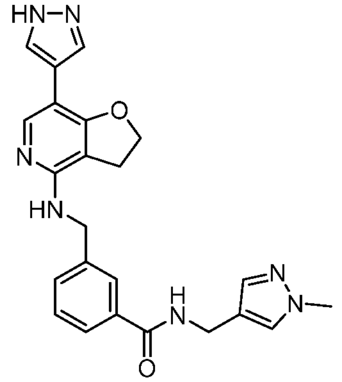
To a mixture of intermediate G (50 mg, 0.14 mmol), 1-cyclopropylpiperin-4-amine (21 mg, 0.149 mmol), DIPEA (0.078 mL, 0.446 mmol) and TBTU (62 mg, 0.193 mmol) in DMF (1 mL) was stirred at RT for 3 h. The reaction mixture was diluted with MeOH and applied to a Isolute® SCX-2 cartridge eluting with MeOH and then 2M methanolic ammonia. The relevant fractions were concentrated in *vacuo* and the crude material was purified by chromatography on silica by eluting with 0-10% 2M methanolic ammonia in DCM to give the title compound (16 mg).

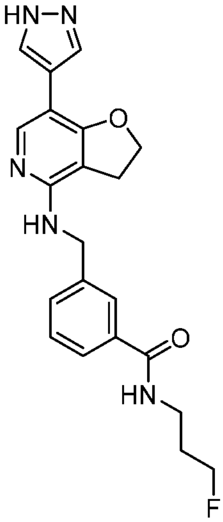
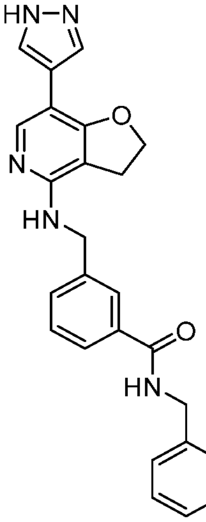
LCMS (Method 5) Rt = 1.75 min, m/z 459.4 [M+H]$^+$

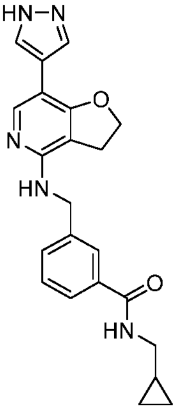
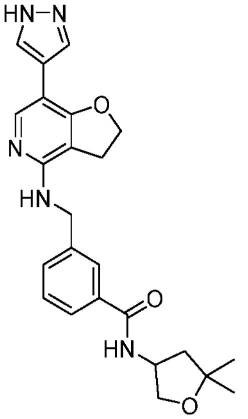
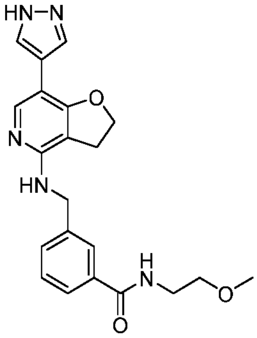
^{1}H NMR (400 MHz, DMSO-d6) δ 12.8 (s, 1H), 8.18 (d, J = 7.7Hz, 1H), 8.07 (s, 1H), 7.86 (s, 2H), 7.79 (s, 1H), 7.65 (d, 7.8Hz, 1H), 7.46 (d, J = 7.8Hz, 1H), 7.35 (t, J = 7.8Hz, 1H), 6.71 (t, J = 6.7Hz, 1H), 4.68 (t, J = 8.8Hz, 2H), 4.60 (d, J = 6.2Hz, 2H), 3.81-3.68 (m, 1H), 3.04 (t, J = 8.8Hz, 2H), 2.96-2.88 (m, 2H), 2.26-2.16 (m, 2H), 1.78-1.69 (m, 2H), 1.62-1.55 (m, 1H), 1.53-1.41 (m, 2H), 0.43-0.37 (m, 2H), 0.30-0.25 (m, 2H).

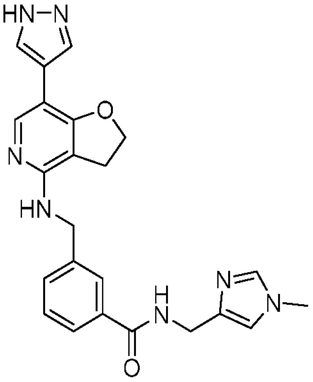
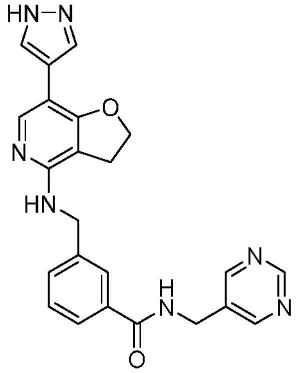
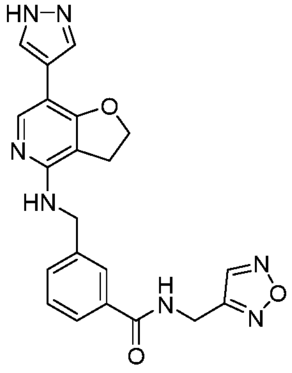
Examples 2 to 31

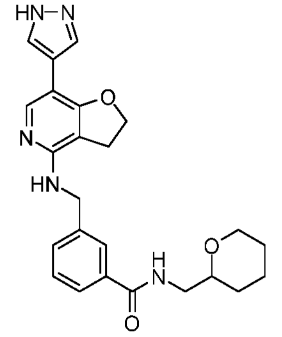
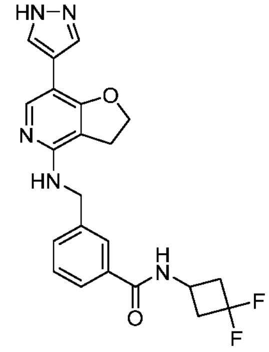
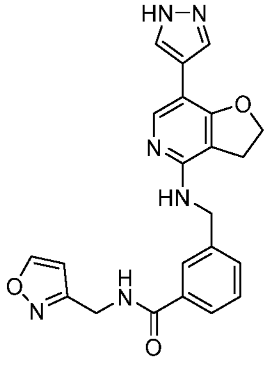
The following examples were prepared from Intermediate G and the amine given in a manner 'analogous' or 'similar' to that used for example 1. Such procedures may involve minor variations, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions (eg. HPLC-MDAP or flash chromatography). In some cases, where modification involved reaction solvent (eg. DCM-DMF mix instead of DMF) or coupling agents (e.g. HATU instead of TBTU), such changes were reported as a note.

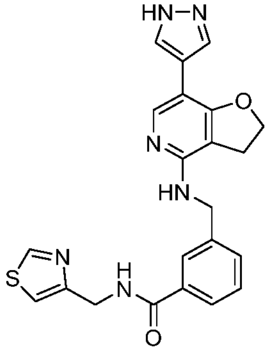
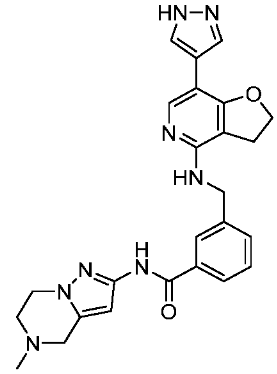
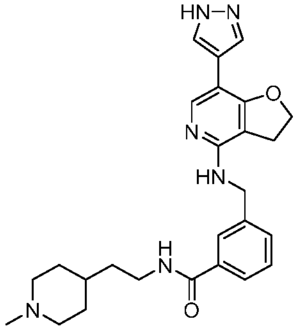
Ex	Structure	Amine	^{1}H NMR	LC-MS
2	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)benzamide	(1-Methyl-1H-pyrazol-4-yl)methanamine	(400 MHz, DMSO-d6) δ 12.58 (s, 1H), 8.50-8.39 (m, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 7.83 (s, 2H), 7.71 (d, J=7.7 Hz, 1H), 7.53-7.50 (m, 2H), 7.39-7.35 (m, 1H), 6.32 (t, J=6.0 Hz, 1H), 6.15 (d, J=2.1 Hz, 1H), 4.70 (t, J=8.8 Hz, 2H), 4.66 (d, J=6.2 Hz, 2H), 4.44 (d, J=5.8 Hz, 2H), 3.08 (t, J=8.9 Hz, 2H), 3.04 (s, 3H).	Rt = 3.32 min, m/z 430.0 [M+H]$^+$ (Method 4)

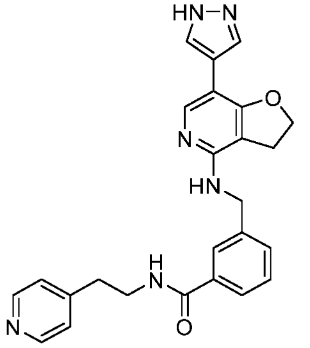
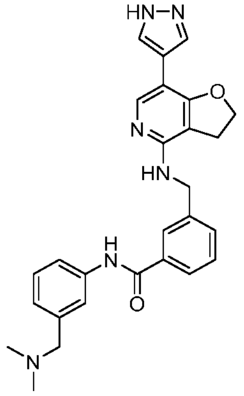
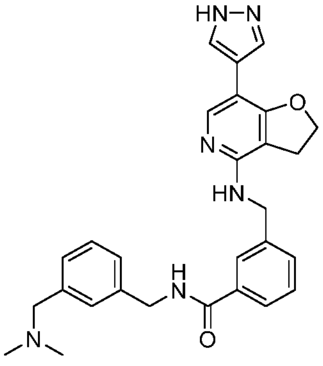
3	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-fluoropropyl)benzamide	3-Fluoropropan-1-amine	(400 MHz, DMSO-d6) δ 12.58 (s, 1H), 8.24-8.16 (m, 1H), 8.08 (s, 1H), 7.91-7.77 (m, 3H), 7.68 (d, J=7.7 Hz, 1H), 7.51 (d, J=7.3 Hz, 1H), 7.40-7.35 (m, 1H), 6.32 (t, J=6.0 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.66 (d, J=6.4 Hz, 2H), 4.59 (t, J=5.9 Hz, 1H), 4.47 (t, J=6.0 Hz, 1H), 3.42-3.37 (m, 2H), 3.08 (t, J=8.7 Hz, 2H), 1.96 (d, J=51.3 Hz, 2H).	Rt = 2.35 min, m/z 396.0 $[M+H]^+$ (Method 3)
4	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-2-ylmethyl)benzamide	pyridin-2-ylmethanamine	(400 MHz, DMSO-d6) δ 12.74 (br s, 1H), 9.02 (br t, J=5.8 Hz, 1H), 8.47 (br d, J=4.6 Hz, 1H), 8.04 (s, 1H), 7.89 - 7.87 (m, 1H), 7.86 (s, 1H), 7.77 -7.74 (m, 1H), 7.71 (br s, 2H), 7.47 (br d, J=7.7 Hz, 1H), 7.39 - 7.34 (m, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.24 - 7.20 (m, 1H), 6.66 (br t, J=6.0 Hz, 1H), 4.65 (t,J=8.9 Hz, 2H), 4.59 (br d, J=6.1 Hz, 2H), 4.52 (d, J=5.9 Hz, 2H), 4.46 - 4.43 (m, 1H), 3.02 (br t, J=8.9 Hz, 2H).	Rt = 0.44 min, m/z 427.2 $[M+H]^+$ (Method 6)

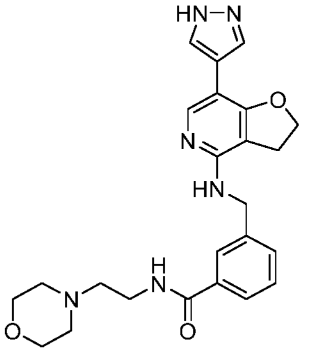
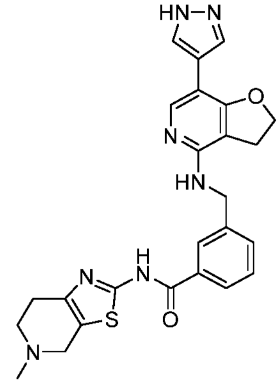
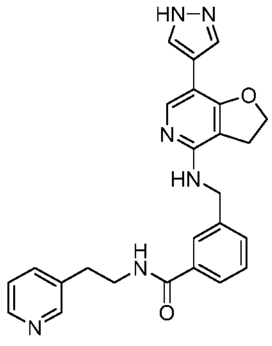
5	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(cyclopropylmethyl)benzamide	Cyclopropyl methanamine	(400 MHz, DMSO-d6) δ 12.58 (s, 1H), 8.30 (t, J=5.6 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 2H), 7.63-7.60 (m, 1H), 7.49-7.44 (m, 1H), 7.27-7.24 (m, 1H), 7.18-7.13 (m, 1H), 6.48 (t, J=6.1 Hz, 1H), 4.48 (t, J=9.0 Hz, 2H), 4.40 (d, J=5.9 Hz, 2H), 3.16-3.10 (m, 2H), 2.91 (t, J=6.2 Hz, 2H), 2.84 (t, J=8.9 Hz, 2H), 0.85-0.77 (m, 1H), 0.23-0.18 (m, 2H).	Rt = 3.75 min, m/z 390.0 $[M+H]^+$ (Method 4)
6	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5,5-dimethyltetrahydrofuran-3-yl)benzamide	5,5-Dimethyltetrahydrofuran-3-amine	(400 MHz, DMSO-d6) δ 12.81 - 12.80 (m, 1H), 8.47 (d, J=6.5 Hz, 1H), 8.08 (s, 1H), 7.84 - 7.81 (m, 3H), 7.71 - 7.67 (m, 1H), 7.50 - 7.47 (m, 1H), 7.38 (t, J=7.7 Hz, 1H), 6.71 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 4.54 (d, J=8.0 Hz, 1H), 4.00 (dd, J=7.0, 8.8 Hz, 1H), 3.61 (dd, J=6.4, 8.8 Hz, 1H), 3.10 - 3.03 (m, 2H), 2.09 (dd, J=8.3, 12.5 Hz, 1H), 1.82 (dd, J=7.3, 12.5 Hz, 1H), 1.29 (s, 3H), 1.19 (s, 3H).	Rt = 2.46 min, m/z 434.2 $[M+H]^+$ (Method 3)
7	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-methoxyethyl)benzamide	2-Methoxyethan-1-amine	(400 MHz, DMSO-d6) δ 12.6 (bs , 1H), 8.48 (m, 1H), 8.17 (s, 1H), 8.09 (s, 1H), 7.87 (s, 2H), 7.84 (s, 1H), 7.70-7.67 (m, 1H), 7.50-7.47 (m, 1H), 7.38 (t, J= 7.7 Hz, 1H), 6.73-6.68 (m, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 3.47 - 3.41 (m, 4H), 3.28 (s, 3H), 3.07 (t, J=7.6 Hz, 2H).	Rt = 2.17 min, m/z 394.0 $[M+H]^+$ (Method 3)

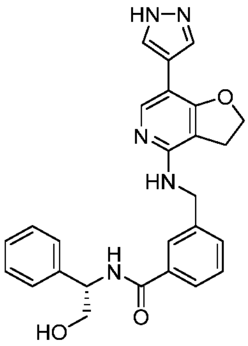
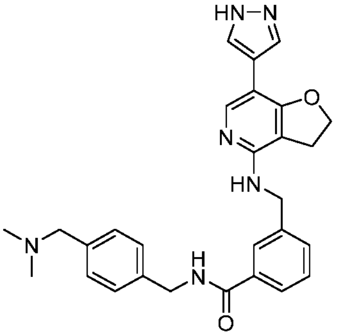
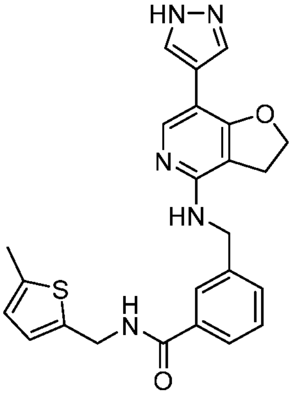
8	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((1-methyl-1H-imidazol-4-yl)methyl)benzamide	(1-Methyl-1H-imidazol-4-yl)methanamine	(400 MHz, DMSO-d6) δ12.80 (d, J=0.9 Hz, 1H), 8.74 (t, J=5.6 Hz, 1H), 8.09 (s, 1H), 7.86 (s, 3H), 7.71 (d, J=7.8 Hz, 1H), 7.47 (d, J=5.9 Hz, 2H), 7.37 (t, J=7.7 Hz, 1H), 6.93 (s, 1H), 6.70 (dd, J= 6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 4.32 (d, J=5.5 Hz, 2H), 3.60 (s, 3H), 3.06 (t, J=8.9 Hz, 2H).	Rt = 1.64 min, m/z 430.0 [M+H]$^+$ (Method 3)
9	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyrimidin-5-ylmethyl)benzamide	Pyrimidin-5-ylmethanamine	(400 MHz, DMSO-d6) δ 12.80 (s, 1H), 9.12 - 9.09 (m, 2H), 8.78 (s, 2H), 8.09 (s, 1H), 7.88 - 7.85 (m, 3H), 7.72 (ddd, J=1.4, 1.4, 7.7 Hz, 1H), 7.53 - 7.49 (m, 1H), 7.40 (t, J=7.7 Hz, 1H), 6.71 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 4.50 (d, J=5.8 Hz, 2H), 3.06 (t, J=8.8 Hz, 2H).	Rt = 2.06 min, m/z 428.0 [M+H]$^+$ (Method 3)
10	 N-((1,2,5-oxadiazol-3-yl)methyl)-3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide	(1,2,5-Oxadiazol-3-yl)methanamine	(400 MHz, DMSO-d6) δ 13.28 (s, 1H), 12.80-12.75 (m, 1H), 9.06 (t, J=5.8 Hz, 1H), 8.09 (s, 1H), 7.87 (s, 3H), 7.74-7.70 (m, 1H), 7.55-7.51 (m, 1H), 7.42 (t, J=7.7 Hz, 1H), 6.73 (t, J=6.0 Hz, 1H), 4.74-4.61 (m, 4H), 4.28 (d, J=5.8 Hz, 2H), 3.10-3.03 (m, 2H).	Rt = 2.3 min, m/z 418.2 [M+H]$^+$ (Method 3)

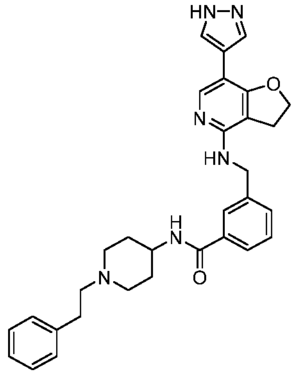
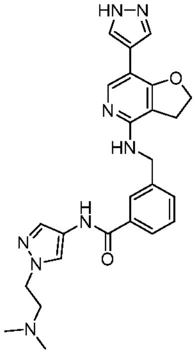
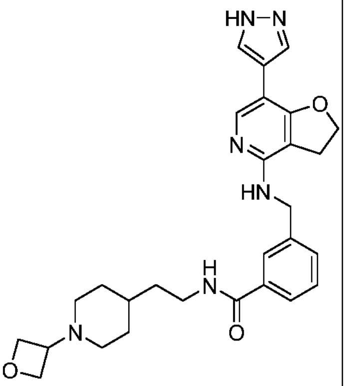
11	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide	(Tetrahydro-2H-pyran-2-yl)methanamine	(400 MHz, DMSO-d6) δ 12.80 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.09 (s, 1H), 7.85-7.83 (m, 2H), 7.82-7.67 (m, 2H), 7.50-7.46 (m, 1H), 7.37 (t, J=7.7 Hz, 1H), 6.71 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 3.87 (dd, J=2.3, 10.8 Hz, 1H), 3.43 (m, 2H), 3.26 (m, 2H), 3.06 (t, J=8.8 Hz, 2H), 1.80-1.75 (m, 1H), 1.61 (d, J=12.5 Hz, 1H), 1.49-1.41 (m, 3H), 1.22-1.12 (m, 1H).	Rt = 2.61 min, m/z 434.2 $[M+H]^+$ (Method 3)
12	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3,3-difluorocyclobutyl)benzamide	3,3-Difluorocyclobutan-1-amine	(400 MHz, DMSO-d6) δ 12.80-12.78 (m, 1H), 8.81 (d, J=6.5 Hz, 1H), 8.09-8.08 (m, 2H), 7.86-7.82 (m, 2H), 7.70 (d, J=7.7 Hz, 1H), 7.53-7.49 (m, 1H), 7.41 (t, J=7.7 Hz, 1H), 6.72 (t, J=6.1 Hz, 1H), 4.74-4.61 (m, 4H), 4.32-4.24 (m, 1H), 3.10 (m, 2H), 2.83-2.68 (m, 2H), 2.68 (m, 2H).	Rt = 2.68 min, m/z 426.2 $[M+H]^+$ (Method 3)
13	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(isoxazol-3-ylmethyl)benzamide	1,2-Oxazol-3-ylmethanamine	(400 MHz, DMSO-d6) δ 13.1 (bs, 1H), 9.07 (t, J = 5.6Hz, 1H), 8.34 (d, J = 1.6Hz, 1H), 8.16 (s, 1H), 8.09 (s, 1H), 7.87 (br s, 3H), 7.74-7.70 (m, 1H), 7.53-7.49 (m, 1H), 7.40 (t, J = 7.7Hz, 1H), 6.72 (t, J = 6.2Hz, 1H), 6.50 (d, J = 8.2Hz, 1H), 4.70 (t, J = 8.6Hz, 2H), 4.63 (d, J = 6.1Hz, 2H), 4.55 (d, J = 6.1Hz, 2H), 3.07 (t, J = 8.6Hz, 2H).	Rt = 2.28 min, m/z 417.0 $[M+H]^+$ (Method 3)

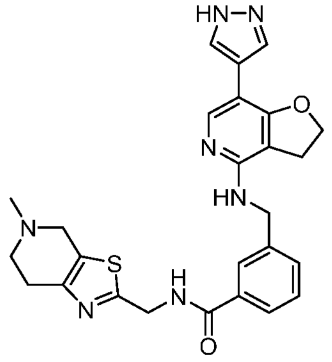
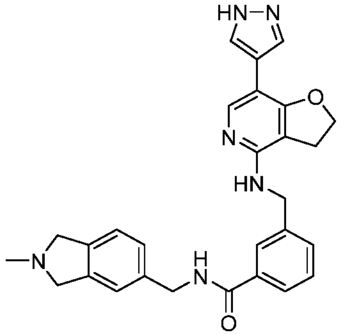
14	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(thiazol-4-ylmethyl)benzamide	Thiazol-4-ylmethanamine	(400 MHz, DMSO-d6) δ 12.8 (s, 1H), 9.07 (d, J = 2.0Hz, 1H), 9.04 (t, J = 5.5Hz, 1H), 8.09 (s, 1H), 7.90-7.83 (m, 3H), 7.77-7.73 (m, 1H), 7.52-7.48 (m, 1H), 7.45-7.43 (m, 1H), 7.40 (t, J = 7.6Hz, 1H), 6.71 (t, J = 5.9Hz, 1H), 4.70 (t, J = 8.9Hz, 2H), 4.62 (t, J = 5.7Hz, 4H), 3.06 (t, J = 8.9Hz, 2H).	Rt = 2.29 min, m/z 433.0 $[M+H]^+$ (Method 3)
15	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)benzamide	5-Methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine	(400 MHz, DMSO-d6) δ 12.81 (s, 1H), 10.73 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.87 (s, 2H), 7.84 (d, J=8.1 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.43 - 7.38 (m, 1H), 6.71 (t, J=6.1 Hz, 1H), 6.42 (s, 1H), 4.71 (t, J=8.8 Hz, 2H), 4.65 (d, J=5.9 Hz, 2H), 4.01 (t, J=5.5 Hz, 2H), 3.57 (s, 2H), 3.07 (t, J=8.8 Hz, 2H), 2.85 (t, J=5.6 Hz, 2H), 2.40 (s, 3H).	Rt = 2.17 min, m/z 471.6 $[M+H]^+$ (Method 13)
16	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(1-methylpiperidin-4-yl)ethyl)benzamide	1-methylpiperidin-4-yl)ethanamine	(400MHz, DMSO-d6) δ 12.75 (br s, 1H), 8.34 (t, J=5.7 Hz, 1H), 8.05 (s, 1H), 7.89 (br s, 1H), 7.78 (s, 2H), 7.63 (dt, J=7.7, 1.5 Hz, 1H), 7.44 (dt, J=7.7, 1.5 Hz, 1H), 7.34 (t, J=7.7 Hz, 1H), 6.65 (t, J=6.0 Hz, 1H), 4.67 (t, J=8.9 Hz, 2H), 4.59 (d, J=5.7 Hz, 2H), 3.27 - 3.24 (m, 2H), 3.03 (t, J=8.9 Hz, 2H), 2.71 - 2.63 (m, 2H), 2.09 (s, 3H), 1.76 (td, J=11.5, 2.0 Hz, , 2H), 1.62 (dd, J=11.8, 2.0 Hz, 2H), 1.42 (q, J=8.0 Hz, 2H), 1.18 - 1.04 (m, 3H).	Rt = 0.33 min, m/z 461.3 $[M+H]^+$ (Method 12) *Note:* *reaction solvent DCM-DMF mix, coupling agent HATU*

17	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-4-yl)ethyl)benzamide	2-(pyridin-4-yl)ethanamine	(400MHz, DMSO-d6) δ 12.74 (br s, 1H), 8.48 (t, J=5.5 Hz, 1H), 8.42 (d, J=5.9 Hz, 2H), 8.04 (s, 1H), 7.88 (br s, 1H), 7.77 (br s, 1H), 7.75 (s, 1H), 7.58 (dt, J=7.7, 1.0 Hz, 1H), 7.43 (dt, J=7.7, 1.0 Hz, 1H), 7.32 (t, J=7.7 Hz, 1H), 7.22 (d, J=5.9 Hz, 2H), 6.66 (t, J=5.8 Hz, 1H), 4.66 (t, J=8.9 Hz, 2H), 4.57 (d, J=6.1 Hz, 2H), 3.48 (q, J=5.8 Hz, 2H), 3.02 (t, J=8.9 Hz, 2H), 2.83 (t, J=7.1 Hz, 2H).	Rt = 0.72 min, m/z 441.2 [M+H]$^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
18	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)phenyl)benzamide	3-((dimethylamino)methyl)aniline	(400MHz, DMSO-d6) δ12.74 (br s, 1H), 10.16 (s, 1H), 8.05 (s, 1H), 7.89 (s, 2H), 7.78 (s, 1H), 7.76 (s, 1H), 7.71 (br s, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.50 (d, J=7.7 Hz, 1H), 7.40 (t, J=7.7 Hz, 1H), 7.25 (t, J=7.8 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 6.68 (t, J=6.0 Hz, 1H), 4.66 (t, J=8.9 Hz, 2H), 4.62 (d, J=5.9 Hz, 2H), 3.34 - 3.33 (m, 2H), 3.03 (t, J=8.9 Hz, 2H), 2.15 (s, 6H).	Rt = 0.39 min, m/z 469.3 [M+H]$^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
19	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)benzyl)benzamide	1-(3-(aminomethyl) phenyl)-N,N-dimethylmethanamine	(400MHz, DMSO-d6) δ12.74 (br s, 1H), 8.95 (t, J=5.9 Hz, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.69 (dt, J=7.7, 1.0 Hz, 1H), 7.45 (dt, J=7.7, 1.0 Hz, 1H), 7.35 (t, J=7.7 Hz, 1H), 7.27 - 7.18 (m, 3H), 7.17 - 7.12 (m, 1H), 7.12 - 7.09 (m, 1H), 6.65 (t, J=5.9 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.58 (d, J=5.9 Hz, 2H), 4.43 (d, J=5.9 Hz, 2H), 3.31 (s, 2H), 3.01 (t, J=8.9 Hz, 2H), 2.08 (s, 6H).	Rt = 0.38 min, m/z 483.3 [M+H]$^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*

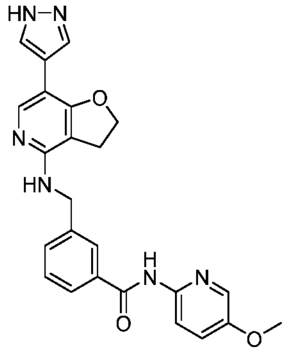
20	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-morpholinoethyl)benzamide	2-morpholinoetha namine	(400MHz, DMSO-d6) δ12.74 (br s, 1H), 8.29 (t, J=5.6 Hz, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.77 (br s, 2H), 7.61 (dt, J=7.7, 1.0 Hz, 1H), 7.43 (dt, J=7.9 Hz, 1H), 7.33 (t, J=7.7 Hz, 1H), 6.65 (t, J=6.0 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.57 (d, J=6.0 Hz, 2H), 3.56 - 3.49 (m, 4H), 3.33 (q, J=6.0 Hz, 2H), 3.01 (t, J=8.9 Hz, 2H), 2.42 (t, J=6.0 Hz, 2H), 2.39 - 2.34 (m, 4H).	Rt = 0.29 min, m/z 449.3 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
21	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)benzamide	5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine	(400MHz, DMSO-d6) δ 12.74 (s, 1H), 12.41 (s, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.93 - 7.85 (m, 2H), 7.76 (s, 1H), 7.53 (d, J=7.7 Hz, 1H), 7.41 (t, J=7.7 Hz, 1H), 6.67 (t, J=6.1 Hz, 1H), 4.66 (t, J=8.8 Hz, 2H), 4.61 (d, J=5.9 Hz, 2H), 3.48 (s, 2H), 3.03 (t, J=8.8 Hz, 2H), 2.72 - 2.60 (m, 4H), 2.35 (s, 3H).	Rt = 0.41 min, m/z 488.1 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
22	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(pyridin-3-yl)ethyl)benzamide	2-(pyridin-3-yl)ethan amine	(400MHz, DMSO-d6) δ12.74 (br s, 1H), 8.48 (t, J=5.5 Hz, 1H), 8.41 (d, J=1.8 Hz, 1H), 8.37 (dd, J=4.8, 1.5 Hz, 1H), 8.04 (s, 1H), 7.88 (br s, 1H), 7.76 (br s, 1H), 7.75 (s, 1H), 7.64 - 7.56 (m, 2H), 7.43 (d, J=7.7 Hz, 1H), 7.32 (t, J=7.7 Hz, 1H), 7.26 (dd, J=7.6, 4.5 Hz, 1H), 6.64 (t, J=6.1 Hz, 1H), 4.66 (t, J=8.9 Hz, 2H), 4.57 (d, J=5.9 Hz, 2H), 3.47 (q, J=6.0 Hz, 2H), 3.01 (t, J=8.9 Hz, 2H), 2.83 (t, J=7.0 Hz, 2H).	Rt = 0.39 min, m/z 441.2 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*

23	 (S)-3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-hydroxy-1-phenylethyl)benzamide	(S)-2-amino-2-phenylethanol	(400MHz, DMSO-d6) δ 12.72 (br s, 1H), 8.59 (d, J=8.1 Hz, 1H), 8.04 (s, 1H), 7.90 - 7.74 (m, 3H), 7.71 (d, J=7.7 Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.39 - 7.31 (m, 3H), 7.30 - 7.24 (m, 2H), 7.22 - 7.16 (m, 1H), 6.65 (t, J=6.1 Hz, 1H), 5.06 - 4.99 (m, 1H), 4.87 (t, J=5.9 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.59 (d, J=6.1 Hz, 2H), 3.71 - 3.58 (m, 2H), 3.01 (t, J=8.8 Hz, 2H).	Rt = 0.58 min, m/z 456.3 $[M+H]^+$ (Method 12) *Note:* *reaction solvent DCM-DMF mix, coupling agent HATU*
24	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(4-((dimethylamino)methyl)benzyl)benzamide	1-(4-(aminomethyl)phenyl)-N,N-dimethylmethanamine hydrochloride	(400MHz, DMSO-d6) δ 12.74 (br s, 1H), 8.93 (t, J=5.8 Hz, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.69 (d, J=7.7 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.34 (t, J=7.7 Hz, 1H), 7.26 - 7.12 (m, 4H), 6.64 (t, J=5.9 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.58 (d, J=5.9 Hz, 2H), 4.42 (d, J=5.9 Hz, 2H), 3.30 (s, 2H), 3.01 (t, J=8.9 Hz, 2H), 2.08 (s, 6H).	Rt = 0.31 min, m/z 483.2 $[M+H]^+$ (Method 12) *Note:* *reaction solvent DCM-DMF mix, coupling agent HATU*
25	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methylthiophen-2-yl)methyl)benzamide	(5-methylthiophen-2-yl)methanamine	(400MHz, DMSO-d6) δ 12.74 (s, 1H), 8.98 (t, J=5.9 Hz, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.65 (d, J=7.7 Hz, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.33 (t, J=7.7 Hz, 1H), 6.73 (d, J=3.5 Hz, 1H), 6.65 (t, J=6.0 Hz, 1H), 6.57 (dd, J=3.5, 1.1 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.57 (d, J=6.0 Hz, 2H), 4.48 (d, J=5.9 Hz, 2H), 3.01 (t, J=8.9 Hz, 2H), 2.33 (s, 3H).	Rt = 0.58 min, m/z 446.3 $[M+H]^+$ (Method 12) *Note:* *reaction solvent DCM-DMF mix, coupling agent HATU*

26	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-phenethylpiperidin-4-yl)benzamide	1-phenethylpiperidin-4-amine	(400MHz, DMSO-d6) δ 12.74 (s, 1H), 8.15 (d, J=7.9 Hz, 1H), 8.04 (s, 1H), 7.88 (br s , 1H), 7.77 (s, 1H), 7.76 (br s, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.43 (d, J=7.7 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.26 - 7.11 (m, 5H), 6.64 (t, J=6.0 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.57 (d, J=6.0 Hz, 2H), 3.77 - 3.65 (m, 1H), 3.01 (t, J=8.9 Hz, 2H), 2.91 (d, J=11.8 Hz, 2H), 2.72 - 2.66 (m, 2H), 2.03 - 1.95 (m, 2H), 1.77 - 1.70 (m, 2H), 1.53 (dq, J=11.8, 3.3 Hz, 2H).	Rt = 0.46 min, m/z 523.4 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
27	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)benzamide	1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-amine hydrochloride	(400MHz, DMSO-d6) δ 12.74 (br s, 1H), 10.33 (s, 1H), 8.05 (s, 1H), 8.02 (s, 1H), 7.89 (br s, 1H), 7.87 (s, 1H), 7.76 (br s, 1H), 7.74 (d, J=7.7 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J=7.7 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 6.67 (t, J=6.0 Hz, 1H), 4.66 (t, J=8.9 Hz, 2H), 4.61 (d, J=6.0 Hz, 2H), 4.13 (t, J=6.5 Hz, 2H), 3.02 (t, J=8.9 Hz, 2H), 2.58 (t, J=6.5 Hz, 2H), 2.13 (s, 6H).	Rt = 0.31 min, m/z 473.4 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
28	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(1-(oxetan-3-yl)piperidin-4-yl)ethyl)benzamide	Intermediate A1	(400MHz, DMSO-d6) δ 12.74 (br s, 1H), 8.32 (t, J=5.5 Hz, 1H), 8.03 (s, 1H), 7.87 (br s, 1H), 7.76 (br s, 2H), 7.61 (d, J=7.8 Hz, 1H), 7.42 (d, J=7.8 Hz, 1H), 7.32 (t, J=7.8 Hz, 1H), 6.63 (t, J=6.1 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.57 (d, J=5.9 Hz, 2H), 4.46 (t, J=6.1 Hz, 2H), 4.35 (t, J=6.1 Hz, 2H), 3.26 - 3.20 (m, 3H), 3.01 (t, J=8.9 Hz, 2H), 2.63 - 2.57 (m, 2H), 1.69 - 1.59 (m, 4H), 1.42 (q, J=6.9 Hz, 2H), 1.29 - 1.21 (m, 1H), 1.16 - 1.07 (m, 2H).	Rt = 0.29 min, m/z 503.4 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*

29	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)methyl)benzamide	Intermediate A2	(400MHz, DMSO-d6) δ 12.73 (br s, 1H), 9.25 (t, J=5.8 Hz, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.82 - 7.74 (br s, 2H), 7.68 (d, J=7.7 Hz, 1H), 7.47 (d, J=7.7 Hz, 1H), 7.36 (t, J=7.7 Hz, 1H), 6.65 (t, J=6.1 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.62 - 4.56 (m, 4H), 3.46 (s, 2H), 3.02 (t, J=8.9 Hz, 2H), 2.71 - 2.61 (m, 4H), 2.31 (s, 3H).	Rt = 0.25 min, m/z 502.0 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling agent HATU*
30	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((2-methylisoindolin-5-yl)methyl)benzamide	Intermediate A3	(400MHz, DMSO-d6) δ 12.74 (br s, 1H), 8.92 (t, J=6.0 Hz, 1H), 8.04 (br s, 1H), 7.88 (br s, 1H), 7.83 (s, 1H), 7.76 (br s, 1H), 7.68 (d, J=7.7 Hz, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.34 (t, J=7.7 Hz, 1H), 7.17 - 7.02 (m, 3H), 6.65 (t, J=6.0 Hz, 1H), 4.65 (t, J=8.9 Hz, 2H), 4.57 (d, J=6.0 Hz, 2H), 4.40 (d, J=6.0 Hz, 2H), 3.72 (s, 4H), 3.01 (t, J=8.9 Hz, 2H), 2.41 (s, 3H).	Rt = 0.29 min, m/z 480.6 $[M+H]^+$ (Method 12) *Note: reaction solvent DCM-DMF mix, coupling*

Example 31



3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methoxypyridin-2-yl)benzamide (Example 31)

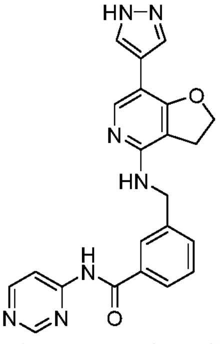
Intermediate G (75 mg, 0.22 mmol), 2-amino-5-methoxypyridine (83 mg, 0.67 mmol), 1-(methylsulfonyl)-1H-benzotriazole (264 mg, 1.34 mmol), triethylamine (0.31 mL, 2.23 mmol) and THF (10 mL) were loaded into a microwave vial and stirred under microwave irradiation at 150°C for 3 h. A further 1 equivalent of 2-amino-5-methoxypyridine and 1-(methylsulfonyl)-1H-benzotriazole and triethylamine were added and the mixture again stirred under microwave irradiation at 150°C for 3 h. The reaction mixture was loaded onto an Isolute® SCX-2 cartridge, washed with MeOH and eluted with 7N NH_3 in MeOH. The samples were concentrated and purified by MDAP (Luna Phenyl-Hexyl 3x50mm, 3µm 5-95% MeOH/H_2O (0.1% FA), 1.7mL/min, RT) to give the title compound (23.1 mg).

LCMS (Method 3): Rt = 2.68 min, m/z 443.2 $[M+H]^+$

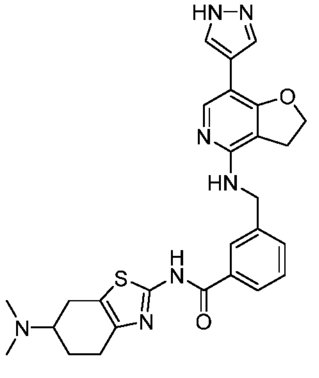
^1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.12 (s, 1H), 8.11 – 8.09 (m, 2H), 8.00 (s, 1H), 7.90 – 7.85 (m, 3H), 7.55 (d, J=7.6 Hz, 1H), 7.50 (d, J=3.2 Hz, 1H), 7.48 (d, J=3.2 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 6.72 (t, J=6.2 Hz, 1H), 4.71 (t, J=9.0 Hz, 2H), 4.66 (d, J=6.0 Hz, 2H), 3.85 (s, 3H), 3.08 (t, J=9.0 Hz, 2H)

Example 32

The following example was prepared using a procedure similar to that used for the synthesis of *example 31* by replacing intermediate G with the amine given.

Ex	Structure	Amine	^1H NMR	LC-MS
32	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyrimidin-4-yl)benzamide	4-Amino-pyrimidine	^1H NMR (400 MHz, DMSO-d6) δ 12.78 (s, 1H), 11.19 (s, 1H), 8.95 (d, J=1.0 Hz, 1H), 8.71 (d, J=5.8 Hz, 1H), 8.20 (dd, J=1.1, 5.8 Hz, 1H), 8.08 (s, 1H), 8.01-7.97 (m, 1H), 7.90-7.84 (m, 3H), 7.60-7.55 (m, 1H), 7.47-7.42 (m, 1H), 6.72 (t, J=6.1 Hz, 1H), 4.69 (t, J=8.8 Hz, 2H), 4.65 (d, J=6.1 Hz, 2H), 3.06 (t, J=8.9 Hz, 2H).	Rt = 2.28 min, m/z 414.3 $[M+H]^+$ (Method 5)

Example 33



3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(dimethylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (Example 35)

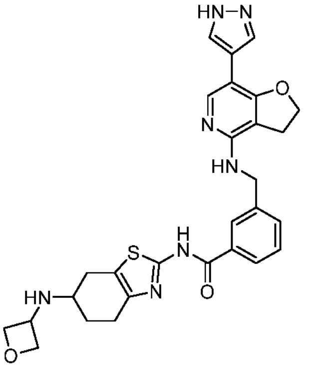
Paraformaldehyde (13 mg, 0.43 mmol) and sodium cyanoborohydride (27 mg, 0.43 mmol) were added to a stirred suspension of intermediate H1 (70 mg, 0.14 mmol) in MeOH (2.0 mL) and DMF (0.5 mL). The resulting mixture was stirred for 20 h then treated with aqueous 1M NaOH (5.0 mL). The mixture was extracted with DCM (2 x 10 mL) then with 10% MeOH in DCM (4 x 5 mL). The combined organic phase was passed through an Isolute® SCX-2 cartridge which was then washed with 1:1 DCM:MeOH and eluted with 20% 2M methanolic ammonia in DCM. Concentration *in vacuo* gave the crude product which was purified by MDAP (Luna Phenylhexyl 21.2x150 mm, 10 µm 5-60% MeOH/H_2O (0.1% FA) 20mL/ min) to afford the desired product as formate salt (21.6 mg)

LCMS (Method 3): Rt = 2.05 min, m/z 516.4 $[M+H]^+$

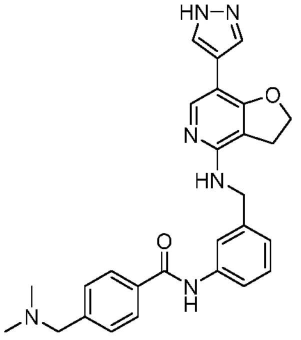
^1H NMR (400 MHz, DMSO-*d6*) δ 12.40 (br s, 2H), 8.18 (s, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 7.93 (d J=7.4 Hz, 1H), 7.87 (s, 2H), 7.57 (d J=7.9 Hz, 1H), 7.45 (t J=7.7 Hz, 1H), 6.73 (t J=6.0 Hz, 1H), 4.71 (t J=8.9 Hz, 2H), 4.65, (d J=6.0 Hz, 2H), 3.08 (t J=8.9 Hz, 2H), 2.90-2.60 (m, 6H), 2.32 (s, 6H), 2.09-2.01 (m, 1H), 1.76-1.64 (m, 1H).

Example 34

The following example was prepared from intermediate H1 and oxetan-3-one using a procedure similar to that used to prepare *example 33*.

Ex	Structure	^{1}H NMR	LC-MS
34	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(oxetan-3-ylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	^{1}H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 8.10 (s, 1H), 8.05 (s, 1H), 7.93 (d, J=7.7 Hz, 1H), 7.87 (s, 1H), 7.53 (d, J=7.4 Hz, 1H), 7.44 - 7.39 (m, 1H), 6.72 (dd, J=6.0, 6.0 Hz, 1H), 4.74 - 4.62 (m, 5H), 4.41 (s, 2H), 4.35 (m, 2H), 4.06 - 3.98 (m, 3H), 3.07 (t, J=8.8 Hz, 2H), 2.92 - 2.79 (m, 2H), 2.70 - 2.57 (m, 2H), 2.39 - 2.33 (m, 1H), 1.95 - 1.83 (m, 1H), 1.61 - 1.56 (m, 1H).	Rt = 2.02 min, m/z 544.0 [M+H]$^+$ (Method 3)

Example 35



N-(3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-4-((dimethylamino)methyl)benzamide (Example 35)

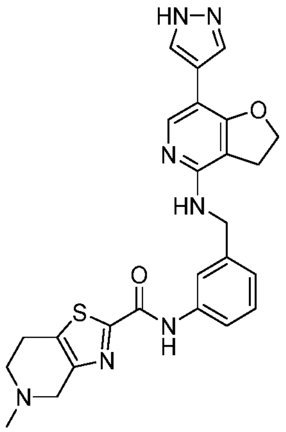
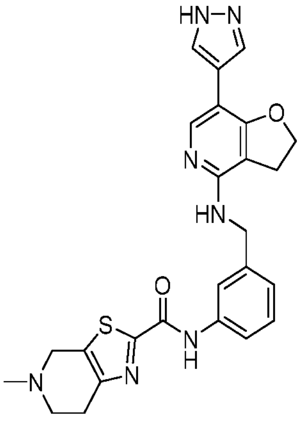
Intermediate K1 was dissolved in acetonitrile (2 mL) and then aqueous 12 M HCl (2 mL) was added. The solution was stirred for 1 h at RT until complete conversion. The reaction mixture was dried under reduced pressure and the resulting crude purified by flash chromatography on C18-silica by eluting 0-20% B with A (A: water/acetonitrile 95/5 + 0.1% HCOOH, B: acetonitrile/water 95/5 + 0.1% HCOOH) to give the desired product (3.8 mg).

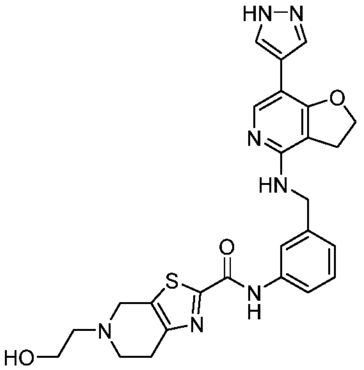
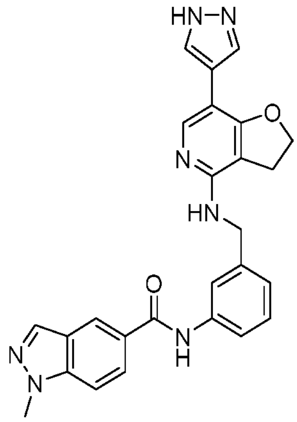
LCMS (Method 13): Rt = 3.24 min, m/z 469.2 [M+H]$^+$

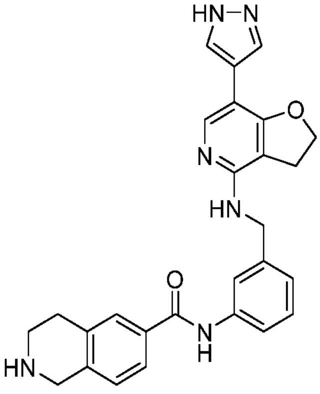
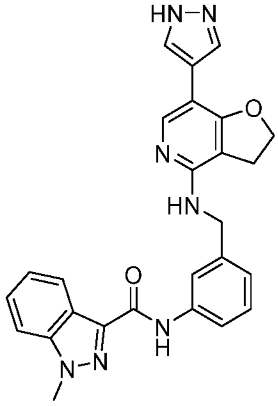
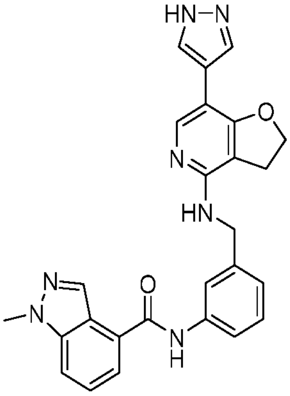
^{1}H NMR (400 MHz, DMSO-d6) δ 10.25 (s, 1H), 8.13 (s, 1H), 8.08 (s, 1H), 7.95 - 8.00 (d, J=7.9Hz, 2H), 7.85 (s, 2H), 7.73 (s, 1H), 7.51 - 7.68 (m, 3H), 7.27 (t, J=7.9 Hz, 1H), 7.09 (d, J=7.9 Hz, 1H), 6.67 (br s, 1H), 6.50 (s, 1H), 4.71 (t, J=4.7 Hz, 2H), 4.60 (d, J=4.6 Hz, 2H), 3.06 (br t, J=9.0 Hz, 2H), 2.60 (s, 6H).

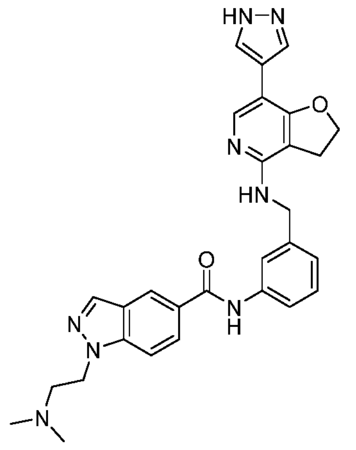
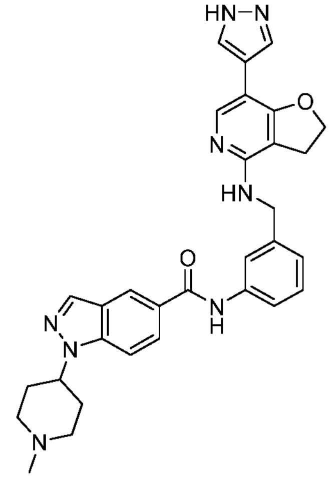
Example 36 to 52

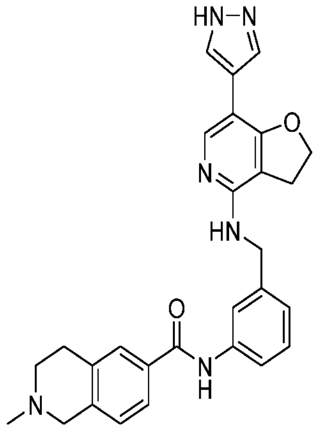
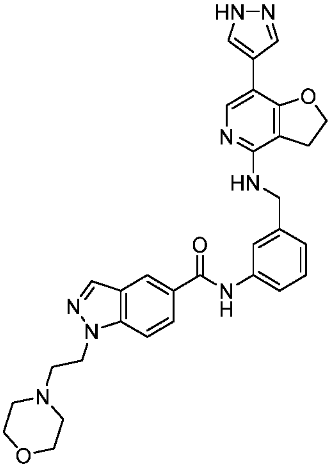
The following examples were prepared in a similar manner of *example 35* by replacing intermediate K1 with the given intermediates in the table below.

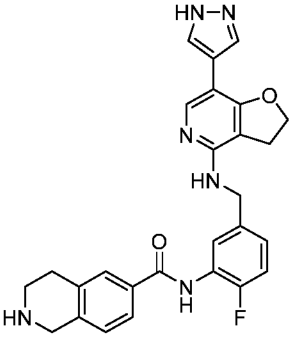
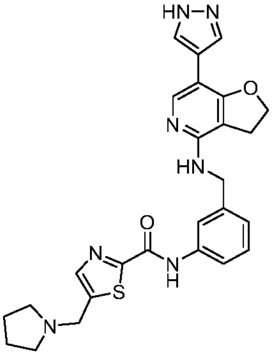
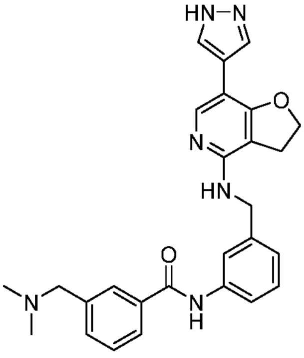
Ex	Structure	Intermediate	^{1}H NMR	LC-MS
36	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxamide	Intermediate K2	(400 MHz, DMSO-d6) δ 10.54 - 10.59 (m, 1H), 8.16 (s, 1H), 8.06 - 8.10 (m, 1H), 7.80 - 7.89 (m, 3H), 7.61 - 7.68 (m, 1H), 7.26 (t, J=7.8 Hz, 1H), 7.09 (d, J=7.7 Hz, 1H), 6.63 (t, J=6.0 Hz, 1H), 4.64 - 4.73 (m, 2 H), 4.57 (d, J=5.9 Hz, 2H), 3.61 (s, 2H), 3.05 (br t, J=8.9 Hz, 2 H), 2.95 (br t, J=5.59 Hz, 2H), 2.68 - 2.73 (m, 2H), 2.42 (s, 3H).	Rt = 3.24 min, m/z 488.2 $[M+H]^+$ (Method 13)
37	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide	Intermediate K3	(400 MHz, DMSO-d6) δ 10.58 (s, 1H), 8.15 (s, 1H), 8.07 (s, 1H), 7.78 - 7.92 (m, 3H), 7.64 (d, J=7.9 Hz, 1H), 7.25 (t, J=7.7 Hz, 1H), 7.09 (d, J=7.9 Hz, 1H), 6.58 - 6.73 (m, 1H), 4.68 (t, J=8.8 Hz, 2H), 4.56 (d, J=5.7 Hz, 2H), 3.69 (s, 2H), 3.05 (t, J=9.0 Hz, 2H), 2.83 - 2.96 (m, 2H), 2.68 - 2.83 (m, 2H), 2.39 (s, 3H).	Rt = 3.19 min, m/z 488.1 $[M+H]^+$ (Method 13)

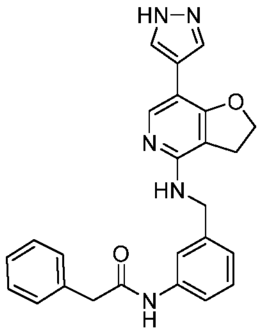
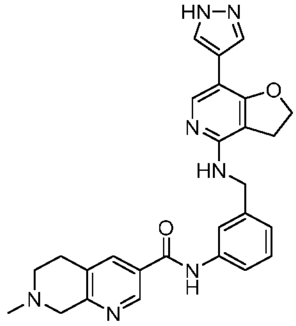
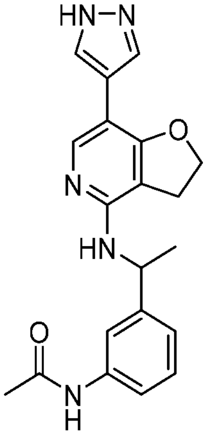
38	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide	Intermediate K4	(400 MHz, DMSO-d6) δ 13.31 (br s, 1H), 11.17 (br s, 1H), 10.83 (s, 1H), 8.63 (br t, J=6.1 Hz, 1H), 8.07 (s, 2 H), 7.99 (s, 1H), 7.89 (s, 1H), 7.77 (br d, J=8.3 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 7.17 (br d, J=7.89 Hz, 1H), 4.97 (br t, J=9.2 Hz, 2H), 3.15 - 4.89 (m, 14 H).	Rt = 3.12 min, m/z 518.2 $[M+H]^+$ (Method 13)
39	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-5-carboxamide	Intermediate K5	(400 MHz, DMSO-d6) δ 12.77 (s, 1H), 10.22 (s, 1 H), 8.45 (s, 1H), 8.23 (d, J=0.9 Hz, 1H), 8.09 (s, 1H), 7.58 - 8.02 (m, 6H), 7.27 (t, J=7.7 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 6.64 (t, J=5.9, 1H), 4.69 (t, J=9.0 Hz, 2H), 4.59 (d, J=4.6 Hz, 2H), 4.09 (s, 3 H), 3.06 (t, J=9.0 Hz, 2H).	Rt = 4.03 min, m/z 466.2 $[M+H]^+$ (Method 13)

40	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide	Intermediate K6	(400 MHz, DMSO-d6) d ppm 13.24 (br s, 1H), 10.33 (s, 1H), 9.46 (br s, 2H), 8.62 (br s, 1H), 7.99 - 8.07 (m, 3H), 7.80 - 7.90 (m, 3H), 7.68 (d, J=9.2 Hz, 1H), 7.23 - 7.49 (m, 2H), 6.87 - 7.23 (m, 1H), 4.97 (t, J=9.0 Hz, 2H), 4.74 (d, J=6.1 Hz, 2H), 4.27 - 4.47 (m, 2H), 3.40 (d, J=6.1 Hz, 2H), 3.25 (t, J=9.2 Hz, 2H), 3.09 (t, J=6.1 Hz, 2H).	Rt = 3.45 min, m/z 467.1 $[M+H]^+$ (Method 13)
41	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-3-carboxamide	Intermediate K7	(400 MHz, DMSO-d6) δ 10.20 (s, 1H), 8.22 (d, J=7.9 Hz, 2H), 8.09 (s, 1H), 7.80 - 7.85 (m, 3H), 7.78 (d, J=8.8 Hz, 1H), 7.70 (d, J=8.3 Hz, 1H), 7.50 (t, J=7.5 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.26 (t, J=7.9 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 6.63 (t, J=6.1 Hz, 1H), 4.69 (t, J=8.8 Hz, 2H), 4.59 (d, J=6.14 Hz, 2H), 4.19 (s, 3 H), 3.07 (t, J=8.8 Hz, 2H).	Rt = 4.74 min, m/z 466.4 $[M+H]^+$ (Method 13)
42	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-4-carboxamide	Intermediate K8	(400 MHz, DMSO-d6) δ 12.16 - 12.95 (br s, 1H), 10.34 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 7.82 - 7.90 (m, 3H), 7.79 (s, 1H), 7.75 (d, J=7.0 Hz, 1H), 7.66 - 7.76 (m, 1H), 7.52 (dd, J=8.3, 7.5 Hz, 1H), 7.28 (t, J=7.9 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 6.66 (m, 1H), 4.69 (t, J=8.8 Hz, 2H), 4.60 (d, J=6.1 Hz, 2H), 4.10 (s, 3 H), 3.06 (t, J=9.0 Hz, 2H).	Rt = 4.07 min, m/z 466.1 $[M+H]^+$ (Method 13)

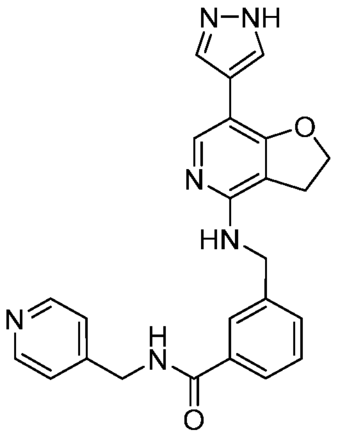
43	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxamide	Intermediate K9	(400 MHz, DMSO-d6) δ 12.77 (br s, 1H), 10.21 (s, 1H), 8.39 - 8.49 (m, 1H), 8.24 (s, 1H), 8.09 (s, 1H), 7.86 - 8.01 (m, 2H), 7.71 - 7.86 (m, 3H), 7.67 (m, J=7.89 Hz, 1H), 7.27 (t, J=7.89 Hz, 1H), 7.07 (m, 1H), 6.65 (t, J=6.14 Hz, 1H), 4.69 (t, J=8.99 Hz, 2H), 4.48 - 4.63 (m, 4H), 3.06 (t, J=8.77 Hz, 2H), 2.77 (br s 2H), 2.20 (br s, 6H).	Rt = 3.36 min, m/z 523.0 $[M+H]^+$ (Method 13)
44	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(1-methylpiperidin-4-yl)-1H-indazole-5-carboxamide	Intermediate K10	(400 MHz, DMSO-d6) δ 10.21 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 8.09 (s, 1H), 7.98 (dd, J=9.0, 1.5 Hz, 1H), 7.78 - 7.89 (m, 3H), 7.75 (s, 1H), 7.60 - 7.70 (m, 1H), 7.27 (t, J=7.9 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 6.65 (t, J=6.1 Hz, 1H), 4.60 - 4.70 (m, 3H), 4.59 (d, J=5.7 Hz, 2H), 2.98 - 3.16 (m, 5H), 2.37 - 2.47 (m, 4H), 2.23 (dq, J=12.1, 3.5 Hz, 2H), 2.00 (br s, 2H).	Rt = 3.43 min, m/z 549.2 $[M+H]^+$ (Method 13)

45	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide	Intermediate K11	(400 MHz, DMSO-d6) δ 12.16 - 13.09 (br s, 1H), 10.23 (s, 1H), 8.07 (s, 1H), 7.88 (br s, 2H), 7.83 (s, 2H), 7.73 - 7.77 (m, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.23 - 7.37 (m, 2H), 7.09 (d, J=7.5 Hz, 1H), 4.73 (t, J=8.1 Hz, 2H), 4.61 (d, J=5.7 Hz, 2H), 4.38 (br s, 2H), 3.35 - 3.61 (m, 2H), 3.01 - 3.24 (m, 4H), 2.89 (s, 3H).	Rt = 3.19 min, m/z 481.2 $[M+H]^+$ (Method 13)
46	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-morpholinoethyl)-1H-indazole-5-carboxamide	Intermediate K12	(400 MHz, DMSO-d6) δ 12.76 (br s, 1H) 10.23 (s, 1H) 8.44 (s, 1H) 8.22 - 8.30 (m, 1H) , 8.13 (s, 1H), 8.08 (s, 1H), 7.97 (d, J=8.8 Hz, 1H), 7.85 - 7.90 (m, 2H), 7.70 - 7.80 (m, 2H), 7.67 (d, J=7.9 Hz, 1H), 7.28 (t, J=7.7 Hz, 1H), 7.08 (d, J=7.5 Hz, 1H), 4.73 (t, J=8.6 Hz, 2H), 4.58 - 4.68 (d, J=6.1 Hz, 4H), 3.40 - 3.50 (br s, 4H), 3.09 (t, J=8.8 Hz, 2H), 2.80 (br s, 2H), 2.40 - 2.50 (br s, 2H), 1.30 - 1.50 (m, 2H).	Rt = 3.40 min, m/z 565.2 $[M+H]^+$ (Method 13)

47	 N-(5-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide	Intermediate K13	(400 MHz, DMSO-d6) δ 9.97 (s, 1H), 8.21 (s, 2H), 8.08 (s, 1H), 7.85 (s, 2H), 7.68 - 7.76 (m, 2H), 7.45 - 7.53 (m, 1H), 7.10 - 7.26 (m, 3H), 6.68 (t, J=6.1 Hz, 1H), 4.68 (t, J=8.8 Hz, 2H), 4.56 (d, J=6.1 Hz, 2H), 4.03 (s, 2H), 2.96 - 3.18 (m, 4H), 2.85 (t, J=5.9 Hz, 2H).	Rt = 3.21 min, m/z 485.1 [M+H]$^+$ (Method 13)
48	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(pyrrolidin-1-ylmethyl)thiazole-2-carboxamide	Intermediate K14	(400 MHz, DMSO-d6) δ 13.30 (br s, 1H), 11.53 - 11.63 (m, 1H), 10.85 (s, 1H), 8.65 (br t, J=6.0 Hz, 1H), 8.26 (s, 1H), 8.07 (s, 2H), 8.02 (s, 1H), 7.88 (s, 1H), 7.78 (br d, J=8.3 Hz, 1H), 7.38 (t, J=7.9 Hz, 1H), 7.18 (d, J=7.7 Hz, 1H), 4.98 (br t, J=9.1 Hz, 2H), 4.74 (br dd, J=9.2, 6.1 Hz, 4H), 3.34 - 3.39 (m, 2H), 3.25 (br t, J=9.1 Hz, 2H), 3.04 - 3.16 (m, 2H), 1.85 - 2.08 (m, 4H).	Rt = 3.24 min, m/z 502.3 [M+H]$^+$ (Method 13)
49	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-3-((dimethylamino)methyl)benzamide	Intermediate K15	(400 MHz, DMSO-d$_6$) δ 10.26 (s, 1H), 8.13 (s, 1H), 8.08 (s, 1H), 8.03 (s, 1H), 7.98 (d, J=7.5 Hz, 1H), 7.85 (s, 2H), 7.72 (s, 1H), 7.65 (s, 2H), 7.53-7.61 (m, 1H), 7.28 (t, J=7.9 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 6.61-6.76 (br s, 1H), 4.69 (m, 2H), 4.59 (d, J=6.1 Hz, 2H), 4.12 (br s, 2H), 3.06 (m, 2H), 2.58 (br s, 6H).	Rt = 3.06 min, m/z 469.2 [M+H]$^+$ (Method 13)

50	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-phenylacetamide	Intermediate K16	(400 MHz, DMSO-d6) δ 12.27 - 13.05 (br s, 1H), 10.33 (s, 1H), 8.05 (s, 1H), 7.76 - 7.97 (m, 2H), 7.43 - 7.59 (m, 2H), 7.20 - 7.34 (m, 7H), 6.93 - 7.07 (m, 1H), 4.65 - 4.87 (m, 2H), 4.56 (d, J=6.1 Hz, 2H), 3.61 (s, 2H), 2.90 - 3.19 (m, 2H).	Rt = 4.08 min, m/z 426.1 [M+H]$^+$ (Method 13)
51	 N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide	Intermediate K17	(400 MHz, DMSO-d6) δ 13.31 (br s, 1H), 11.47 (br s, 1H), 10.60 (s, 1H), 8.97 (d, J=2.2 Hz, 1H), 8.64 (t, J=6.1 Hz, 1H), 8.24 (d, J=1.8 Hz, 1H), 8.07 (s, 2H), 8.02 (s, 1H), 7.85 (s, 1H), 7.69 (d, J=8.3 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 7.15 (d, J=7.9 Hz, 1H), 4.97 (t, J=9.2 Hz, 2H), 4.76 (d, J=6.1 Hz, 2H), 4.32 - 4.58 (m, 4H), 3.30 - 3.45 (m, 2H), 3.25 (t, J=9.2 Hz, 2H), 2.95 (d, J=4.4 Hz, 3 H).	Rt = 3.03 min, m/z 482.1 [M+H]$^+$ (Method 13)
52	 N-(3-(1-((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)ethyl)phenyl)acetamide	Intermediate I3	(400 MHz, DMSO-d6) δ 9.83 (s, 1H), 8.02 (s, 1H), 7.83 (s, 2 H), 7.51 (s, 1H), 7.43 (br d, J=8.1 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 7.06 (d, J=7.7 Hz, 1H), 6.33 (d, J=7.9 Hz, 1H), 5.17 - 5.26 (m, 1H), 4.68 (t, J=9.0 Hz, 2H), 3.08 (t, J=8.9 Hz, 2H), 2.01 (s, 3H), 1.44 (d, J=7.0 Hz, 3H).	Rt = 0.41 min, m/z 364.3 [M+H]$^+$ (Method 6)

Example 53



3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyridin-4-ylmethyl)benzamide (Example 53)

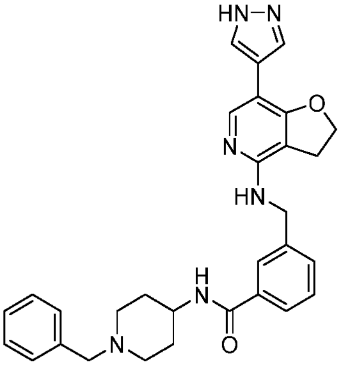
Intermediate E3 (90 mg, 0.205 mmol), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (114 mg, 0.410 mmol), tripotassium phosphate (130 mg, 0.615 mmol) were dissolved in THF (1 mL) and water (1 mL). The reaction was purged with argon for 10 min, then chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (24.18 mg, 0.031 mmol) was added and the resulting mixture heated at 95°C for 1 h. Reaction was quenched with water and the resulting mixture extracted with DCM. The organic phase was washed with saturated aqueous NaCl, passed down a phase separator, and the solvent evaporated *in vacuo*. The resulting crude was purified by flash chromatography on C18-silica by gradient elution with 0-30% B in A (A: water/acetonitrile 95/5+ 0.1% HCOOH, B:acetonitrile/water 95/5 + 0.1% HCOOH). The appropriate fractions were pooled, treated with aqueous 1M HCl and dried under reduced pressure to afford the title compound (32 mg).

LCMS (Method 6): Rt = 0.27 min, m/z 427.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d6) δ 13.02 - 13.85 (br s, 1H), 9.53 (br s, 1H), 8.83 (d, J=6.6 Hz, 2H), 8.53 - 8.73 (m, 1H), 7.99 - 8.16 (m, 4H), 7.85 - 7.98 (m, 3H), 7.62 - 7.64 (d, 1H), 7.44 - 7.56 (m, 1H), 4.96 (t, J=9.2 Hz, 2H), 4.83 (d, J=6.1 Hz, 2H), 4.73 (d, J=5.7 Hz, 2H), 3.25 (t, J=9.2 Hz, 2H).

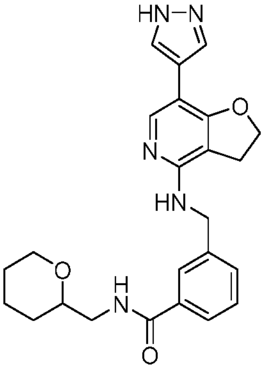
Example 54

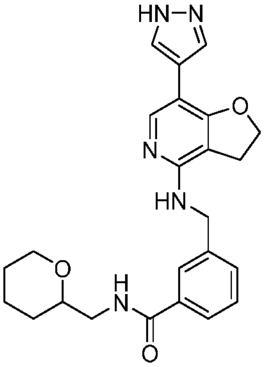
The following example was prepared from intermediate E4 using a procedure similar to that used to prepare *example 53*.

Ex	Structure	^{1}H NMR	LC-MS
54	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-benzylpiperidin-4-yl)benzamide	(400 MHz, DMSO-d6) δ 12.28 - 12.93 (br s, 1H), 8.20 (d, J=7.9 Hz, 1H), 8.14 (s, 1H), 8.07 (s, 1H), 7.85 (s, 2H), 7.80 (s, 1H), 7.65 (d, J=7.5 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.17 - 7.39 (m, 6H), 6.67 (t, J=5.9 Hz, 1H), 4.68 (t, J=8.8 Hz, 2H), 4.60 (d, J=5.7 Hz, 2H), 3.68 - 3.85 (m, 1H), 3.52 (br s, 2H), 3.04 (t, 2H), 2.85 (d, J=11.0 Hz, 2H), 2.09 (br s, 2H), 1.78 (d, J=10.5 Hz, 2H), 1.50 - 1.68 (m, 2H)	Rt = 3.24 min, m/z 509.1 [M+H]$^+$ (Method 13)

Example 55 and 56

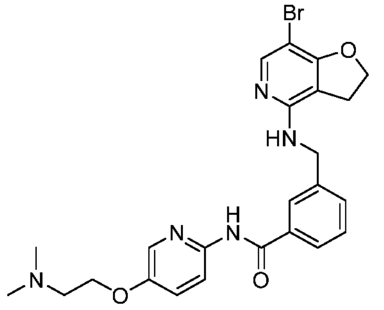
Example 55 and example 56 were enantiomerically resolved starting from racemic *example 11*, using the following chiral chromatographic conditions: YMC Cellulose-C 5µm, eluents: 30/70 IPA (0.5% DEA)/CO_2, flow 15 mL/min at 120 bar, column temperature 40°C. Two fractions were isolated and characterized as example 55 (enantiomer 1) and example 56 (enantiomer 2).

Ex	Structure	^{1}H NMR	LC-MS	Chiral LC
55	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (*Enantiomer 1*)	(400 MHz, d6-DMSO) δ 12.80 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.09 (s, 1H), 7.85-7.83 (m, 2H), 7.82-7.67 (m, 2H), 7.50-7.46 (m, 1H), 7.37 (t, J=7.7 Hz, 1H), 6.71 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 3.87 (dd, J=2.3, 10.8 Hz, 1H), 3.46 - 3.39 (m, 1H), 3.29 - 3.23 (m, 2H), 3.06 (t, J=8.8 Hz, 2H), 1.80-1.75 (m, 1H), 1.61 (d, J=12.5 Hz, 1H), 1.49-1.41 (m, 3H), 1.22-1.12 (m, 2H).	Rt = 2.68 min, m/z 434.0 [M+H]$^+$ (Method 3)	Rt = 8.62 min Conditions: YMC Cellulose-C 30/70 IPA (0.1% DEA)/CO_2

56	 3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (*Enantiomer 2*)	(400 MHz, d6-DMSO) δ 12.80 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.09 (s, 1H), 7.85-7.83 (m, 2H), 7.82-7.67 (m, 2H), 7.50-7.46 (m, 1H), 7.37 (t, J=7.7 Hz, 1H), 6.71 (t, J=6.1 Hz, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.62 (d, J=6.0 Hz, 2H), 3.87 (dd, J=2.3, 10.8 Hz, 1H), 3.45 - 3.40 (m, 1H), 3.30 - 3.23 (m, 2H), 3.06 (t, J=8.8 Hz, 2H), 1.80-1.75 (m, 1H), 1.61 (d, J=12.5 Hz, 1H), 1.49-1.41 (m, 3H), 1.22-1.12 (m, 2H).	Rt = 2.68 min, m/z 434.0 $[M+H]^+$ (Method 3)	Rt = 10.10 min Conditions: YMC Cellulose-C 30/70 IPA (0.1% DEA)/CO_2

Example 57

Step A

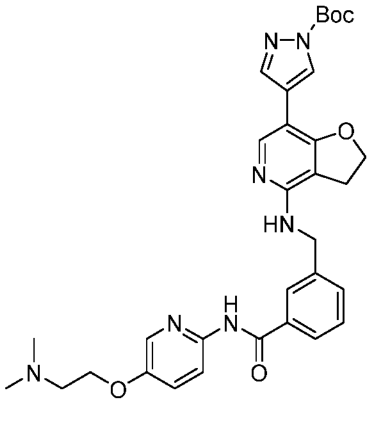


3-(((7-Bromo-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-(2-(dimethylamino)ethoxy)pyridin-2-yl)benzamide (Intermediate 57A)

To a solution of Intermediate D1 (400 mg, 1.15 mmol), 5-(2-dimethylaminoethoxy)pyridine-2-ylamine (230 mg, 1.26 mmol) and TBTU (440 mg, 1.37 mmol) in DCM (12 mL) was added DIPEA (0.60 mL, 3.44 mmol). The reaction mixture was stirred at room temperature for 18 h. A further amount of TBTU (369 mg, 1.15 mmol) was added and the mixture was stirred for 48 h. The reaction mixture was diluted with DCM and extracted with water. The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo* to obtain the title compound (380 mg).

LCMS (Method 2): Rt = 1.46 min, m/z 512.3/514.3 $[M+H]^+$

Step B

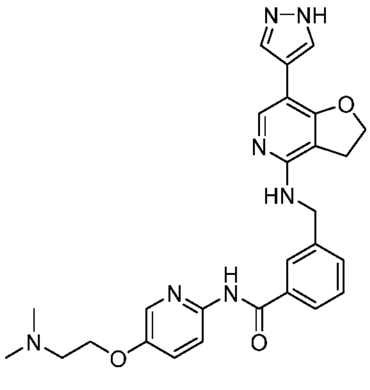


tert-Butyl 4-(4-((3-((5-(2-(dimethylamino)ethoxy)pyridin-2-yl)carbamoyl)-benzyl)amino)-2,3-dihydrofuro[3,2-c]pyridin-7-yl)-1H-pyrazole-1-carboxylate (Intermediate 57B)

To a degassed mixture Intermediate 57A (100 mg, 0.195 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (63 mg, 0.215 mmol) and cesium carbonate (95 mg, 0.293 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) added [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloro-methane (16 mg, 0.0195 mmol) and the reaction mixture was heated and stirred at 80°C for 1 h. The reaction mixture was cooled, filtered through a pad of Celite® and concentrated. The crude compound was loaded on an Isolute® SCX-2 cartridge and eluted with 2N ammonia in MeOH. The basic fractions were concentrated to afford the title compound (81 mg).

LCMS (Method 2): Rt = 1.50 min, m/z 600.5 $[M+H]^+$

Step C



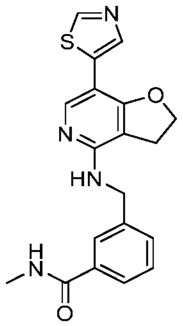
3-(((7-(1H-Pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-(2-(dimethylamino)ethoxy)pyridin-2-yl)benzamide (Example 57)

To a solution Intermediate 57B (60%, 80 mg, 0.080 mmol) in dichloromethane (2 mL) added trifluoroacetic acid (0.25 mL, 3.20 mmol) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated to dryness and submitted for MDAP (Sunfire C18 3x50mm, 3µm 5-95% ACN / H_2O (10mM NH_4CO_3), 1.7mL/min, RT then Luna Phenyl-Hexyl 21.2x150mm, 10µm 5-60% MeOH / H_2O +0.1% FA, 20mL/min, RT). The desired product was obtained as an off-white solid (15 mg).

LCMS (Method 3): Rt = 1.98 min, m/z 500 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6) δ 10.60 (s, 1H), 8.18 (s, 1H), 8.12 - 8.08 (m, 3H), 7.99 (s, 1H), 7.90 - 7.85 (m, 3H), 7.54 (d, J=7.7 Hz, 1H), 7.50 (dd, J=3.1, 9.2 Hz, 1H), 7.42 (t, J=7.7 Hz, 1H), 6.75 - 6.70 (m, 1H), 4.71 (t, J=8.9 Hz, 2H), 4.66 (d, J=5.9 Hz, 2H), 4.14 (t, J=5.7 Hz, 2H), 3.07 (t, J=8.8 Hz, 2H), 2.66 (t, J=5.8 Hz, 2H), 2.25 (s, 6H).

Example A



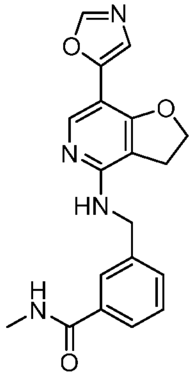
N-Methyl-3-(((7-(thiazol-5-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide (Example A)

A degassed mixture of intermediate E1 (29 mg, 0.08 mmol), 5-(tributylstannyl)thiazole (33 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium(0) (4.6 mg, 0.004 mmol) and copper(I) thiophene-2-carboxylate (1.5 mg, 0.008 mmol) in dioxane (5 mL) was heated at 150°C under microwave irradiation for 1 h. The reaction mixture, diluted with MeOH, was passed down an Isolute® SCX-2 cartridge eluting with MeOH and then 2M methanolic ammonia. The solution was concentrated in *vacuo* and the residue was purified by MDAP (Sunfire acetonitrile Basic 5-60, Sunfire C18 19x150mm, 10µm, 5-60% acetonitrile/H_2O (10mM NH_4CO_3), 20mL/min, RT) to give the desired product (7.8 mg).

LCMS (Method 3): Rt = 2.29 min, m/z 367.0 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.45-8.35 (m, 1H), 8.16 (s, 1H), 8.15 (d, J=0.7 Hz, 1H), 7.83-7.80 (m, 1H), 7.68-7.66 (m, 1H), 7.49-7.46 (m, 1H), 7.41-7.36 (m, 1H), 7.11-7.06 (m, 1H), 4.77 (t, J=8.9 Hz, 2H), 4.65 (d, J=6.0 Hz, 2H), 3.10 (t, J=8.9 Hz, 2H), 2.78 (d, J=4.5 Hz, 3H).

Example B



N-Methyl-3-(((7-(oxazol-5-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)benzamide (Example B)

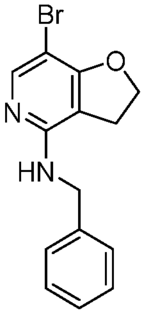
A mixture of intermediate E1 (75 mg, 0.21 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (48 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.021 mmol) and cesium carbonate (0.20 g, 0.62 mmol) in DMF (4 mL) and water (0.4 mL) was degassed with argon and heated at 100°C for 18 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo* and the residue was purified by MDAP (Luna Phenyl-Hexyl 3x50mm, 3µm 5-95% MeOH/H_2O (0.1% FA), 1.7 mL/min, RT) to give the product (13.4 mg).

LCMS (Method 3): Rt = 2.16 min, m/z 351.0 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6) δ 8.43-8.38 (m, 1H), 8.33 (s, 1H), 8.13 (s, 1H), 7.82 (s, 1H), 7.68 (ddd, J=1.5, 1.5, 8.0 Hz, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.39 (t, J=7.7 Hz, 1H), 7.18 (s, 1H,), 7.12 (t, J=6.1 Hz, 1H), 4.78 (t, J=9.0 Hz, 2H), 4.67 (d, J=6.0 Hz, 2H), 3.09 (t, J=8.9 Hz, 2H), 2.78 (d, J=4.5 Hz, 3H).

Example C

Step A

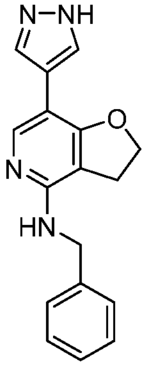


N-Benzyl-7-bromo-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Intermediate CA)

Intermediate CA was prepared using a procedure similar to that used for the synthesis of Intermediate C1 by replacing methyl 3-formylbenzoate with benzaldehyde.

LCMS (Method 16): Rt = 1.57 min, m/z 305.1/307.1 $[M+H]^+$

Step B



N-Benzyl-7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-amine (Example C)

A degassed mixture of Intermediate CA (50 mg, 0.164 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (58 mg, 0.197 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with DCM, (14 mg, 0.0164 mmol), cesium carbonate (53 mg, 0.164 mmol) in 1,4-dioxane (1.5 mL) and water (0.15 mL) was heated at 90°C for 20 h. A further portion of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (58 mg, 0.197 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane, (14 mg, 0.0164 mmol), and cesium carbonate (53 mg, 0.164 mmol) were added and the resulting mixture was allowed to stir for a further 2 h.. The reaction mixture was loaded onto an Isolute® SCX-2 cartridge and washed with DCM, then MeOH, then the product eluted with MeOH/NH_3 2N and concentrated *in vacuo*. The residue was purified by

MDAP (Sunfire C18 19x150mm, 10µm 20-80% ACN / H_2O (10mM NH_4CO_3), 20mL/min, RT) to give the product (10.74 mg).

LCMS (Method 3) RT = 2.59 min, m/z 293.3 $[MH]^+$

^{1}H NMR (400 MHz, DMSO-d6) δ 12.79 (s, 1H), 8.09 (s, 1H), 7.91 (s, 1H), 7.83 (s, 1H), 7.36 - 7.27 (m, 4H), 7.20 (tt, J=1.7, 7.1 Hz, 1H), 6.67 - 6.62 (m, 1H), 4.70 (t, J=8.9 Hz, 2H), 4.59 (d, J=6.0 Hz, 2H), 3.05 (t, J=8.9 Hz, 2H).

PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION.

In vitro inhibitory activity assay description ROCK1 and ROCK2 (Method A)

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 $MgCl_2$ 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 (2uL) and either Rho kinase 1 or 2 (4µl) were mixed and incubated for 30 min. Reactions were initiated by addition of ATP (4µL) such that the final concentration of ATP in the assay was 10µM. After a 1hour incubation 10µl of ADP-Glo Reagent was added and after a further 45 minutes incubation 20uL of Kinase Detection Buffer was added and the mixture incubated for a further 30 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 Log_{10} compound concentration using a sigmoidal fit with a variable slope and fixing the maximum to 100% and the minimum to 0%. To determine the Ki values the Cheng-Prusoff equation was utilized ($Ki=IC_{50}/(1+[S]/Km)$).

In vitro inhibitory activity assay description ROCK1 and ROCK2 (Method B)

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 $MgCl_2$ 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 25oC. Compound (2µL) and either Rho kinase 1 or 2 (4µl) were mixed and incubated for 30 min. Reactions were initiated by addition of ATP (4µL) such that the final concentration of ATP in the assay was 200µM. After a 1hour incubation 10µl of ADP-Glo Reagent was added and after a further 45 minute incubation 20µL of Kinase Detection Buffer was added and the mixture incubated for a further 30 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 Ki values the Cheng-Prusoff equation was utilized ($Ki=IC_{50}/(1+[S]/Km)$).

The Ki values obtained with Method A and with Method B were consistent.

Compounds according to the invention showed Ki values lower that 500 nM on both isoforms.

The results for individual compounds of the examples are provided below in Table 1 and are expressed as range of activity.

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 10µL assay containing 40mM Tris pH7.5, 20mM MgCl2 0.1mg/mL BSA, 50µM DTT and 260µM 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 (6µl) were mixed and incubated for 30 min. Reactions were initiated by addition of ATP (4µL) such that the final concentration of ATP in the assay was 10µM. After a 30 minute 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 IC_{50} (concentration of compound required to inhibit 50% of the enzyme activity) data were fit to a plot of % inhibition vs Log_{10} compound concentration using a sigmoidal fit with a variable slope and fixing the maximum to 100% and the minimum to 0%. To determine the Ki values the Cheng-Prusoff equation was utilized ($Ki=IC_{50}/(1+[S]/Km)$).

In vitro inhibitory activities for PKA were reported as selectivity ratio vs. ROCK2. Selectivity ratio PKA/ROCK2 was calculated by dividing the Ki value for PKA by Ki value of ROCK2 (method B) and reported into table 1.

Table 1.

Ex No.	**Method A**		**Method B**		**Ratio Ki PKA/ROCK2**
	ROCK 1	ROCK 2	ROCK 1	ROCK 2	
1			+++	+++	***
2			++	+++	***
3			++	++	***
4			++	++	
5			++	++	***
6			++	++	***
7			++	+++	
8			++	+++	***
9			++	++	
10			+++	+++	***
11			+++	+++	***
12			++	++	***
13			++	+++	
14			+++	+++	
15	+++	+++	+++	+++	***
16	+++	+++	+++	+++	***
17	+++	+++			
18	+++	+++			
19	+++	+++			

20	+++	+++			
21	+++	+++			
22	+++	+++			
23	+++	+++			
24	+++	+++			
25	+++	+++			
26	+++	+++			
27	+++	+++			
28	+++	+++	+++	+++	***
29	++	+++			
30	+++	+++			
31			+++	+++	***
32			+++	+++	***
33	+++	+++	+++	+++	***
34	+++	+++	+++	+++	***
35	+++	+++			
36	+++	+++			
37	+++	+++			
38	+++	+++			
39	+++	+++			
40	+++	+++			
41	+	++			
42	++	+++			
43	+++	+++	+++	+++	
44	+++	+++	+++	+++	
45	+++	+++	+++	+++	
46	+++	+++	+++	+++	
47	+++	+++			
48	+++	+++	+++	+++	
49	+++	+++			
50	++	++			
51	+++	+++			
52	++	++			
53	+++	+++			
54	+++	+++			
55			+++	+++	***
56			+++	+++	***
57			+++	+++	***
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:

+ + + : Ki $\leq$ 3 nM

+ + : 3 < Ki $\leq$ 30 nM

+ : Ki > 30 nM

The Compounds according to the invention showed advantageously Ki values equal to or lower than 30 nM , preferably even equal to or lower that 3 nM, at least on ROCK2; further preferably lower than 30 nM, preferably even equal to or lower that 3 nM, on both isoforms. . The compounds according to the invention are more potent than the *comparative example A and B.*

Moreover, preferred compounds according to the invention exhibit marked selectivity versus PKA. The compounds according to the invention are at least 5 fold, preferably equal to or more than 10 fold, selective in terms of ROCK2 selectivity vs PKA. Overall the compounds of the invention are more selective than the *comparative example C.*

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

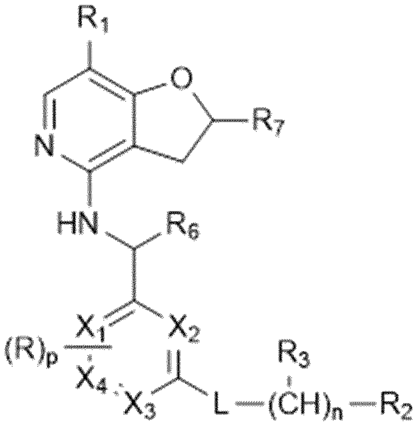
*** : ratio $\geq$ 10

** : 5 < ratio < 10

* : ratio $\leq$ 5

CLAIMS

1. A compound of formula (I)



I

wherein

X₁, X₂, X₃ and **X₄** are all CH or one of X_1, X_2, X_3 and X_4 is N and the others are CH;

p is zero or an integer from 1 to 4;

each R, when present, is halogen in each occurrence independently selected from $(C_1\text{-}C_6)$alkyl and halogen selected from F, Cl, Br and I;

R_1 is pyrazolyl;

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

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

R_2 and R_3 are in each occurrence independently selected from the group consisting of

-H,

halogen,

-OH,

$-(CH_2)_mNR_4R_5$,

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

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

(C_1-C_6) alkoxy,

(C_1-C_6) alkoxy (C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)haloalkoxy,

(C_1-C_6)haloalkoxy (C_1-C_6)alkyl,

(C_3-C_{10})cycloalkyl,

aryl, heteroaryl and (C_3-C_6)heterocycloalkyl,

each of which cycloalkyl, aryl, heteroaryl and heterocycloalkyl

is in its turn optionally and independently substituted with one or more groups selected from

halogen,

-OH,

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6) alkoxy,

(C_1-C_6) alkoxy (C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)haloalkoxy,

$-(CH_2)_mNR_4R_5$,

$-O-(CH_2)_mNR_4R_5$,

alkanoyl,

aryl, heteroaryl, cycloalkyl,

aryl-(C_1-C_6)alkyl,

(C_3-C_6)heterocycloalkyl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl,

each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is still further optionally substituted by one or more group selected independently from halogen, -OH, (C_1-C_8)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl;

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

R_4 and R_5, the same or different, are selected from the group consisting of

-H,

(C_1-C_6)alkyl,

$(C_1\text{-}C_6)$haloalkyl,
$(C_1\text{-}C_6)$hydroxyalkyl,
$(C_3\text{-}C_6)$heterocycloalkyl;
R_6 and R7 are independently selected from the group consisting of -H, $(C_1\text{-}C_6)$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, wherein X_3 and X_4 are all CH groups and X_1 or X_2 are in the alternative independently a CH group or a nitrogen atom ;
R_1 is pyrazol-4-yl;
all the other variables being as defined in claim 1;
single enantiomers, diastereoisomers and mixtures thereof in any proportion and/or pharmaceutically acceptable salts and solvates thereof.

3. A compound according to Claim 2, wherein X_1 , X_2, X_3 , X_4 are all CH group;
each R, when present, is halogen in each occurrence independently selected from F, Cl, Br and I;
R_1 is pyrazolyl;
L is -C(O)NH- or -NHC(O)- ;
n is 0;
R_2 is in each occurrence independently selected from the group consisting of
$(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$hydroxyalkyl,
$(C_1\text{-}C_6)$ alkoxy $(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$haloalkyl,
$(C_1\text{-}C_6)$haloalkoxy $(C_1\text{-}C_6)$alkyl;
all the other variables being as defined in claim 1,
single enantiomers, diastereoisomers and mixtures thereof in any proportion and/or pharmaceutically acceptable salts and solvates thereof.

4. A compound according to Claim 1, wherein $\mathbf{X_1}$, $\mathbf{X_2}$, $\mathbf{X_3}$ and $\mathbf{X_4}$ are all CH;
p is zero or an integer from 1 to 4;
each R, when present, is halogen in each occurrence independently selected from F, Cl, Br and I;

R_1 is pyrazolyl;

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

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

R_3 when present is H, or (C_1-C_6)hydroxyalkyl, and

R_2 is selected from the group consisting of

aryl, heteroaryl and (C_3-C_6)heterocycloalkyl,

each of which aryl, heteroaryl and heterocycloalkyl

is in its turn optionally and independently substituted with one or more groups selected from

(C_1-C_6)alkyl,

(C_1-C_6)hydroxyalkyl,

(C_1-C_6) alkoxy,

(C_1-C_6) alkoxy (C_1-C_6)alkyl,

-$(CH_2)_mNR_4R_5$,

-O-$(CH_2)_mNR_4R_5$,

aryl, heteroaryl, cycloalkyl,

aryl-(C_1-C_6)alkyl,

(C_3-C_6)heterocycloalkyl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl,

each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is still further optionally substituted by one or more group selected independently from halogen, -OH, (C_1-C_8)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl;

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

R_4 and R_5, the same or different, are selected from the group consisting of

-H,

(C_1-C_6)alkyl,

(C_1-C_6)haloalkyl,

(C_1-C_6)hydroxyalkyl,

(C_3-C_6)heterocycloalkyl;

or pharmaceutically acceptable salts and solvates thereof.

5. A compound according to Claim 4, wherein R_2 is selected from (pyridinyl)methyl, (pyridinyl)ethyl, methoxypyridinyl, ((dimethylamino)ethoxy)pyridinyl, or from 1-

(2-(dimethylamino)ethyl)-1H-indazole-5-yl, 1-(2-morpholinoethyl)-1H-indazole-5-yl, 1-(1-methylpiperidin-4-yl)-1H-indazole-5-yl.

6. A compound of formula (I) according to Claim 1, wherein **X_1, X_2, X_3** and **X_4** are all CH;
p is zero or 1;
each R, when present, is F;
R_1 is **pyrazol 4-yl**;
L is -C(O)NH- or -NHC(O)- ;
n is in each occurrence independently 0 or an integer selected from 1, 2;
R_2 and R_3 are in each occurrence independently selected from the group consisting of
-H,
(C_1-C_6)alkyl which is methyl,
(C_1-C_6) alkoxy (C_1-C_6)alkyl which is 2-methoxyethyl,
(C_1-C_6)haloalkyl which is 3-fluoropropyl,
(C_3-C_{10})cycloalkyl which is cyclopropyl, cyclobutyl,
aryl which is phenyl;
heteroaryl which is pyridinyl, pyrazolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrimidinyl, 1,2,5-oxadiazol-3-yl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl, 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl, 1,2,3,4-tetrahydroisoquinoline-6yl, 5,6,7,8-tetrahydro-1,7-naphthyridinyl, 1H-indole-5yl, isoindolin-yl, 1H-indazole-5yl,
and
(C_3-C_6)heterocycloalkyl which is piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydro-2H-pyran-yl;
each of which cycloalkyl, aryl, heteroaryl and heterocycloalkyl
is in its turn optionally and independently substituted with one or more groups selected from
halogen which is Fluoro,
(C_1-C_6)alkyl which is methyl,
(C_1-C_6)hydroxyalkyl, which is hydroxyethyl,

(C_1-C_6) alkoxy, which is methoxy,

-$(CH_2)_mNR_4R_5$ which is (dimethylamino)methyl, 2-(dimethylamino)ethyl, dimethylamino wherein R_4 and R_5 are methyl and m is 0, 1or 2, oxetan-3-ylamino wherein R_4 is H, R_5 is oxetanyl and m is 0,

-O-$(CH_2)_mNR_4R_5$ which is ((dimethylamino)ethoxy)pyridinyl;

cycloalkyl which is cyclopropyl,

aryl-(C_1-C_6)alkyl, which is benzyl, phenethyl,

(C_3-C_6)heterocycloalkyl, which is oxetan-3-yl, piperidin-4-yl,

(C_3-C_8)heterocycloalkyl-(C_1-C_6)alkyl, which is morpholinoethyl, pyrrolidin-1-ylmethyl,

each of said heterocycloalkyl is still further optionally substituted by (C_1-C_8)alkyl which is methyl;

R_6 is -H, or methyl; and R_7 is -H

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

7. A compound according to claim 1 selected from:

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

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

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

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

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5,5-dimethyltetrahydrofuran-3-yl)benzamide;

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

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(pyrimidin-5-ylmethyl)benzamide;

N-((1,2,5-oxadiazol-3-yl)methyl)-3-(((7-(1H-pyrazol-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-((tetrahydro-2H-pyran-2-yl)methyl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(isoxazol-3-ylmethyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(thiazol-4-ylmethyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-(1-methylpiperidin-4-yl)ethyl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)phenyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(3-((dimethylamino)methyl)benzyl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)benzamide;

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

(S)-3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(2-hydroxy-1-phenylethyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(4-((dimethylamino)methyl)benzyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methylthiophen-2-yl)methyl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)methyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((2-methylisoindolin-5-yl)methyl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-methoxypyridin-2-yl)benzamide;

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(dimethylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(6-(oxetan-3-ylamino)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-4-((dimethylamino)methyl)benzamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine-2-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-

yl)amino)methyl)phenyl)-1-methyl-1H-indazole-5-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-3-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-methyl-1H-indazole-4-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-(dimethylamino)ethyl)-1H-indazole-5-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(1-methylpiperidin-4-yl)-1H-indazole-5-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-1-(2-morpholinoethyl)-1H-indazole-5-carboxamide;

N-(5-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-2-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-5-(pyrrolidin-1-ylmethyl)thiazole-2-carboxamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-3-((dimethylamino)methyl)benzamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-2-phenylacetamide;

N-(3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)phenyl)-7-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine-3-carboxamide;

N-(3-(1-((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)ethyl)phenyl)acetamide;

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

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

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (Enantiomer 1);

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)benzamide (Enantiomer 2);

3-(((7-(1H-pyrazol-4-yl)-2,3-dihydrofuro[3,2-c]pyridin-4-yl)amino)methyl)-N-(5-(2-(dimethylamino)ethoxy)pyridin-2-yl)benzamide;

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

8. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carrier or excipient.

9. A pharmaceutical composition according to claim 8 suitable to be administered by inhalation, selected from inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

10. A device comprising the pharmaceutical composition according to claim 9, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a soft mist nebulizer.

11. A pharmaceutical composition according to claim 8 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, and elixirs formulations.

12. A compound or a pharmaceutical composition according to any one of claims 1 to 7 or 8 for use as a medicament.

13. A compound or a pharmaceutical composition for use according to claim 12, in the prevention and /or treatment of 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).

14. A combination of a compound as defined in any one of the claims 1 to 7 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); prostaciclin 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 selective cleavage agents; agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroylase 1 (TPH1) inhibitors and multi-kinase inhibitors.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/085380

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/048 A61K31/506 A61P11/00 A61P11/06
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/238628 A1 (CHIESI FARM SPA [IT]) 19 December 2019 (2019-12-19) cited in the application page 1, line 2 - line 6; claim 1 -----	1-14
A	WO 2004/039796 A1 (BAYER HEALTHCARE AG [DE]; FEURER ACHIM [DE] ET AL.) 13 May 2004 (2004-05-13) cited in the application page 44, line 7; claim 1 ----- -/--	1-14

☒ 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

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"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	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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1

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OLIVIER DEFERT ET AL: "Rho kinase inhibitors: a patent review (2014 - 2016)", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 27, no. 4, 16 January 2017 (2017-01-16), pages 507-515, XP055400492, GB ISSN: 1354-3776, DOI: 10.1080/13543776.2017.1272579 page 509; figures 1-2 -----	1-14
A	YANGBO FENG ET AL: "Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential", JOURNAL OF MEDICINAL CHEMISTRY, vol. 59, no. 6, 30 October 2015 (2015-10-30), pages 2269-2300, XP055535566, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.5b00683 page 2275 - page 2276; figures 5-6 -----	1-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2021/085380

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019238628 A1	19-12-2019	AR 114926 A1	28-10-2020
		EP 3807273 A1	21-04-2021
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		WO 2004039796 A1	13-05-2004

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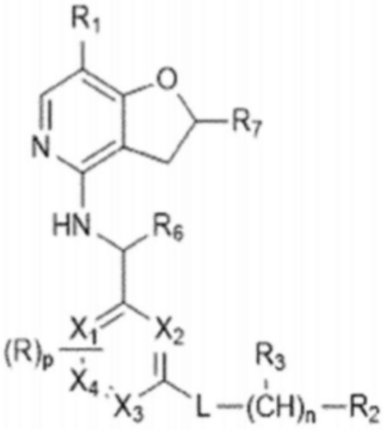
(54)发明名称

作为RHO-激酶抑制剂的二氢呋喃并吡啶衍生物

(57)摘要

本发明涉及抑制Rho激酶的为二氢呋喃并吡啶衍生物的式(I)的化合物，制备这类化合物的方法，包含它们的药物组合物及其治疗用途。特别地，本发明的化合物可以用于治疗许多与ROCK酶机制相关的病症，例如肺病，包括哮喘，慢性阻塞性肺病(COPD)，特发性肺纤维化(IPF)和肺动脉高压(PAH)。

1.式(I)的化合物



I

其中

X_1,X_2,X_3和X_4均为CH,或X_1,X_2,X_3和X_4之一为N且其它的为CH;

p为0或1至4的整数;

每个R在存在时为卤素,在每次出现时独立地选自(C_1-C_6)烷基和卤素,所述卤素选自F,Cl,Br和I;

R_1为吡唑基;

L为-C(O)NH-或-NHC(O)-;

n在每次出现时独立地为0或选自1,2或3的整数;

R_2和R_3在每次出现时独立地选自

-H,

卤素,

-OH,

-$(CH_2)_mNR_4R_5$,

(C_1-C_6)烷基,

(C_1-C_6)羟基烷基,

(C_1-C_6)烷氧基,

(C_1-C_6)烷氧基(C_1-C_6)烷基,

(C_1-C_6)卤代烷基,

(C_1-C_6)卤代烷氧基,

(C_1-C_6)卤代烷氧基(C_1-C_6)烷基,

(C_3-C_{10})环烷基,

芳基,杂芳基和(C_3-C_6)杂环烷基,

该环烷基,芳基,杂芳基和杂环烷基中每一个

又任选且独立地被一个或多个基团取代,所述基团选自

卤素,

-OH,

(C_1-C_6)烷基,

(C_1-C_6)羟基烷基，

(C_1-C_6)烷氧基，

(C_1-C_6)烷氧基(C_1-C_6)烷基，

(C_1-C_6)卤代烷基，

(C_1-C_6)卤代烷氧基，

$-(CH_2)_mNR_4R_5$，

$-O-(CH_2)_mNR_4R_5$，

烷酰基，

芳基，杂芳基，环烷基，

芳基-(C_1-C_6)烷基，

(C_3-C_6)杂环烷基，

(C_3-C_8)杂环烷基-(C_1-C_6)烷基，

所述芳基，杂芳基，环烷基，杂环烷基中每一个仍然进一步任选地被一个或多个基团取代，所述基团独立地选自卤素，-OH，(C_1-C_8)烷基，(C_1-C_6)卤代烷基，(C_1-C_6)羟基烷基；

m在每次出现时独立地为0或选自1，2或3的整数；

R_4和R_5相同或不同，选自

-H，

(C_1-C_6)烷基，

(C_1-C_6)卤代烷基，

(C_1-C_6)羟基烷基，

(C_3-C_6)杂环烷基；

R_6和R7独立地选自-H，(C_1-C_6)烷基；

其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

2.权利要求1的化合物，其中X_3和X_4均为CH基团，且X_1或X_2可选择地独立地为CH基团或氮原子；

R_1为吡唑-4-基；

所有其它变量如在权利要求1中所定义；

其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

3.权利要求2的化合物，其中X_1，X_2，X_3，X_4均为CH基团；

每个R在存在时为卤素，所述卤素在每次出现时独立地选自F，Cl，Br和I；

R_1为吡唑基；

L为-C(O)NH-或-NHC(O)-；

n为0；

R_2在每次出现时独立地选自

(C_1-C_6)烷基，

(C_1-C_6)羟基烷基，

(C_1-C_6)烷氧基(C_1-C_6)烷基，

(C_1-C_6)卤代烷基，

(C_1-C_6)卤代烷氧基(C_1-C_6)烷基；

所有其它变量如在权利要求1中所定义，

其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

4.权利要求1的化合物，其中X_1，X_2，X_3和X_4均为CH；

p为0或1至4的整数；

每个R在存在时为卤素，所述卤素在每次出现时独立地选自F，Cl，Br和I；

R_1为吡唑基；

L为-C(O)NH或-NHC(O)-；

n在每次出现时独立地为0或选自1，2或3的整数；

R_3在存在时为H，或(C_1-C_6)羟基烷基，且

R_2选自

芳基，杂芳基和(C_3-C_6)杂环烷基，

该芳基，杂芳基和杂环烷基中每一个

又任选且独立地被一个或多个基团取代，所述基团选自

(C_1-C_6)烷基，

(C_1-C_6)羟基烷基，

(C_1-C_6)烷氧基，

(C_1-C_6)烷氧基(C_1-C_6)烷基，

$-(CH_2)_mNR_4R_5$，

$-O-(CH_2)_mNR_4R_5$，

芳基，杂芳基，环烷基，

芳基-(C_1-C_6)烷基，

(C_3-C_6)杂环烷基，

(C_3-C_8)杂环烷基-(C_1-C_6)烷基，

所述芳基，杂芳基，环烷基，杂环烷基中每一个仍然进一步任选地被一个或多个基团取代，所述基团独立地选自卤素，-OH，(C_1-C_8)烷基，(C_1-C_6)卤代烷基，(C_1-C_6)羟基烷基；

m在每次出现时独立地为0或选自1，2或3的整数；

R_4和R_5相同或不同，选自

-H，

(C_1-C_6)烷基，

(C_1-C_6)卤代烷基，

(C_1-C_6)羟基烷基，

(C_3-C_6)杂环烷基；

或其药学上可接受的盐和溶剂合物。

5.权利要求4的化合物，其中R_2选自

(吡啶基)甲基，(吡啶基)乙基，甲氧基吡啶基，

((二甲基氨基)乙氧基)吡啶基，或选自

1-(2-(二甲基氨基)乙基)-1H-吲唑-5-基，

1-(2-吗啉代乙基)-1H-吲唑-5-基，

1-(1-甲基哌啶-4-基)-1H-吲唑-5-基。

6.权利要求1的式(I)的化合物，其中X_1，X_2，X_3和X_4均为CH；

p为0或1；

每个R在存在时为F；

R_1为吡唑-4-基；

L为-C(O)NH-或-NHC(O)-；

n在每次出现时独立地为0或选自1，2的整数；

R_2和R_3在每次出现时独立地选自

-H，

(C_1-C_6)烷基，其为甲基，

(C_1-C_6)烷氧基(C_1-C_6)烷基，其为2-甲氧基乙基，

(C_1-C_6)卤代烷基，其为3-氟丙基，

(C_3-C_{10})环烷基，其为环丙基，环丁基，

芳基，其为苯基；

杂芳基，其为吡啶基，吡唑基，噻吩基，咪唑基，噁唑基，异噁唑基，噻唑基，嘧啶基，1，2，5-噁二唑-3-基，4，5，6，7-四氢吡唑并[1，5-a]吡嗪-2-基，4，5，6，7-四氢噻唑并[5，4-c]吡啶-2-基，4，5，6，7-四氢苯并[d]噻唑-2-基，1，2，3，4-四氢异喹啉-6-基，5，6，7，8-四氢-1，7-萘啶基，1H吲哚-5-基，异二氢吲哚基，1H-吲唑-5-基，

和

(C_3-C_6)杂环烷基，其为哌啶基，吗啉基，四氢呋喃基，四氢-2H-吡喃基；

该环烷基，芳基，杂芳基和杂环烷基中每一个

又任选且独立地被一个或多个基团取代，所述基团选自

卤素，其为氟，

(C_1-C_6)烷基，其为甲基，

(C_1-C_6)羟基烷基，其为羟基乙基，

(C_1-C_6)烷氧基，其为甲氧基，

$-(CH_2)_mNR_4R_5$，其为(二甲基氨基)甲基，2-(二甲基氨基)乙基，二甲基氨基，其中R_4和R_5为甲基，且m为0，1或2，氧杂环丁烷-3-基氨基，其中R_4为H，R_5为氧杂环丁烷基，且m为0，

$-O-(CH_2)_mNR_4R_5$，其为((二甲基氨基)乙氧基)吡啶基；

环烷基，其为环丙基，

芳基-(C_1-C_6)烷基，其为苄基，苯乙基，

(C_3-C_6)杂环烷基，其为氧杂环丁烷-3-基，哌啶-4-基，

(C_3-C_8)杂环烷基-(C_1-C_6)烷基，其为吗啉代乙基，吡咯烷-1-基甲基，

所述杂环烷基中每一个仍然进一步任选地被(C_1-C_8)烷基取代，所述(C_1-C_8)烷基为甲基；

R_6为-H或甲基；且R_7为-H；

其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐

和溶剂合物。

7.权利要求1的化合物，选自：

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-环丙基哌啶-4-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-吡唑-3-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-氟丙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-2-基甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(环丙基甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5,5-二甲基四氢呋喃-3-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-甲氧基乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-咪唑-4-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-5-基甲基)苯甲酰胺；

N-((1,2,5-噁二唑-3-基)甲基)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3,3-二氟环丁基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(异噁唑-3-基甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(噻唑-4-基甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-

N-(5-甲基-4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-甲基哌啶-4-基)乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-4-基)乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二甲基氨基)甲基)苯基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二

甲基氨基)甲基)苄基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-吗啉代乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-3-基)乙基)苯甲酰胺；

(S)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-羟基-1-苯基乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(4-((二甲基氨基)甲基)苄基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基噻吩-2-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苯乙基哌啶-4-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-(氧杂环丁烷-3-基)哌啶-4-基)乙基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((2-甲基异二氢吲哚-5-基)甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲氧基吡啶-2-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-4-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(二甲基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(氧杂环丁烷-3-基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-4-((二甲基氨基)甲基)苯甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[4,5-c]吡啶-2-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(2-羟基乙基)-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-5-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-3-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-4-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(1-甲基哌啶-4-基)-1H-吲唑-5-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-甲基-1,2,3,4-四氢异喹啉-6-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-吗啉代乙基)-1H-吲唑-5-甲酰胺；

N-(5-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-2-氟苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(吡咯烷-1-基甲基)噻唑-2-甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-3-((二甲基氨基)甲基)苯甲酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-苯基乙酰胺；

N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-7-甲基-5,6,7,8-四氢-1,7-萘啶-3-甲酰胺；

N-(3-(1-((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)乙基)苯基)乙酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-4-基甲基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苄基哌啶-4-基)苯甲酰胺；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体1)；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体2)；

3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-(2-(二甲基氨基)乙氧基)吡啶-2-基)苯甲酰胺；

其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐

和溶剂合物。

8.药物组合物,包含与一种或多种药学上可接受的载体或赋形剂混合的如权利要求1至7任一项中所定义的化合物或其药学上可接受的盐或溶剂合物。

9.权利要求8的药物组合物,其适合于通过吸入施用,选自可吸入散剂,含抛射剂的计量气雾剂或不含抛射剂的可吸入制剂。

10.包含权利要求9的药物组合物的装置,其可以是单剂量或多剂量干粉吸入器,定量吸入器和软雾雾化器。

11.权利要求8的药物组合物,其适合于通过口服途径施用,选自软胶囊,胶囊剂,胶囊形片剂,颗粒剂,锭剂和整装散剂或水性和非水性溶液,乳剂,混悬剂,糖浆剂和酏剂制剂。

12.权利要求1至7或8任一项的化合物或药物组合物,用作药物。

13.权利要求12的用途的化合物或药物组合物,用于预防和/或治疗肺病,所述肺病选自哮喘,慢性阻塞性肺病COPD,特发性肺纤维化(IPF),肺高压(PH),且特别是肺动脉高压(PAH)。

14.如权利要求1至7任一项中所定义的化合物与一种或多种活性成分的组合,所述活性成分选自以下类别:有机硝酸酯和NO供体;吸入的NO;可溶性鸟苷酸环化酶(sGC)刺激剂;前列环素类似物PGI2和前列环素受体激动剂;抑制环鸟苷一磷酸(cGMP)和/或环腺苷一磷酸(cAMP)的降解的化合物;人嗜中性弹性蛋白酶抑制剂;抑制信号转导级联的化合物;用于降血压的活性物质;中性内肽酶抑制剂;渗透剂;ENaC阻断剂;抗炎药,包括皮质类固醇和趋化因子受体拮抗剂;抗组胺药;镇咳药;抗生素和DNA酶药物物质和选择性裂解剂;抑制Smad2和Smad3的ALK5和/或ALK4磷酸化的活性剂;色氨酸羟化酶1(TPH1)抑制剂和多激酶抑制剂。

作为RHO-激酶抑制剂的二氢呋喃并吡啶衍生物

发明领域

[0001] 本发明涉及抑制Rho激酶的新化合物(下文称为ROCK抑制剂);制备这些化合物的方法,包含它们的药物组合物及其治疗用途。

[0002] 发明背景

[0003] 本发明的化合物是Rho-相关卷曲螺旋形成蛋白激酶(ROCK)的ROCK-I和/或ROCK-II同种型的活性或功能的抑制剂。

[0004] Rho-相关卷曲螺旋形成蛋白激酶(ROCK)属于丝氨酸-苏氨酸激酶的AGC(PKA/PKG/PKC)家族。已经描述了ROCK的两种人同种型,ROCK-I(也称为p160 ROCK或ROKβ或ROCK1)和ROCK-II(ROKα或ROCK2)为约160kDa的蛋白质,其包含N-末端Ser/Thr激酶结构域,随后是卷曲螺旋结构,pleckstrin同源性结构域和C-末端的富含半胱氨酸的区域(Riento,K.;Ridley,A.J.Rocks:multifunctional kinases in cell behaviour.Nat.Rev.mol.Cell Biol.2003,4,446-456)。

[0005] ROCK-II和ROCK-I均在许多人和啮齿动物组织中表达,包括心脏,胰腺,肺,肝,骨骼肌,肾和脑(上文Riento和Ridley,2003)。在患有肺高压的患者中,与对照相比,ROCK活性在肺组织和循环嗜中性粒细胞两者中显著更高。(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)。在嗜中性粒细胞ROCK活性与肺高压的严重程度和持续时间之间建立了显著相关性(Duong-Quy等人,2013)。

[0006] 目前存在大量证据表明ROCK参与许多途径,这些途径有助于与几种急性和慢性肺病(包括哮喘,COPD,支气管扩张和ARDS/ALI)相关的病理学。鉴于ROCK的生物效应,选择性抑制剂具有治疗呼吸系统疾病中的许多病理机制的潜力,例如平滑肌高反应性,支气管收缩,气道炎症和气道重塑,神经调节和由于呼吸道病毒感染引起的恶化(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年10月;1(1):25-33)。实际上,Rho激酶抑制剂Y-27632引起支气管扩张并减少肺嗜酸粒细胞增多运输和气道高反应性(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)。已经在患有特发性肺纤维化(IPF)的人和该疾病的动物模型中证明了肺ROCK活化。ROCK抑制剂可以预防这些模型中的纤维化,并且更重要的是,诱导已经建立的纤维化的消退,因此表明ROCK抑制剂为阻止肺纤维化进展的潜在有力的药理学活性剂(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)。

[0007] 文献中已经描述了作为Rho激酶抑制剂的各种化合物。参见例如WO2004/039796,其公开了苯基氨基嘧啶化合物衍生物;WO2006/009889公开了吲唑化合物衍生物;WO2010/032875公开了烟酰胺化合物衍生物;WO2009/079008了公开吡唑衍生物;WO2014/118133公

开了嘧啶衍生物，并且本发明的同一申请人的WO2018/115383公开了双环二氢嘧啶，且WO2018/138293，WO2019/048479，WO2019/121223，WO2019/121233，WO2019/121406，WO2019/238628，WO2020/016129公开了酪氨酸-酰胺化合物衍生物和类似物。

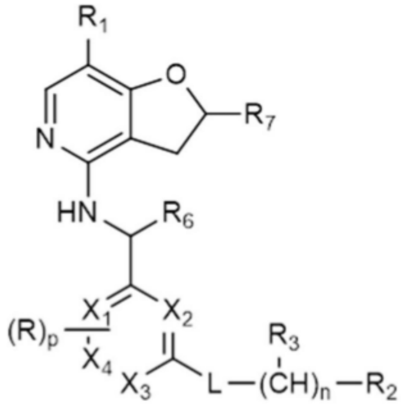
[0008] 所公开的化合物表现出与本发明的化合物的实质性结构差异。

[0009] 在许多治疗领域中仍然存在开发新的和药理学上改善的ROCK抑制剂的潜力。

[0010] 鉴于由ROCK酶介导的病理反应的数量，持续需要可用于治疗许多病症的这类酶的抑制剂。本发明涉及至少对于常见的新核心骨架不同于本领域公开的结构的新化合物。事实上，本发明涉及以2,3-二氢呋喃并[3,2-c]吡啶部分为特征的化合物，特别是2,3-二氢呋喃并[3,2-c]吡啶-4-胺，特别优选N-(3-(((2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)甲酰胺和3-(((2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺衍生物，它们是Rho-相关卷曲螺旋形成蛋白激酶(ROCK)的ROCK-I和ROCK-II同种型的抑制剂，具有治疗上期望的特征，特别有希望用于一些肺病，包括哮喘，慢性阻塞性肺病(COPD)，特发性肺纤维化(IPF)和肺高压(PH)且特别是肺动脉高压(PAH)。本发明的化合物可以制备成通过与其药代动力学性质一致的任何途径施用。本发明的化合物作为ROCK-I和ROCK-II同种型的抑制剂是有活性的，它们是有效的，并且有利地具有其它改善的特性，例如选择性和其它指示优选施用途径的体外特性。

[0011] 发明概述

[0012] 本发明涉及一类用作Rho激酶(ROCK)抑制剂的式(I)的化合物

[0013] 

I

[0014] 其中变量X_1，X_2，X_3和X_4，p，R，R_1，L，n，R_2和R_3，R_4和R_5，R_6和R_7如发明详述中所定义；或其药学上可接受的盐和溶剂合物。

[0015] 在一个方面，本发明涉及式(I)的化合物，其用作药物。在一个方面，本发明提供了本发明的化合物在制备药物中的用途。

[0016] 在另一个方面，本发明提供了本发明的化合物在制备用于治疗任何与ROCK酶机制相关的疾病的药物中的用途，也就是说，所述疾病的特征在于ROCK酶异常活性和/或其中期望抑制活性，且特别是通过相对于其它激酶选择性抑制ROCK酶同种型。

[0017] 在另一个方面，本发明提供了预防和/或治疗如上定义的任何与ROCK酶机制相关的疾病的方法，所述方法包括向需要这种治疗的患者施用治疗有效量的本发明的化合物。

[0018] 在一个具体方面，本发明的化合物单独使用或与其它活性成分组合使用，并且可以施用用于预防和/或治疗肺病，包括哮喘，慢性阻塞性肺病(COPD)，特发性肺纤维化

(IPF)，肺高压(PH)，且特别是肺动脉高压(PAH)。

[0019] 发明详述

[0020] 定义

[0021] 术语“药学上可接受的盐”是指式(I)的化合物的衍生物，其中母体化合物通过用常规预期为药学上可接受的任何碱或酸将任何游离酸或碱性基团(如果存在的话)转化为相应的加成盐来适当地修饰。

[0022] 因此，所述盐的合适实例可以包括碱性残基例如氨基的无机或有机酸加成盐，以及酸残基例如羧基的无机或有机碱加成盐。

[0023] 可以适用于制备本发明的盐的无机碱的阳离子包括碱金属或碱土金属例如钾，钠，钙或镁的离子。通过使起碱作用的主要化合物与无机或有机酸反应形成盐而获得的那些包含，例如盐酸，氢溴酸，硫酸，磷酸，甲磺酸，樟脑磺酸，乙酸，草酸，马来酸，富马酸，琥珀酸和柠檬酸的盐。

[0024] 许多有机化合物可以与它们在其中反应或从其中沉淀或结晶的溶剂形成配合物。这些配合物称作“溶剂合物”，其是本发明的另一个目的。式(I)的化合物或其药学上可接受的盐或溶剂合物的多晶型物和结晶形式是本发明的另一个目的。

[0025] 术语“卤素”或“卤素原子”包括氟，氯，溴和碘原子；意指氟，氯，溴，碘作为取代基。

[0026] 术语“(C_1-C_6)烷基”是指直链或支链烷基，其中碳原子数在1-6的范围内。具体的烷基是例如甲基，乙基，正丙基，异丙基，叔丁基等。

[0027] 表述“(C_1-C_6)卤代烷基”是指上文所定义的“(C_1-C_6)烷基”，其中一个或多个氢原子被一个或多个彼此可以相同或不同的卤素原子替代。实例包括卤代，多卤代和其中所有氢原子均被卤素原子替代的全卤代烷基，例如三氟甲基或二氟甲基。

[0028] 作为类比，术语“(C_1-C_6)羟基烷基”和“(C_1-C_6)氨基烷基”是指上文所定义的“(C_1-C_6)烷基”，其中一个或多个氢原子分别被一个或多个羟基(OH)或氨基替代，实例为羟基甲基和氨基甲基等。

[0029] 氨基烷基的定义包括被一个或多个氨基($-NR_8R_9$)取代的烷基(即“(C_1-C_6)烷基”)。氨基烷基的实例为单-氨基烷基，例如$R_8R_9N-(C_1-C_6)$烷基。取代基R_8和R_9在下文的发明详述中定义为R_4和R_5。

[0030] 术语“(C_3-C_{10})环烷基”，同样“(C_3-C_8)环烷基”或“(C_3-C_6)环烷基”是指包含指示的环碳原子数的饱和环状烃基。实例包括环丙基环丁基，环戊基，环己基和环庚基以及多环系统例如金刚烷基。

[0031] 表述“芳基”是指具有6-20个，优选6-15个环原子的单，双-或三-环碳环系统，其中至少一个环为芳族的。表述“杂芳基”是指具有5-20个，优选5-15个环原子的单-，双-或三-环环系统，其中至少一个环为芳族的并且其中至少一个环原子为杂原子(例如N，S或O)。

[0032] 芳基或杂芳基单环环系统的实例包括，例如苯基，噻吩基，吡咯基，吡唑基，咪唑基，异噁唑基，噁唑基，异噻唑基，噻唑基，吡啶基，嘧啶基，吡嗪基，哒嗪基，三嗪基，呋喃基残基等。

[0033] 芳基或杂芳基双环环系统的实例包括萘基，联苯基，嘌呤基，蝶啶基，吡唑并嘧啶基，苯并三唑基，苯并咪唑基，喹啉基，异喹啉基，吲哚基，异吲哚基，吲唑基，苯并噻吩基，苯并二噁英基，二氢苯并二噁英基，茚基，二氢茚基，二氢苯并[1,4]二噁英基，苯并噻唑-2-

基，二氢苯并二氮杂环庚三烯基，苯并噁嗪基，1,2,3,4-四氢异喹啉-6-基，4,5,6,7-四氢噻唑并[4,5-c]吡啶，4,5,6,7-四氢苯并[d]噻唑-2-基，5,6,7,8-四氢-1,7-萘啶残基等。

[0034] 芳基或杂芳基三环环系统的实例包括芴基残基以及上述杂芳基双环环系统的苯并稠合衍生物。

[0035] 衍生的表述“(C_3-C_{10})杂环烷基”，同样“(C_3-C_8)杂环烷基”或“(C_3-C_6)杂环烷基”是指具有指定碳数的饱和或部分不饱和的单环环烷基，其中至少一个环碳原子被至少一个杂原子(例如N，NH，S或O)替代，或可以带有-氧代(=O)取代基。所述杂环烷基(即杂环残基或基团)进一步任选地在环中可利用的点上被取代，即在碳原子上或在可利用的用于取代的杂原子上。杂环烷基的实例由如下表示：氧杂环丁烷基，四氢-呋喃基，吡咯烷基，咪唑烷基，噻唑烷基，哌嗪基，哌啶基，吗啉基，硫代吗啉基，二氢-或四氢-吡啶基，四氢吡喃基，吡喃基，2H-或4H-吡喃基，二氢-或四氢呋喃基，二氢异噁唑基，吡咯烷-2-酮基，二氢吡咯基，5-氧代吡咯烷-3-基，(1R,5S,6r)-3-氧杂双环[3.1.0]己-6-基，八氢环戊二烯并[c]吡咯-5-基，4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-基；4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基残基等。

[0036] 术语“芳基(C_1-C_6)烷基”是指与直链或支链烷基连接的芳基环，其中组成碳原子数在1-6的范围内，例如苯基甲基(即苄基)，苯基乙基或苯基丙基。

[0037] 同样，术语“杂芳基(C_1-C_6)烷基”是指与直链或支链烷基连接的杂芳基环，其中组成碳原子数在1-6的范围内，例如呋喃基甲基。

[0038] 术语“烷酰基”是指HC(O)-或烷基羰基(例如(C_1-C_6)烷基C(O)-)，其中基团“烷基”具有上述所定义的含义。实例包括甲酰基，乙酰基，丙酰基，丁酰基。

[0039] 术语“(C_1-C_{10})烷氧基”或“(C_1-C_{10})烷氧基”，同样“(C_1-C_6)烷氧基”或“(C_1-C_6)烷氧基”等是指所指示碳数的通过氧桥连接至分子的其余部分的直链或支链烃。“(C_1-C_6)烷硫基”是指通过硫桥连接的上述烃。

[0040] 衍生的表述“(C_1-C_6)卤代烷氧基”或“(C_1-C_6)卤代烷氧基”是指上述所定义的通过氧桥连接的卤代烷基。(C_1-C_6)卤代烷氧基的实例为三氟甲氧基。

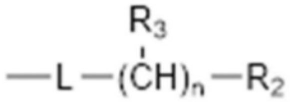
[0041] 同样，衍生的表述“(C_3-C_6)杂环烷基-(C_1-C_6)烷基”和“(C_3-C_6)环烷基-(C_1-C_6)烷基”是指上述所定义的通过所指示碳数的烷基连接至分子的其余部分的杂环烷基和环烷基，例如，相当于直链式(C_3-C_6)杂环烷基-$(CH_2)_m$-或(C_3-C_6)环烷基-$(CH_2)_m$-，例如哌啶-4-基-甲基，环己基乙基。

[0042] 衍生的表述“(C_1-C_6)烷氧基-(C_1-C_6)烷基”是指上述所定义的通过所指示碳数的烷基连接至分子的其余部分的烷氧基，例如甲氧基甲基。

[0043] 同样，“(C_1-C_6)卤代烷氧基(C_1-C_6)烷基”是指上述所定义的通过所指示碳数的烷基连接至分子的其余部分的(C_1-C_6)卤代烷氧基”，例如二氟甲氧基丙基。

[0044] 氧代部分由(O)表示，作为其它常见表示例如(=O)的替代。因此，就通式而言，羰基在本文中优选表示为-C(O)-，作为其它常见表示如-CO-，-(CO)-或-C(=O)-的替代。通常，括号内的基团是侧基，不包括在链中，并且当认为有用时，使用括号来帮助消除线性化学式的歧义；例如磺酰基-SO_2-也可以表示为-$S(O)_2$-来消除歧义，例如关于亚磺基-S(O)O-。

[0045] 同样，本文中的基团-$(CHR_3)_n$-R_2为式(I)和(Ia)中发现的表征基团的末端部分的线性表示。

[0046] 

$$-L-(\overset{R_3}{\overset{|}{C}}H)_n-R_2$$

[0047] 在数值索引的情况下，陈述(值)“p为零”或“p为0”是指带有索引p的取代基或基团(例如(R)p)不存在，也就是说在需要时不存在除H以外的取代基。同样，当标记连接到桥接二价基团(例如(CH_2)n)时，陈述“n在每次出现时为0…”或“n为0”意指桥连基团不存在，也就是说它是键。

[0048] 每当碱性氨基或季铵基团存在于式(I)的化合物中时，可以存在选自氯离子，溴离子，碘离子，三氟乙酸根，甲酸根，硫酸根，磷酸根，甲磺酸根，硝酸根，马来酸根，乙酸根，柠檬酸根，富马酸根，酒石酸根，草酸根，琥珀酸根，苯甲酸根，对甲苯磺酸根，扑酸根和萘二磺酸根的生理学上可接受的阴离子。同样，在酸性基团例如COOH基团的存在下，也可以存在相应的生理阳离子盐，例如包括碱金属或碱土金属离子。

[0049] 当式(I)的化合物包含一个或多个立体中心时，它们可以作为光学立体异构体存在。

[0050] 当本发明的化合物具有至少一个立体中心时，它们可以相应地作为对映异构体存在。当本发明的化合物具有两个或多个立体中心时，它们可以另外作为非对映异构体存在。应当理解，所有这些单一对映异构体，非对映异构体及其任何比例的混合物均包括在本发明的范围内。带有立体中心的碳的绝对构型(R)或(S)以基于基团的优先级的Cahn-Ingold-Prelog命名规则为基础来指定。

[0051] 当在化合物的化学名称附近报告时，“单一立体异构体”，“单一非对映异构体”或“单一对映异构体”表示异构体作为单一非对映异构体或对映异构体分离(例如通过手性色谱法)，但未确定/指定相关立体中心的绝对构型。

[0052] 阻转异构体由围绕单键的受阻旋转产生，其中旋转的空间应变势垒足够高以允许构象异构体的分离(Bringmann G等人，Angew.Chemie Int.Ed.44(34),5384-5427,2005.doi:10.1002/anie.200462661)。

[0053] Oki将阻转异构体定义为构象异构体，其在指定温度下以超过1000秒的半衰期互变(Oki M,Topics in Stereochemistry 14,1-82,1983)。

[0054] 阻转异构体与其它手性化合物的不同之处在于，在许多情况下，它们可以热平衡，而在其它形式的手性异构化通常仅可能是化学异构化。

[0055] 阻转异构体的分离可以通过手性拆分方法，例如选择性结晶来实现。在阻转-对映选择性或阻转选择性合成中，一种阻转异构体以另一种为代价形成。阻转选择性合成可以通过使用手性助剂如Corey Bakshi Shibata(CBS)催化剂(衍生自脯氨酸的不对称催化剂)或通过基于热力学平衡的方法(当异构化反应有利于一种阻转异构体超过另一种阻转异构体时)来进行。

[0056] 式(I)的化合物的外消旋形式以及单独的阻转异构体(基本上不含其相应的对映异构体)和富含立体异构体的阻转异构体混合物包括在本发明的范围内。

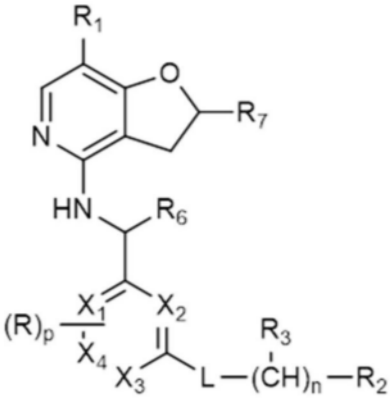
[0057] 本发明还涉及式(I)的化合物的相应氘代衍生物。在本发明的上下文中，氘代衍生物意指氢原子占据的至少一个位置被高于其天然丰度的量的氘占据。优选地，该位置处的氘的百分比为至少90%，更优选地至少95%，甚至更优选99%。

[0058] 上文和下文对于式(I)的化合物描述的所有优选基团或实施方案可以彼此组合，

并且加以必要的变更也适用。

[0059] 如上所述，本发明涉及用作ROCK抑制剂的如下所述的式(I)的化合物，其制备方法，包含它们(单独或与一种或多种活性成分组合)与一种或多种药学上可接受的载体的混合物的药物组合物。

[0060] 本发明的第一方面涉及一类式(I)的化合物

[0061] 

I

[0062] 其中

[0063] X_1，X_2，X_3和X_4均为CH，或X_1，X_2，X_3和X_4之一为N且其它的为CH；

[0064] p为0或1至4的整数；

[0065] 每个R在存在时为卤素，在每次出现时独立地选自(C_1-C_6)烷基和卤素，所述卤素选自F，Cl，Br和I；其中优选地R为F，Cl或甲基；

[0066] R_1为吡唑基，优选吡唑-4-基；

[0067] L为-C(O)NH-或-NHC(O)-；

[0068] n在每次出现时独立地为0(即R_3不存在)或选自1，2或3的整数；

[0069] R_2和R_3在每次出现时独立地选自

[0070] -H，

[0071] 卤素，

[0072] -OH，

[0073] $-(CH_2)_mNR_4R_5$，

[0074] (C_1-C_6)烷基，

[0075] (C_1-C_6)羟基烷基，

[0076] (C_1-C_6)烷氧基，

[0077] (C_1-C_6)烷氧基(C_1-C_6)烷基，

[0078] (C_1-C_6)卤代烷基，

[0079] (C_1-C_6)卤代烷氧基，

[0080] (C_1-C_6)卤代烷氧基(C_1-C_6)烷基，

[0081] (C_3-C_{10})环烷基，

[0082] 芳基，杂芳基和(C_3-C_6)杂环烷基，

[0083] 该环烷基，芳基，杂芳基和杂环烷基中每一个又任选且独立地被一个或多个基团取代，所述基团选自卤素，

[0084] -OH，

[0085] (C_1-C_6)烷基，

[0086] (C_1-C_6)羟基烷基，

[0087] (C_1-C_6)烷氧基，

[0088] (C_1-C_6)烷氧基(C_1-C_6)烷基，

[0089] (C_1-C_6)卤代烷基，

[0090] (C_1-C_6)卤代烷氧基，

[0091] $-(CH_2)_mNR_4R_5$，

[0092] $-O-(CH_2)_mNR_4R_5$，

[0093] 烷酰基，

[0094] 芳基，杂芳基，环烷基，

[0095] 芳基-(C_1-C_6)烷基，

[0096] (C_3-C_6)杂环烷基，

[0097] (C_3-C_8)杂环烷基-(C_1-C_6)烷基，

[0098] 所述芳基，杂芳基，环烷基，杂环烷基中每一个仍然进一步任选地被一个或多个基团取代，所述基团独立地选自卤素，-OH，(C_1-C_8)烷基，(C_1-C_6)卤代烷基，(C_1-C_6)羟基烷基；

[0099] m在每次出现时独立地为0或选自1，2或3的整数；

[0100] R_4和R_5相同或不同，选自

[0101] -H，

[0102] (C_1-C_6)烷基，

[0103] (C_1-C_6)卤代烷基，

[0104] (C_1-C_6)羟基烷基，

[0105] (C_3-C_6)杂环烷基；

[0106] R_6和R_7独立地选自-H，(C_1-C_6)烷基；

[0107] 其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

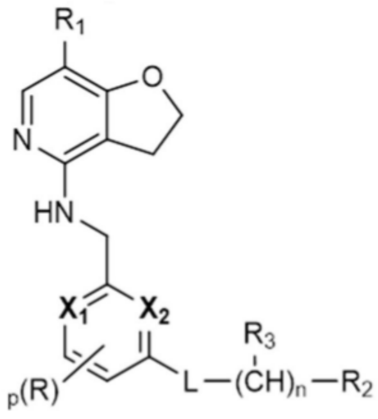
[0108] 在一个优选的实施方案中，本发明涉及式(I)的化合物，其中X_3和X_4均为CH基团，且X_1或X_2可选择地独立地为CH基团或氮原子；

[0109] R_1为吡唑-4-基；

[0110] 所有其它变量如上所定义。

[0111] 所述优选组的化合物由式(Ia)表示

[0112]



Ia

[0113] 特别优选的是如上所定义的式(I)的化合物，

[0114] 其中X_1,X_2,X_3,X_4均为CH基团；

[0115] 每个R在存在时为卤素，所述卤素在每次出现时独立地选自F,Cl,Br和I，其中优选地R为F；

[0116] R_1为吡唑基，优选吡唑-4-基；

[0117] L为-C(O)NH-或-NHC(O)-；

[0118] n为0(即R_3不存在)；

[0119] R_2在每次出现时独立地选自

[0120] (C_1-C_6)烷基，

[0121] (C_1-C_6)羟基烷基，

[0122] (C_1-C_6)烷氧基(C_1-C_6)烷基，

[0123] (C_1-C_6)卤代烷基，

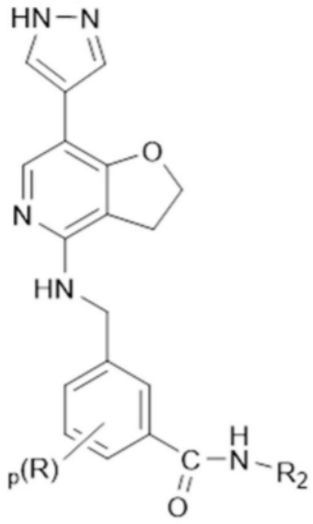
[0124] (C_1-C_6)卤代烷氧基(C_1-C_6)烷基；

[0125] 所有其它变量如上所定义，

[0126] 其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

[0127] 所述优选组的化合物由式(Ib)表示

[0128]



Ib

[0129] 在另一个优选的实施方案中，本发明涉及式(I)的化合物，其中X_1，X_2，X_3和X_4均为CH；

[0130] p为0或1至4的整数；

[0131] 每个R在存在时为卤素，所述卤素在每次出现时独立地选自F，Cl，Br和I，其中优选地R为F；

[0132] R_1为吡唑基，优选吡唑-4-基；

[0133] L为-C(O)NH或-NHC(O)-；

[0134] n在每次出现时独立地为0或选自1，2或3的整数；

[0135] R_3在存在时为H，且

[0136] R_2选自

[0137] 芳基，杂芳基和(C_3-C_6)杂环烷基，

[0138] 该芳基，杂芳基和杂环烷基中每一个

[0139] 又任选且独立地被一个或多个基团取代，所述基团选自

[0140] (C_1-C_6)烷基，

[0141] (C_1-C_6)羟基烷基，

[0142] (C_1-C_6)烷氧基，

[0143] (C_1-C_6)烷氧基(C_1-C_6)烷基，

[0144] $-(CH_2)_mNR_4R_5$，

[0145] $-O-(CH_2)_mNR_4R_5$，

[0146] 芳基，杂芳基，环烷基，

[0147] 芳基-(C_1-C_6)烷基，

[0148] (C_3-C_6)杂环烷基，

[0149] (C_3-C_8)杂环烷基-(C_1-C_6)烷基，

[0150] 所述芳基，杂芳基，环烷基，杂环烷基中每一个仍然进一步任选地被一个或多个基团取代，所述基团独立地选自卤素，-OH，(C_1-C_8)烷基，(C_1-C_6)卤代烷基，(C_1-C_6)羟基烷基；

[0151] m在每次出现时独立地为0或选自1，2或3的整数；

[0152]　R_4和R_5相同或不同，选自

[0153]　-H，

[0154]　(C_1-C_6)烷基，

[0155]　(C_1-C_6)卤代烷基，

[0156]　(C_1-C_6)羟基烷基，

[0157]　(C_3-C_6)杂环烷基；

[0158]　其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

[0159]　在该最后的实施方案中特别优选的是这样的化合物，其中R_2选自(吡啶基)甲基，(吡啶基)乙基，甲氧基吡啶基，((二甲基氨基)乙氧基)吡啶基，或选自1-(2-(二甲基氨基)乙基)-1H-吲唑-5-基，1-(2-吗啉代乙基)-1H-吲唑-5-基，1-(1-甲基哌啶-4-基)-1H-吲唑-5-基；

[0160]　所有其它变量和取代如上所定义，

[0161]　其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

[0162]　因此，一组特别优选的化合物为：

[0163]

实施例	化学名
43	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酰胺
44	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(1-甲基哌啶-4-基)-1H-吲唑-5-甲酰胺
46	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-吗啉代乙基)-1H-吲唑-5-甲酰胺
17	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-4-基)乙基)苯甲酰胺
22	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-3-基)乙基)苯甲酰胺
31	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲氧基吡啶-2-基)苯甲酰胺
53	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-4-基甲基)苯甲酰胺
57	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-(2-(二甲基氨基)乙氧基)吡啶-2-基)苯甲酰胺

[0164]　本发明的另一组优选的化合物为具有式(I)的那些，其中

[0165]　X_1，X_2，X_3和X_4均为CH；

[0166] p为0或1；

[0167] 每个R在存在时为F；

[0168] R_1为吡唑-4-基；

[0169] L为-C(O)NH-或-NHC(O)-；

[0170] n在每次出现时独立地为0或选自1,2的整数；

[0171] R_2和R_3在每次出现时独立地选自

[0172] -H,

[0173] (C_1-C_6)烷基,其为甲基,

[0174] (C_1-C_6)烷氧基(C_1-C_6)烷基,其为2-甲氧基乙基,

[0175] (C_1-C_6)卤代烷基,其为3-氟丙基,

[0176] (C_3-C_{10})环烷基,其为环丙基,环丁基,

[0177] 芳基,其为苯基；

[0178] 杂芳基,其为吡啶基,吡唑基,噻吩基,咪唑基,噁唑基,异噁唑基,噻唑基,嘧啶基,1,2,5-噁二唑-3-基,4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-基,4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基,4,5,6,7-四氢苯并[d]噻唑-2-基,1,2,3,4-四氢异喹啉-6-基,5,6,7,8-四氢-1,7-萘啶基,1H吲哚-5-基,异二氢吲哚基,1H-吲唑-5-基,

[0179] 和

[0180] (C_3-C_6)杂环烷基,其为哌啶基,吗啉基,四氢呋喃基,四氢-2H-吡喃基；

[0181] 该环烷基,芳基,杂芳基和杂环烷基中每一个,

[0182] 又任选且独立地被一个或多个基团取代,所述基团选自

[0183] 卤素,其为氟；

[0184] (C_1-C_6)烷基,其为甲基；

[0185] (C_1-C_6)羟基烷基,其为羟基乙基；

[0186] (C_1-C_6)烷氧基,其为甲氧基；

[0187] $-(CH_2)_mNR_4R_5$,其为(二甲基氨基)甲基,2-(二甲基氨基)乙基,二甲基氨基,其中R_4和R_5为甲基,且m为0,1或2,氧杂环丁烷-3-基氨基,其中R_4为H,R_5为氧杂环丁烷基,且m为0；

[0188] $-O-(CH_2)_mNR_4R_5$,其为((二甲基氨基)乙氧基)吡啶基；

[0189] 环烷基,其为环丙基,

[0190] 芳基-(C_1-C_6)烷基,其为苄基,苯乙基,

[0191] (C_3-C_6)杂环烷基,其为氧杂环丁烷-3-基,哌啶-4-基,

[0192] (C_3-C_8)杂环烷基-(C_1-C_6)烷基,其为吗啉代乙基,吡咯烷-1-基甲基,

[0193] 所述杂环烷基中每一个仍然进一步任选地被(C_1-C_8)烷基取代,所述(C_1-C_8)烷基为甲基；

[0194] R_6为-H或甲基；和R_7为-H,

[0195] 其单一对映异构体,非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

[0196] 本发明还提供了药物组合物,其包含与一种或多种药学上可接受的载体或赋形剂混合的式(I)的化合物或其药学上可接受的盐(单独或与一种或多种如下详细描述的另一种活性成分组合)。

[0197] 根据具体的实施方案，本发明提供了下表中所列出的化合物，其单一对映异构体，非对映异构体及其任意比例的混合物和/或其药学上可接受的盐和溶剂合物。

[0198]

实施例编号	化学名
1	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-环丙基哌啶-4-基)苯甲酰胺
2	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-吡唑-3-基)甲基)苯甲酰胺
3	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-氟丙基)苯甲酰胺
4	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-2-基甲基)苯甲酰胺
5	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(环丙基甲基)苯甲酰胺
6	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5,5-二甲基四氢呋喃-3-基)苯甲酰胺

[0199]

实施例编号	化学名
7	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-甲氧基乙基)苯甲酰胺
8	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-咪唑-4-基)甲基)苯甲酰胺
9	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-5-基甲基)苯甲酰胺
10	N-((1,2,5-噁二唑-3-基)甲基)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺
11	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺
12	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3,3-二氟环丁基)苯甲酰胺
13	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(异噁唑-3-基甲基)苯甲酰胺
14	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(噻唑-4-基甲基)苯甲酰胺
15	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲基-4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-基)苯甲酰胺
16	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-甲基哌啶-4-基)乙基)苯甲酰胺
17	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-4-基)乙基)苯甲酰胺
18	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二甲基氨基)甲基)苯基)苯甲酰胺
19	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二甲基氨基)甲基)苄基)苯甲酰胺

[0200]

实施例编号	化学名
20	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-吗啉代乙基)苯甲酰胺**
21	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)苯甲酰胺**
22	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-3-基)乙基)苯甲酰胺**
23	**(S)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-羟基-1-苯基乙基)苯甲酰胺**
24	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(4-((二甲基氨基)甲基)苄基)苯甲酰胺**
25	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基噻吩-2-基)甲基)苯甲酰胺**
26	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苯乙基哌啶-4-基)苯甲酰胺**
27	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)苯甲酰胺**
28	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-(氧杂环丁烷-3-基)哌啶-4-基)乙基)苯甲酰胺**
29	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)甲基)苯甲酰胺**
30	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((2-甲基异二氢吲哚-5-基)甲基)苯甲酰胺**
31	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲氧基吡啶-2-基)苯甲酰胺**
32	**3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-4-基)苯甲酰胺**

[0201]

实施例编号	化学名
33	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(二甲基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺
34	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(氧杂环丁烷-3-基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺
35	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-4-((二甲基氨基)甲基)苯甲酰胺
36	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[4,5-c]吡啶-2-甲酰胺
37	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺
38	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(2-羟基乙基)-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺
39	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-5-甲酰胺
40	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺
41	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-3-甲酰胺
42	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-4-甲酰胺
43	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酰胺

[0202]

实施例编号	化学名
44	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(1-甲基哌啶-4-基)-1H-吲唑-5-甲酰胺
45	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-甲基-1,2,3,4-四氢异喹啉-6-甲酰胺
46	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-吗啉代乙基)-1H-吲唑-5-甲酰胺
47	N-(5-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-2-氟苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺
48	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(吡咯烷-1-基甲基)噻唑-2-甲酰胺
49	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-3-((二甲基氨基)甲基)苯甲酰胺
50	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-苯基乙酰胺
51	N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-7-甲基-5,6,7,8-四氢-1,7-萘啶-3-甲酰胺
52	N-(3-(1-((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)乙基)苯基)乙酰胺
53	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-4-基甲基)苯甲酰胺
54	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苄基哌啶-4-基)苯甲酰胺
55	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体 1)
56	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体 2)
57	3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-(2-(二甲基氨基)乙氧基)吡啶-2-基)苯甲酰胺

[0203] 本发明的化合物,包括上文列出的所有化合物,可以使用以下一般方法和程序或通过使用本领域技术人员容易获得的略微修改的方法由容易获得的起始材料制备。尽管本文可以示出或描述本发明的特定实施方案,但是本领域技术人员将认识到,本发明的所有实施方案或方面可以使用本文所述的方法或通过使用其它已知的方法,试剂和起始材料来

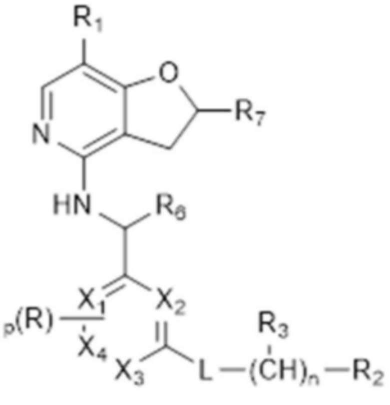
制备。当给出了典型或优选工艺条件(即反应温度,时间,反应剂的摩尔比,溶剂,压力等)时,除非另有说明,否则也可以使用其它工艺条件。虽然最佳反应条件可以根据所用的特定反应物或溶剂的不同而变化,但是本领域技术人员可以通过常规优化方法容易地确定这些条件。

[0204] 因此,以下描述和以下方案中报告的制备方法不应被视为限制可用于制备本发明的化合物的合成方法的范围。

[0205] 在一些情况下,需要掩蔽或保护敏感或反应性部分的步骤,根据一般化学原理(Protective group in organic syntheses,3rd ed.T.W.Greene,P.G.M.Wuts),可以使用通常已知的保护基团(PG)。用于需要羧酸保护的中间体的合适的保护基团(本文报告为PG_1)可以为C_1-C_4酯(PG_1:甲基,异丙基,叔丁基或乙基),优选甲基。用于需要氨基保护的中间体的合适的保护基团(本文报告为PG_2)可以为氨基甲酸酯,例如叔丁基氨基甲酸酯(PG_2:叔丁氧基羰基或Boc),苄基氨基甲酸酯(PG_2:苄基氧基羰基或Cbz),乙基氨基甲酸酯(PG_2:乙氧基羰基)或甲基氨基甲酸酯(PG_2:甲氧基羰基),优选PG_2为Boc。用于需要五元杂环的环NH保护的中间体的合适的保护基团PG_3可以为THP(2-四氢呋喃基)或Boc。

[0206] 为清楚起见在此再次报告的式(I)的化合物(包括上文列出的所有化合物)通常可以根据以下方案中所示的方法制备。当具体细节或步骤不同于一般方案时,其已经在具体实施例和/或另外的方案中进行了详细说明。

[0207]



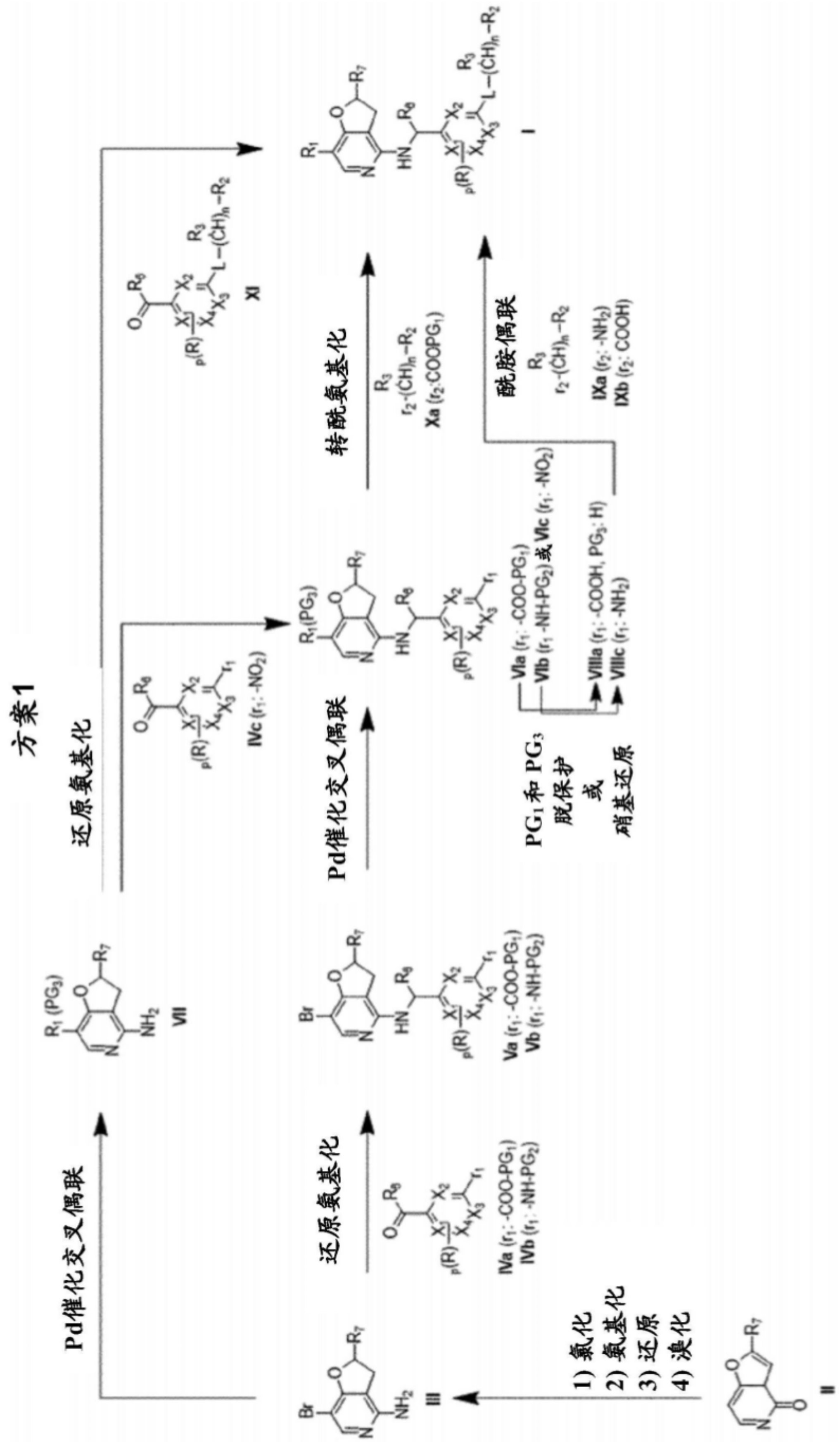
I

[0208] 式(I)的化合物可以包含一个或多个立体中心。对映异构体纯的化合物可以根据通常已知的反应,例如根据下文描述的反应,借助于对映异构体纯的起始材料和中间体来制备。这些中间体可以是可商购的或由本领域技术人员从商业来源容易地生产。

[0209] 在另一种方法中,对映异构体纯的化合物可以通过手性色谱纯化从相应的外消旋体来制备。立体化学纯的化合物可以通过手性分离从非对映异构体的混合物来获得,或者(每当在式(I)的化合物中存在两个或多个立体中心-即手性中心-时)逐步通过非对映异构体的色谱分离,然后进一步通过手性分离成单一立体异构体来获得。

[0210] 实施例1至32,35至48,51至52可以根据方案1来制备,方案1为本发明的实施例提供至少一种非限制性合成途径。

[0211] 方案1



[0212] 可以通过4个连续步骤将中间体II转化成中间体III，包括1)氯化，2)氨基化，3)还原和4)溴化。

[0213] 例如，氯化步骤可以通过中间体II与合适的氯化剂(纯净的或在含有有机溶剂例如DCM或二噁烷的溶液中)例如$POCl_3$或$SOCl_2$一起回流进行。

[0214] 氨基化步骤可以下列步骤进行：通过导入掩蔽的氨例如二苯甲酮亚胺经Buchwald型钯催化的反应，使用例如三(二亚苄基丙酮)二钯(0)/BINAP催化剂系统，然后通过使连接的二苯甲酮亚胺与羟基胺反应，得到相应的呋喃并[3,2-c]吡啶-4-胺。还原呋喃并[3,2-c]吡啶-4-胺以得到2,3-二氢呋喃并[3,2-c]吡啶-4-胺(步骤3)可以例如通过在Pd/C催化剂存在下在高H_2压力(例如10bar)下和在50℃或更高的温度下氢化呋喃并[3,2-c]吡啶-4-胺在MeOH/乙酸中的溶液来进行。最终，可以通过经与溴化剂例如N-溴琥珀酰亚胺在极性无质子溶剂例如乙腈中在低温(例如-10至0℃)下反应几小时溴化2,3-二氢呋喃并[3,2-c]吡啶-4-胺(步骤4)得到中间体III。

[0215] 可以合并中间体III和羰基中间体IVa(或IVb)，通过还原氨基化反应得到中间体Va(或Vb)，所述还原氨基化反应可以在适当的溶剂例如DCM或THF中，在路易斯酸例如氯(三异丙氧基)钛(IV)或四异丙醇钛(IV)存在下，随后添加还原剂例如三乙酰氧基硼氢化钠或氰基硼氢化钠，在有机酸例如乙酸或三氟乙酸存在下进行。

[0216] 可以通过经金属催化的偶联反应例如Suzuki偶联，Stille偶联等(Strategic application of named reactions in organic synthesis，L.Kurti，B.Czako，Ed.2005)直接引入基团R_1将中间体Va转化成中间体VIa。例如，Suzuki偶联可以通过使中间体Va与基团R_1的相应硼酸或硼频哪醇酯反应来进行(在一些情况中，R_1包含环NH部分，其需要被掩蔽以减少反应性或为了合成便利性，它可以适当地被PG_3基团例如THP或Boc保护)，所述反应在Pd催化剂例如三(二亚苄基丙酮)二钯(0)，$PdCl_2(dppf)_2$.DCM加合物或四三苯基膦钯(0)存在下，在有机溶剂例如二噁烷，THF或DMF中，含有或不含水，使用无机碱例如碱性碳酸盐(例如Cs_2CO_3)或无机磷酸盐(例如K_3PO_4)，在加热(90-150℃)下进行。硼酸和硼酸频哪醇酯通常为商购的，或者可以易于由本领域技术人员由商购试剂为原料制备。

[0217] 可以使用与中间体III转化成Va所述类似的方法，通过还原氨基化由中间体VII和IVc制备中间体VIc。中间体VII可以使用上述与中间体Va转化成中间体VIa所述类似的方法得自中间体III。

[0218] 从中间体VIa中除去PG_1(当PG_1为甲基时)以得到中间体VIIIa(PG_3为H)可以通过酸性或碱性水解进行。例如，PG_1的酸性水解(当PG_1为甲基时)可以通过加热(至多100℃)VIa与浓含水酸例如盐酸或硫酸(如果PG_3存在，则其同时在相同反应羰基下除去)进行。

[0219] 可以通过经使用还原系统例如催化氢化，使用Fe/Sn在酸性条件下的氧化还原反应或使用氢化物的硝基的还原将中间体VIc转化成中间体VIIIc。当PG_3为THP时，通过使用在MeOH中的Pd/C的催化氢化将VIc还原成VIIIc，以便保留NH保护基。

[0220] 在本发明的另一个实施方案中，中间体VIIIc可以如下制备：如对Va所做的那样使中间体Vb反应，得到中间体VIb，中间体VIb可以容易地通过简单除去胺上的保护基PG2转化成VIIIc。

[0221] 酸中间体VIIIa(PG_3为H)与氨基中间体IXa(或可替代地酸IXb与胺VIIIc)的反应得到式I的化合物可以在合适的酰胺偶联反应条件下进行。例如，酸中间体VIIIa可以在活化剂例如TBTU，HATU或COMU存在下与有机碱例如DIPEA或TEA，在合适的有机溶剂例如DCM或DMF中，在通常约RT的温度下反应几小时至过夜的时间。可以考量的可替代选择的酰胺偶联

条件涉及中间体VIIIa和IXa在作为偶联剂的1-(甲基磺酰基)-1H-苯并三唑存在下与有机碱例如TEA，在至多150℃的温度下反应几小时(例如4h)。如果式I的化合物在R_2或R_3上包含伯胺或仲胺，则该氨基部分需要在酰胺偶联步骤中被掩蔽，所述掩蔽通过使用适当保护的(通常为Boc)中间体IXa或IXb进行。

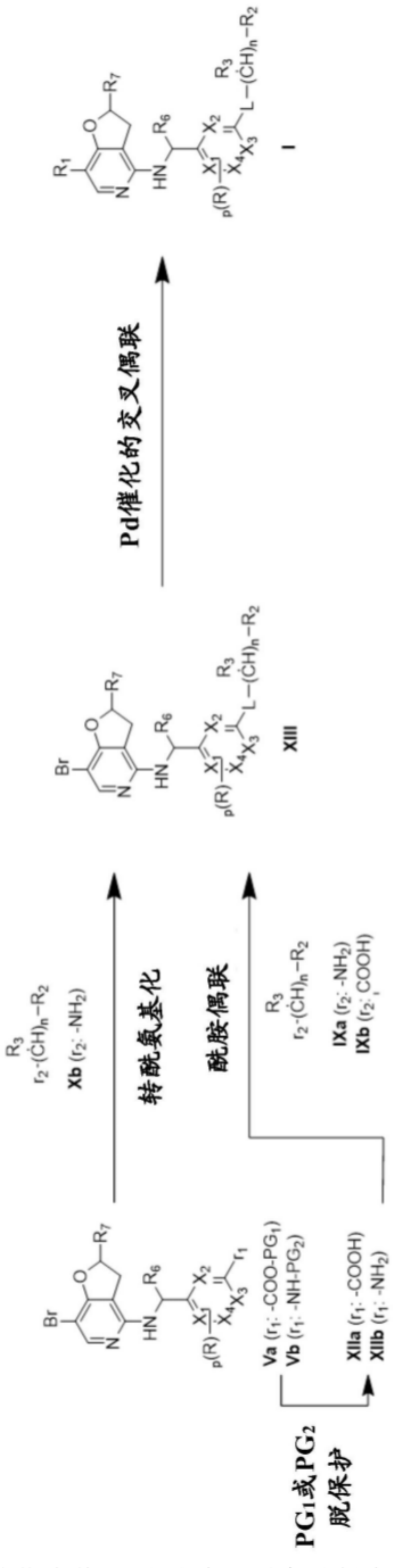
[0222] 在另一种方法中，式I的化合物(其中L为-NHC(O)-)可以通过转酰氨基化反应由氨基中间体VIIIc和甲酯中间体Xa合成。例如，该反应可以通过使甲酯中间体和氨基中间体在合适的有机溶剂例如THF或DCM中，在合适的路易斯酸例如双(三甲基铝)-1,4-二氮杂双环[2.2.2]辛烷加合物或$InCl_3$存在下，在至多120℃的温度下反应来进行。

[0223] 在一种不同的方法中，可以通过还原氨基化，使用与中间体III转化成中间体Va所述类似的条件，由中间体VII和中间体XI制备式I的化合物。

[0224] 其中，为便利起见，R_1上的PG_3基团(即THP)在合成顺序的自始至终得到保持，其可以通过加热(至多100℃)被保护的前体与浓含水酸例如盐酸或硫酸至多1h或更少的时间而容易地除去。

[0225] 在另一种方法中，式(I)的化合物可以根据方案2制备，方案2为实施例49至50，53至54和57提供至少一种合成途径。

[0226] 方案2



[0227] 式I的化合物可以通过下列步骤得自中间体XIII:通过金属催化的交叉偶联反应例如Suzuki偶联,Stille偶联等(Strategic application of named reactions in organic synthesis,L.Kurti,B.Czako,Ed.2005)以与中间体Va转化成VIa所述相同的方式(方案1)直接引入基团R_1,其中为了合成便利性,R_1硼酸或频哪醇酯需要被PG_3基团(即THP或Boc)保护,PG_3可以通过加热(至多100℃)被保护的前体与浓含水酸例如盐酸或硫酸至多1h或更少的时间而容易地除去。

[0228] 中间体XIII可以通过羧酸中间体XIIa与氨基中间体IXa(或酸IXb和胺XIIb)的酰胺偶联,使用与上述VIIIa和中间体IXa反应(方案1)类似的条件得到。中间体XIIa和XIIb可以通过PG_1或PG_2的分别脱保护得自Va和Vb(方案1中所述)。

[0229] 可以通过酸性或酸性水解进行PG_1的脱保护。碱性水解Va(当PG_1为Me或iPr时)得到XIIa可以通过使用无机碱例如LiOH或NaOH,在有机溶剂例如含有水的THF和/或甲醇中,通常在RT下进行1h至过夜的时间来进行。

[0230] 从中间体Vb(为便于描述,Vb的制备报告在方案1)中除去PG_2(当PG_2为Boc基团时)得到中间体XIIb可以通过酸脱保护来进行。例如,酸性Boc裂解可以通过用浓盐酸或三氟乙酸处理来进行。

[0231] 或者,中间体XIII(其中L为-C(O)NH-)可以通过转酰氨基化反应,按照与中间体VIIIc和氨基中间体Xa反应所述类似的方式(方案1)得自酯中间体Va和胺中间体Xb。

[0232] 如果为了便利性,则R_1上的PG_3基团(即THP)在合成顺序的自始至终得以保持,其可以通过加热(至多100℃)被保护的前体与浓含水水例如盐酸或硫酸至多1h或更少的时间而容易地除去。

[0233] 其中式I的化合物在R_2/R_3中包含仲胺或叔胺或酰胺,这类化合物可以通过经还原氨基化反应,或酰胺化,使用一般可接受的方法进一步加工式I的化合物(其中R_2/R_3包含仲胺或叔胺)而得到。实施例33和34通过加工R_2/R_3中包含伯胺或仲胺的式I的前体而制备。

[0234] 如本文详述中所述,本发明的化合物为激酶活性,特别是Rho-激酶活性的抑制剂。

[0235] 在一个方面,本发明提供了式(I)的化合物,其用作药物,优选用于预防和/或治疗肺病。

[0236] 在另一个方面,本发明提供了化合物(I)或其药学上可接受的盐在制备用于治疗与ROCK酶机制相关的病症的药物中的用途,特别是用于治疗例如肺病这样的病症。

[0237] 特别地,本发明提供了式(I)的化合物,其用于预防和/或治疗肺病,其选自哮喘,慢性阻塞性肺病(COPD),特发性肺纤维化(IPF),肺高压(PH)且特别是肺动脉高压(PAH)。

[0238] 此外,本发明提供了用于预防和/或治疗与ROCK酶机制相关的病症的方法,所述方法包括向有这类治疗需求的患者施用治疗有效量的本发明的化合物。

[0239] 特别地,本发明提供了用于预防和/或治疗其中病症为呼吸系统疾病的方法,所述呼吸系统疾病选自哮喘,慢性阻塞性肺病(COPD),特发性肺纤维化(IPF),肺高压(PH)且特别是肺动脉高压(PAH)。

[0240] 优选的是本发明的化合物在预防上述病症中的用途。

[0241] 同样优选的是本发明的化合物在治疗上述病症中的用途。

[0242] 一般而言,为ROCK抑制剂的化合物可以用于治疗与ROCK酶机制相关的许多病症。

[0243] 在一个实施方案中,可以用本发明的化合物治疗的病症包括青光眼,炎性肠病(IBD)和肺病,所述肺病选自哮喘,慢性阻塞性肺病(COPD),间质性肺病例如特发性肺纤维化(IPF)和肺动脉高压(PAH)。

[0244] 在另一个实施方案中，可以用本发明的化合物治疗的病症选自哮喘，慢性阻塞性肺病(COPD)和间质性肺病例如特发性肺纤维化(IPF)和肺动脉高压(PAH)。

[0245] 在另一个实施方案中，所述病症选自特发性肺纤维化(IPF)和肺动脉高压(PAH)。

[0246] 本发明的治疗方法包括向有需要的患者施用安全和有效量的式(I)的化合物或其药学上可接受的盐。如本文所用，关于式(I)的化合物或其药学上可接受的盐或其它药物活性剂的“安全和有效量”是指足以治疗患者病症但足够低以避免严重副作用并且其仍然可以由本领域技术人员通过常规方式确定的化合物的量。式(I)的化合物或其药学上可接受的盐可以一次施用或根据给药方案施用，其中在给定的时间期限内以不同的时间间隔施用多个剂量。典型的日剂量可以根据所选择的特定施用途径的不同而变化。

[0247] 本发明还提供了式(I)的化合物与一种或多种药学上可接受的载体或赋形剂混合的药物组合物，所述载体或赋形剂例如在Remington’s Pharmaceutical Sciences Handbook，XVII Ed.，Mack Pub.，N.Y.，U.S.A.中所述的那些。

[0248] 本发明还涉及本发明的化合物及其药物组合物在不同施用药途径中的用途。

[0249] 本发明的化合物及其药物组合物的施用可以根据患者需要进行，例如口服，经鼻，肠胃外(皮下，静脉内，肌内，胸骨内和通过输注)，通过吸入，直肠，阴道，局部，局限性，透皮和通过眼部施用。

[0250] 各种固体口服剂型可用于施用本发明的化合物，包括例如片剂，软胶囊，胶囊剂，胶囊形片剂，颗粒剂，锭剂和整装散剂的固体形式。本发明的化合物可以单独施用或与各种药学上可接受的载体，稀释剂(例如蔗糖，甘露糖醇，乳糖，淀粉)和已知的赋形剂组合施用，所述赋形剂包括助悬剂，增溶剂，缓冲剂，粘合剂，崩解剂，防腐剂，着色剂，矫味剂，润滑剂等。定时释放胶囊，片剂和凝胶也是有利的。

[0251] 各种液体口服剂型也可用于施用本发明的化合物，包括水性和非水性溶液，乳剂，混悬剂，糖浆剂和酏剂。这类剂型还可以包含合适的已知惰性稀释剂(例如水)和合适的已知赋形剂(例如防腐剂，润湿剂，甜味剂，矫味剂)以及用于乳化和/或悬浮本发明的化合物的试剂。本发明的化合物可以以等渗无菌溶液的形式注射，例如静脉内注射。其它制剂也是可能的。

[0252] 用于直肠施用本发明的化合物的栓剂可以通过将化合物与合适的赋形剂例如可可脂，水杨酸盐和聚乙二醇混合来制备。

[0253] 用于阴道施用的制剂可以为霜剂，凝胶，糊剂，泡沫或喷雾制剂的形式，除了活性成分之外，还已知其包含例如合适的载体。

[0254] 对于局部施用，药物组合物可以为适于施用至皮肤，眼，耳或鼻的霜剂膏，软膏，搽剂，洗剂，乳剂，混悬剂，凝胶，溶液，糊剂，散剂，喷雾剂和滴剂的形式。局部施用还可以涉及通过例如透皮贴剂的方式进行透皮施用。

[0255] 本发明的一些优选化合物表现出适于吸入途径施用的特征。

[0256] 用于吸入递送的药物的优化需要某些特征，其允许将化合物施用至肺以维持足够的局部浓度(肺滞留)以发挥期望的持续时间的药理学作用，并且在不需要的区室(即血浆)中无相关水平。为了减弱肺吸收，需要优化化合物的一个或多个特征，例如但不限于使膜渗透性最小化，降低溶出速率或将一定程度的碱性引入化合物中以增强与富含磷脂的肺组织的结合或通过溶酶体捕获。在一些实施方案中，本发明的化合物显示吸入化合物所期望的

上述特征中的一种或多种。

[0257] 本发明的其它优选化合物表现出适于口服途径施用的特征。

[0258] 用于口服递送的药物的优化需要某些特征，其允许口服施用的化合物被GI(胃肠)道吸收并且难以被清除，以便得到良好的生物利用度(F%)，从而在血浆和靶组织中维持足够的浓度持续足以维持药理学作用的时间。为了增强口服生物利用度，需要优化化合物的一种或多种特征，例如但不限于使膜渗透性最大化和减少代谢热点(优化体外清除率)。在一些实施方案中，本发明的化合物显示口服化合物的一个或多个上述特征。

[0259] 为了治疗呼吸道疾病，本发明的化合物可以通过吸入施用。

[0260] 可吸入制剂包括可吸入散剂，含抛射剂的计量气雾剂或不含抛射剂的可吸入制剂。

[0261] 对于作为干粉施用，可以使用现有技术已知的单剂量或多剂量吸入器。在这种情况下，粉末可以填充在明胶，塑料或其它胶囊，药筒或泡罩包装中或储存器中。

[0262] 可以将稀释剂或载体(通常是无毒的并且对本发明的化合物是化学惰性的)，例如乳糖或适于改善可吸入级分的任何其它添加剂添加到粉末状的本发明的化合物中。

[0263] 含有抛射剂气体例如氢氟烷烃的吸入气雾剂可以包含溶液或分散形式的本发明的化合物。抛射剂驱动的制剂还可以包含其它成分，例如共溶剂，稳定剂和任选的其它赋形剂。

[0264] 包含本发明的化合物的不含抛射剂的可吸入制剂可以是在水，醇或水醇介质中的溶液或混悬剂的形式，并且它们可以通过现有技术中已知的喷射或超声雾化器或通过软雾雾化器例如**Respimat®**递送。

[0265] 进一步优选地，本发明提供了式(I)的化合物和/或其药物组合物，其通过吸入施用途径特别用于预防和/或治疗哮喘，慢性阻塞性肺病COPD，特发性肺纤维化(IPF)，肺高压(PH)且特别是肺动脉高压(PAH)，优选用于预防和/或治疗哮喘，慢性阻塞性肺病COPD，特发性肺纤维化(IPF)。

[0266] 进一步优选地，本发明提供了式(I)的化合物和/或其药物组合物，其通过口服施用途径特别用于预防和/或治疗哮喘，慢性阻塞性肺病COPD，特发性肺纤维化(IPF)，肺高压(PH)且特别是肺动脉高压(PAH)，优选用于预防和/或治疗肺高压(PH)且特别是肺动脉高压(PAH)。

[0267] 无论施用途径和待治疗的疾病如何，本发明的化合物可以作为单独的活性剂施用或以与其它药物活性成分组合的方式(即作为以固定剂量组合或在单独配制的活性成分的组合疗法中施用的共治疗剂)施用，所述其它药物活性成分选自有机硝酸酯和NO供体；吸入的NO；可溶性鸟苷酸环化酶(sGC)刺激剂；前列环素类似物PGI2和前列环素受体激动剂；抑制环鸟苷一磷酸(cGMP)和/或环腺苷一磷酸(cAMP)的降解的化合物，例如磷酸二酯酶(PDE)1,2,3,4和/或5的抑制剂，尤其是PDE 5抑制剂；人嗜中性弹性蛋白酶抑制剂；抑制信号转导级联的化合物，例如酪氨酸激酶和/或丝氨酸/苏氨酸激酶抑制剂；抗血栓形成剂，例如血小板聚集抑制剂，抗凝血剂或纤溶酶原物质；用于降低血压的活性物质，例如钙拮抗剂，血管紧张素II拮抗剂，ACE抑制剂，内皮素拮抗剂，肾素抑制剂，醛固酮合酶抑制剂，α受体阻断剂，β受体阻断剂，盐皮质激素受体拮抗剂；中性内肽酶抑制剂；渗透剂；ENaC阻断剂；抗炎药，包括皮质类固醇和趋化因子受体拮抗剂；抗组胺药；镇咳药；抗生素例如大环内酯和DNA

酶药物物质和选择性裂解剂，例如重组人脱氧核糖核酸酶I(rhDNase)；抑制Smad2和Smad3的ALK5和/或ALK4磷酸化的活性剂；色氨酸羟化酶1(TPH1)抑制剂和多激酶抑制剂，β2-激动剂，皮质类固醇，抗胆碱能药或抗毒蕈碱药，促分裂原活化蛋白激酶(p38 MAP激酶)抑制剂，核因子κ-B激酶亚单位β(IKK2)抑制剂，白三烯调节剂，非类固醇抗炎剂(NSAID)，粘液调节剂，粘液溶解剂，祛痰剂/粘液动力学调节剂，肽粘液溶解剂，JAK抑制剂，SYK抑制剂，PI3Kδ或PI3Kγ抑制剂及其组合。

[0268] 在一个优选的实施方案中，本发明的化合物与以下联合给药：磷酸二酯酶V，例如西地那非，伐地那非和他达拉非；有机硝酸酯和NO供体(例如硝普钠，硝酸甘油，单硝酸异山梨醇酯，二硝酸异山梨醇酯，吗多明或SIN-1和吸入的NO)；合成的前列环素类似物PGI2，例如伊洛前列素，曲前列环素，依前列醇和贝前列素；前列环素受体激动剂，例如司来帕格和WO2012/007539的化合物；可溶性鸟苷酸环化酶(sGC)刺激剂如利奥西呱和酪氨酸激酶如伊马替尼，索拉非尼和尼洛替尼以及内皮素拮抗剂(例如马西替坦，波生坦，西他生坦和安贝生坦)。

[0269] 在另一个实施方案中，本发明的化合物与β2-激动剂如沙丁胺醇，沙美特罗和维兰特罗，皮质类固醇如丙酸氟替卡松或糠酸氟替卡松，氟尼缩松，糠酸莫米松，罗氟奈德和环索奈德，地塞米他松，抗胆碱能药或抗毒蕈碱药如异丙托溴铵，氧托溴铵，噻托溴铵，奥昔布宁及其组合联合给药。

[0270] 在另一个实施方案中，本发明的化合物与促分裂原活化蛋白激酶(p38 MAP激酶)抑制剂，核因子κ-B激酶亚单位β(IKK2)抑制剂，白三烯调节剂，非类固醇抗炎剂(NSAID)，粘液调节剂，粘液溶解剂，祛痰剂/粘液动力学调节剂，JAK的肽粘液溶解抑制剂，Syk抑制剂，PI3Kδ或PI3Kγ的抑制剂联合给药。

[0271] 本发明还涉及试剂盒，其包含单独的或与一种或多种药学上可接受的载体和/或赋形剂组合或混合的本发明的化合物的药物组合物，以及可以是单剂量或多剂量干粉吸入器，定量吸入器或喷雾器的装置。

[0272] 本发明的化合物的剂量取决于多种因素，包括待治疗的具体疾病，症状的严重程度，施用途径，剂量间隔的频率，所用的具体化合物，化合物的功效，毒理学特征和药代动力学特征。

[0273] 有利地，式(I)的化合物可以例如以0.001至10000mg/天，优选0.1至500mg/天的剂量施用。

[0274] 当式(I)的化合物通过吸入途径施用时，它们优选以0.001至500mg/天，优选0.1至100mg/天的剂量给予。

[0275] 适合于通过吸入施用的包含本发明的化合物的药物组合物是各种可吸入形式，例如可吸入散剂(DPI)，含抛射剂的计量气雾剂(PMDI)或不含抛射剂的可吸入制剂(例如UDV)。

[0276] 本发明还涉及包含含有本发明的化合物的药物组合物的装置，其可以为单剂量或多剂量干粉吸入器，定量吸入器和喷雾器，特别是软雾喷雾器。

[0277] 尽管为了治疗呼吸道疾病，本发明的化合物可以通过吸入施用；但是在一些情况下，它们可以优选通过口服途径施用。

[0278] 当式(I)的化合物通过口服途径施用时，它们优选以0.001mg至100mg/kg人体重，

通常0.01mg至约50mg/kg，例如0.1至10mg/kg的剂量每天单次或多次施用。

[0279] 适合于通过口服途径施用的包含本发明的化合物的药物组合物可以为各种固体或液体形式，例如片剂，软胶囊，胶囊剂，胶囊形片剂，颗粒剂，锭剂和整装散剂或水和非水溶液，乳剂，混悬剂，糖浆剂和酏剂制剂。

[0280] 下列实施例更详细地示例本发明。

[0281] 中间体和实施例的制备

[0282] 一般实验详述

[0283] 用Structure to Name Enterprise 10.0Cambridge Software或最新版本产生化合物的化学名称。

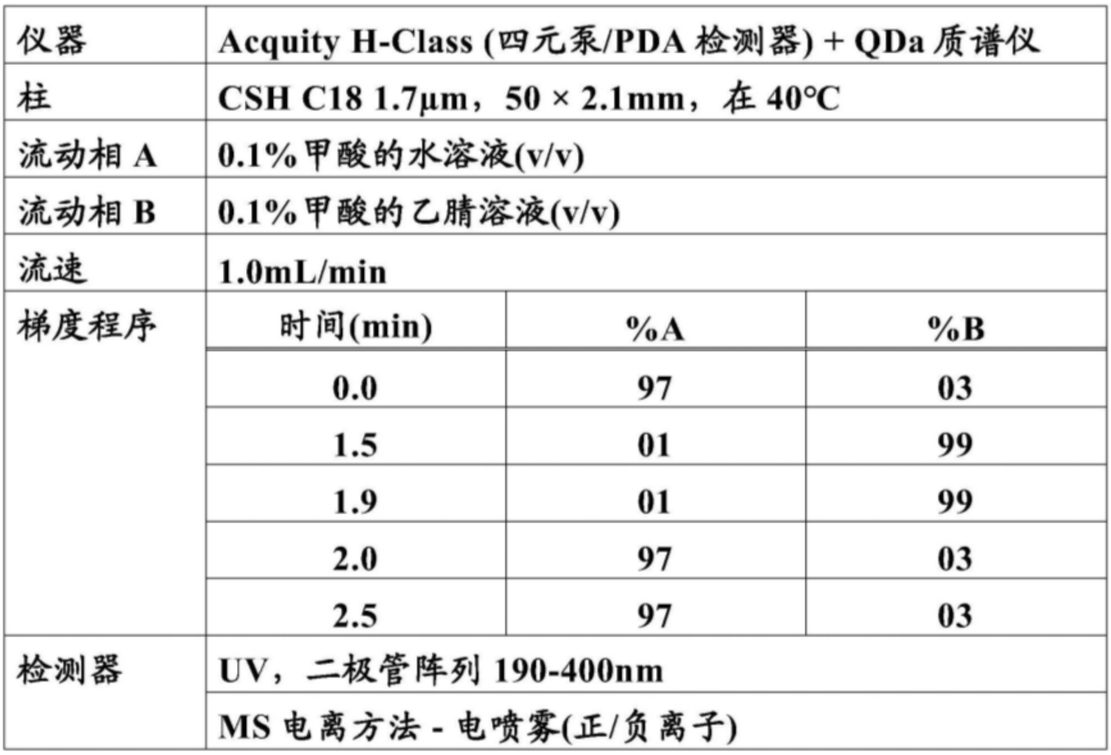
[0284] 通过“色谱法”或“快速色谱法”纯化是指使用Biotage SPL纯化系统或等同的MPLC系统，应用预填充聚丙烯柱的纯化，所述预填充聚丙烯柱包含具有平均尺寸为50μm和标称**60Å**孔隙率的不规则颗粒的非结合(unbounded)活化二氧化硅。当指定‘NH-二氧化硅’和‘C18-二氧化硅’时，它们分别是指氨基丙基链键合的二氧化硅和十八烷基碳链(C18)-键合的二氧化硅。汇集包含所需产物的级分(通过TLC和/或LCMS分析鉴定)，真空浓缩或冷冻干燥。

[0285] 如果使用**Isolute®** SCX-2柱，则‘**Isolute®** SCX-2柱’是指包含无封端的丙磺酸官能化的二氧化硅强阳离子交换吸附剂的预填充聚丙烯柱。

[0286] LCMS方法

[0287] 方法1

[0288]



仪器	**Acquity H-Class (四元泵/PDA 检测器) + QDa 质谱仪**		
柱	**CSH C18 1.7μm，50 × 2.1mm，在 40°C**		
流动相 A	**0.1% 甲酸的水溶液(v/v)**		
流动相 B	**0.1% 甲酸的乙腈溶液(v/v)**		
流速	**1.0mL/min**		
梯度程序	**时间(min)**	**%A**	**%B**
	0.0	**97**	**03**
	1.5	**01**	**99**
	1.9	**01**	**99**
	2.0	**97**	**03**
	2.5	**97**	**03**
检测器	**UV，二极管阵列 190-400nm**		
	MS 电离方法 - 电喷雾(正/负离子)		

[0289] 方法2

[0290]

仪器	Waters Acquity Classic + 996 PDA 检测器 + Waters ZMD 质谱仪		
柱	CSH C18 1.7μm，50 × 2.1mm，在 40℃		
流动相 A	0.1%甲酸的水溶液(v/v)		
流动相 B	0.1%甲酸的乙腈溶液(v/v)		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	97	3
	0.15	97	3
	2.3	1	99
	2.4	1	99
	2.5	97	3
检测器	UV，二极管阵列 190-400nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0291] 方法3

[0292] [0293]

仪器	UPLC + Waters DAD + Waters SQD2，单四极杆 UPLC-MS		
柱	HSS C18 1.8μm 100 x 2.1mm。(加保护柱)，维持在 40℃		
流动相 A	0.1%甲酸的水溶液(v/v)		
流动相 B	0.1%甲酸的乙腈溶液(v/v)		
流速	0.4mL/min		
梯度程序	时间(min)	%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
检测器	UV，二极管阵列 210nm-400nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0294] 方法4

[0295]

仪器	UPLC + Waters DAD + Waters SQD2，单四极杆 UPLC-MS		
柱	BEH Shield RP18 1.7μm 100 x 2.1mm。(加保护柱)，维持在 40℃		
流动相 A	10mM 碳酸氢铵水溶液		
流动相 B	乙腈		
流速	0.4mL/min		
梯度程序	时间(min)	%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
检测器	UV，二极管阵列 210nm-400nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0296] 方法5

[0297]

仪器	Acquity i-Class (四元泵/PDA 检测器) + Quattro 微型质谱仪
柱	BEH C18 1.7μm，100 × 2.1mm，维持在 40℃
流动相 A	0.1%甲酸的水溶液(v/v)

[0298]

流动相B	0.1%甲酸的乙腈溶液(v/v)		
流速	0.4mL/min		
梯度程序	时间(min)	%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
检测器	UV，二极管阵列200-500nm		
	MS电离方法-电喷雾(正/负离子)		

[0299] 方法6

[0300]

仪器	Acquity UPLC (二元泵/PDA检测器) + QDa质谱仪		
柱	CSH C18 1.7μm，50 × 2.1mm，在40°C		
流动相A	0.05%甲酸(v/v)的95/5水/乙腈溶液		
流动相B	0.05%甲酸(v/v)的5/95水/乙腈溶液		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	95	05
	1.50	05	95
	1.90	05	95
	2.0	05	95
	2.3	05	95
检测器	UV，二极管阵列200-500nm		
	MS电离方法-电喷雾(正/负离子)		

[0301] 方法7和方法8

[0302]

仪器	Shimadzu LCMS-2020 单四极杆液相色谱质谱仪		
柱	Aquity HSS C18 1.8μm，50 × 2.1mm，在 25℃		
流动相 A	0.1%甲酸(v/v)的水溶液		
流动相 B	0.1%甲酸(v/v)的乙腈溶液		
流速	0.5mL/min		
梯度程序	时间(min)	%A	%B
	0.00	95	05
	4.00	05	95
	5.00	05	95
	5.20	95	05
	6.00	95	05
检测器	UV，254nm 和 214nm(方法 13) UV，254nm 和 220nm(方法 14)		
	MS 电离方法 - 电喷雾(正/负离子)		

[0303] 方法9

[0304]

仪器	Shimadzu LCMS-2020 单四极杆液相色谱质谱仪		
柱	Aquity HSS C18 1.8μm，50 × 2.1mm，在 25℃		
流动相 A	0.1%甲酸(v/v)的水溶液		
流动相 B	0.1%甲酸(v/v)的乙腈溶液		
流速	0.5mL/min		
梯度程序	时间(min)	%A	%B
	0.00	95	05
	10.00	05	95
	10.50	05	95
	11.00	95	05
	12.00	95	05
检测器	UV，254nm 和 214nm		

[0305]

	MS 电离方法 - 电喷雾(正/负离子)

[0306] 方法10

[0307]

仪器	带有DAD检测器/Agilent Technologies InfinityLab LC/MSD的Agilent Technologies 1260 Infinity II		
柱	BEH C18 1.7μm，50 × 2.1mm，在25℃		
流动相A	0.05%氢氧化铵水溶液(v/v)		
流动相B	乙腈		
流速	0.5mL/min		
梯度程序	时间(min)	%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
检测器	UV，二极管阵列190 - 400nm		
	MS电离方法 - 电喷雾(正/负离子)		

[0308] 方法11

[0309]

仪器	Acquity UPLC(二元泵/PDA检测器) + QDa质谱仪		
柱	CSH C18 1.7μm，50 × 2.1mm，在40℃		
流动相A	0.05%甲酸(v/v)的95/5水/乙腈溶液		
流动相B	0.05%甲酸(v/v)的5/95水/乙腈溶液		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	95	05
	3.50	05	95
	3.90	05	95
	4.00	05	95
	4.3	05	95
检测器	UV，二极管阵列200-500nm		
	MS电离方法 - 电喷雾(正/负离子)		

[0310]

[0311] 方法12

[0312]

仪器	Acquity UPLC(二元泵/PDA 检测器) + QDa 质谱仪		
柱	BEH C18 1.7μm，50 × 2.1mm，在 40°C		
流动相 A	0.05%甲酸(v/v)的 95/5 水/乙腈溶液		
流动相 B	0.05%甲酸(v/v)的 5/95 水/乙腈溶液		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	95	05
	1.50	05	95
	1.90	05	95
	2.0	05	95
	2.3	05	95
检测器	UV，二极管阵列 200-500nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0313] 方法13

[0314]

仪器	Acquity UPLC(二元泵/PDA 检测器) + QDa 质谱仪
柱	CSH C18 1.7μm，50 × 2.1mm，在 50°C
流动相 A	甲酸铵水溶液(25mM) pH 3
流动相 B	0.1%甲酸的乙腈溶液
流速	0.35mL/min

[0315]

梯度程序	时间(min)	%A	%B
	0.00	99	01
	0.50	99	01
	3.00	70	30
	6.50	50	50
	7.50	20	80
	8.10	99	01
	10.00	99	01
检测器	UV，二极管阵列 200-500nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0316] 方法14

[0317]

仪器	Acquity UPLC(二元泵/PDA 检测器) + QDa 质谱仪		
柱	Kinetex C8 1.7μm，50 × 2.1mm，在 40°C		
流动相 A	0.05% 甲酸(v/v)的 95/5 水/乙腈溶液		
流动相 B	0.05% 甲酸(v/v)的 5/95 水/乙腈溶液		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	95	05
	1.50	05	95
	1.90	05	95
	2.0	05	95
	2.3	05	95
检测器	UV，二极管阵列 200-500nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0318] 方法15

[0319]

[0320]

仪器	Acquity UPLC(二元泵/PDA 检测器) + QDa 质谱仪		
柱	Kinetex C8 1.7μm，50 × 2.1mm，在 40°C		
流动相 A	0.05% 甲酸(v/v)的 95/5 水/乙腈溶液		
流动相 B	0.05% 甲酸(v/v)的 5/95 水/乙腈溶液		
流速	1.0mL/min		
梯度程序	时间(min)	%A	%B
	0.0	95	05
	3.50	05	95
	3.90	05	95
	4.00	05	95
	4.3	05	95
检测器	UV，二极管阵列 200-500nm		
	MS 电离方法 - 电喷雾(正/负离子)		

[0321] 方法16

[0322]

仪器	Acquity H-Class(四元泵/PDA检测器)+QDa质谱仪		
柱	Acquity BEH C18 1.7μm，50×2.1mm，在40℃		
流动相A	0.03%氨的水溶液(v/v)(7.66mM)		
流动相B	0.03%氨的乙腈溶液(v/v)(7.66mM)		
流速	0.8mL/min		
梯度程序	时间(min)	%A	%B
	0.0	97	3
	1.5	3	97
	2.3	3	97
	2.4	97	3
	2.5	97	3
检测器	UV，二极管阵列190-400nm		
	MS电离方法-电喷雾(正/负离子)		

[0323] NMR方法

[0324] NMR光谱在运行Topspin 2.1的Bruker Avance 400MHz,5mm QNP探针H,C,F,P,单Z梯度,双通道仪器上获得,或在运行Topspin 3.0的Bruker Avance III 400MHz,5mm BBFO Plus探针,单Z梯度,双通道仪器上获得,或在具有在400MHz下操作的5mm反向检测三重共振探针的Varian Unity Inova 400光谱仪上获得。化学位移报告为相对于四甲基硅烷的以ppm计的δ值。偶合常数(J值)以赫兹(Hz)给出,并且使用以下缩写报告多重性:s＝单重峰,d＝双重峰,t＝三重峰,q＝四重峰,m＝多重峰,br＝宽峰,nd＝未测定。

[0325] SFC方法

[0326] 使用超临界流体色谱法(SFC)纯化化合物时,则使用Waters Thar Prep100制备型SFC系统(P200 CO_2泵,2545改性剂泵,2998UV/VIS检测器,具有叠加注射模块的2767液体处理器)或Waters Thar Investigator半制备型系统(Waters流体递送模块,2998UV/VIS检测器,Waters级分采集模块)。使用指定的柱和条件纯化化合物,并且通过真空离心浓缩包含期望的产物的级分。

[0327] 在碱性条件下使用的改性剂为二乙胺(0.1%V/V)。替代的改性剂例如甲酸(0.1%V/V),乙酸(0.1%V/V)用作酸性改性剂。

[0328] MDAP方法

[0329] 使用Waters Fractionlynx制备型HPLC系统(2525泵,2996/2998UV/VIS检测器,2767液体处理器)或Gilson制备型HPLC系统(322泵,155UV/VIS检测器,GX-281液体处理器)或等效系统,通过反相HPLC纯化化合物。通过在260nm处的阈值吸光度值和在ESI条件下观察到的靶分子离子的存在触发采集。将包含期望的产物的级分冻干。所用条件的具体细节,包括柱,溶剂,梯度和改性剂(酸性或碱性)仅作为示例提供,并且仅提供用于帮助。当没有提供特定条件时,本领域技术人员可以容易地优化它们。

[0330] 在以下方法中,一些起始材料通过“中间体”或“实施例”编号标识,步骤名称上有

指示。当提及使用“相似”或“类似”方法时，如本领域技术人员将理解的，这样的方法可以涉及微小的变化，例如反应温度，试剂/溶剂量，反应时间，后处理条件或色谱纯化条件。

[0331] 在指出的情况下，实施例中化合物的立体化学是基于以下假设指定的：在起始材料的拆分的立体中心处的绝对构型在任何后续反应条件中得以维持。所有溶剂和市售试剂均按原样使用。在没有描述起始材料的制备的情况下，这些是可商购的，文献中已知的或本领域技术人员使用标准方法容易获得的。

[0332] 缩写

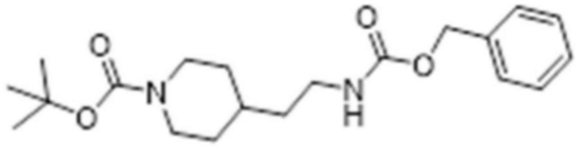
[0333] ACN(乙腈)，BINAP(2,2’-双(二苯基膦基)-1,1’-联萘)，COMU((1-氰基-2-乙氧基-2-氧代亚乙基氨基氧基)二甲基氨基-吗啉代-碳鎓六氟磷酸盐)，DCM(二氯甲烷)，DIPEA或DIEA(N-乙基二异丙基胺)，DMF(N,N-二甲基甲酰胺)，DMSO(二甲亚砜)，dppf(1,1’-二茂铁二基-双(二苯基膦))，EtOH(乙醇)，EtOAc(乙酸乙酯)，FA(甲酸)，HATU(1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧六氟磷酸盐，N-[(二甲基氨基)-1H-1,2,3-三唑并-[4,5-b]吡啶-1-基亚甲基]-N-甲基甲胺六氟磷酸盐N-氧化物)，HPLC(高效液相色谱法)，LCMS(液相色谱法-质谱法)，MDAP(质量定向自动纯化)，MeOH(甲醇)，Me-THF(2-甲基四氢呋喃)，MTBE(甲基叔丁基醚)，NMP(N-甲基吡咯烷酮)，NMR(核磁共振)，Rt(保留时间)，RT(室温)，SCX(强阳离子交换)，TBTU(2-(1H-苯并三唑-1-基)-1,1,3,3-四甲基铵四氟硼酸盐)，TFA(三氟乙酸)，THF(四氢呋喃)，XPhos Pd G2氯(2-二环己基膦基-2’,4’,6’-三异丙基-1,1’-联苯)[2-(2’-氨基-1,1’-联苯)]钯(II)。

[0334] 中间体的制备

[0335] 中间体A1

[0336] 步骤A

[0337]



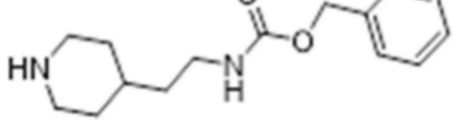
[0338] 4-(2-(((苄基氧基)羰基)氨基)乙基)哌啶-1-甲酸叔丁酯(中间体A1-a)

[0339] 将4-(2-氨基乙基)哌啶-1-甲酸叔丁酯(0.3g，1.3mmol)溶于DCM(4.0mL)，然后在搅拌下加入(2,5-二氧代吡咯烷-1-基)碳酸苄酯(0.33g，1.3mmol)，然后加入三乙胺(0.18mL，1.3mmol)。将该溶液在RT搅拌3h。反应混合物用DCM(30mL)稀释，有机层用饱和NH_4Cl水溶液(50mL)洗涤，然后用饱和$NaHCO_3$水溶液(50mL)洗涤，用Na_2SO_4干燥，浓缩至干，得到标题化合物(0.48g)，其不经进一步纯化用于下一步。

[0340] LCMS(方法6)：Rt＝1.22min，m/z 385.1$[M+Na]^+$

[0341] 步骤B

[0342]



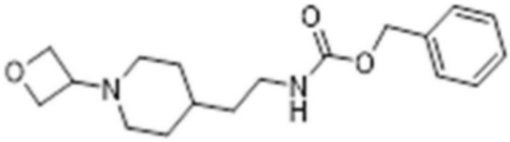
[0343] (2-(哌啶-4-基)乙基)氨基甲酸苄酯(中间体A1-b)

[0344] 在0℃将中间体A1-a(0.48g，1.313mmol)溶于DCM(15mL)/TFA(5mL)的混合物，将该溶液在RT搅拌3h。减压干燥该反应混合物，用**Isolute®** SCX-2柱纯化粗产物，得到标题化

合物(0.36g)。

[0345] LCMS(方法6):Rt＝0.41min,m/z 263.0[M+H]$^+$

[0346] 步骤C

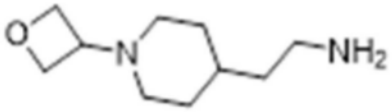
[0347] 

[0348] (2-(1-(氧杂环丁烷-3-基)哌啶-4-基)乙基)氨基甲酸苄酯(中间体A1-c)

[0349] 将在DCM(10mL)中的中间体A1-b(0.20g,0.76mmol)和氧杂环丁烷-3-酮(0.055g,0.76mmol)在RT搅拌15min,,然后一次性加入三乙酰氧基硼氢化钠(0.24g,1.14mmol)。将该溶液在RT搅拌4h,然后用DCM稀释,用饱和$NaHCO_3$水溶液洗涤有机相,用Na_2SO_4干燥,浓缩至干,通过**Isolute®** SCX-2柱纯化,得到标题化合物(0.24g)。

[0350] LCMS(方法6):Rt＝0.43min,m/z 319.3[M+H]$^+$

[0351] 步骤D

[0352] 

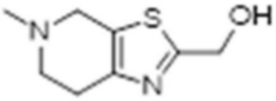
[0353] 2-(1-(氧杂环丁烷-3-基)哌啶-4-基)乙-1-胺(中间体A1)

[0354] 在真空/H_2循环中给在EtOH(5mL)中的中间体A1-c(0.10g,0.31mmol),乙酸(0.019g,0.31mmol)和Pd/C(0.100g,0.942mmol)脱气(3次),然后在RT下氢化4h。过滤该反应混合物,蒸发至干,得到标题化合物(0.058g),其不经进一步纯化用于下一步。

[0355] LCMS(方法6):Rt＝0.12min,m/z 185.3[M+H]$^+$

[0356] 中间体A2

[0357] 步骤A

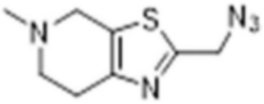
[0358] 

[0359] (5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)甲醇(中间体A2-a)

[0360] 向0℃冷却的5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸盐酸盐(0.2g,0.85mmol)在THF(5mL)中的悬浮液中滴加氢化铝锂的THF溶液(1.0mL,1.00mmol),在RT下持续搅拌1h。通过添加饱和Na_2SO_4水溶液使该反应停止,过滤该混合物,用Na_2SO_4干燥,浓缩至干,得到标题化合物(0.125g)。

[0361] LCMS(方法6):Rt＝0.13min,m/z 185.0[M+H]$^+$

[0362] 步骤B

[0363] 

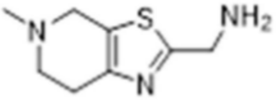
[0364] 2-(叠氮基甲基)-5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶(中间体A2-b)

[0365] 将中间体A2-a(0.125g,0.68mmol),叠氮磷酸二苯酯(0.146mL,0.68mmol)和1,8-二氮杂双环[5.4.0]十一碳-7-烯(0.101mL,0.68mmol)溶于无水THF(5mL),将得到的溶液在90℃在微波照射下加热1h。蒸发该反应混合物至干,用NH-二氧化硅纯化,用0-10％MeOH的

DCM溶液洗脱，得到标题化合物(80mg)。

[0366] LCMS(方法6)：Rt＝0.14min，m/z 210.0[M+H]$^+$

[0367] 步骤C

[0368] 

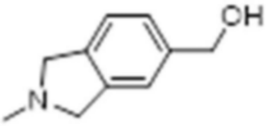
[0369] (5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)甲胺(中间体A2)

[0370] 将中间体A2-b(0.08g，0.38mmol)溶于THF(5mL)和水(0.5mL)的混合物，然后加入三苯基膦(0.301g，1.15mmol)，将该溶液回流2h。减压干燥该混合物，用**Isolute®** SCX-2柱纯化，得到标题化合物(15mg)。

[0371] LCMS(方法6)：Rt＝0.10min，m/z 184.0[M+H]$^+$

[0372] 中间体A3

[0373] 步骤A

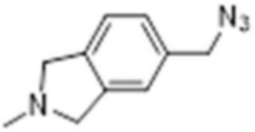
[0374] 

[0375] (2-甲基异二氢吲哚-5-基)甲醇(中间体A3-a)

[0376] 使用与用于合成中间体A2-a类似的方法，通过用2-甲基异二氢吲哚-5-甲酸甲酯替代步骤A中的5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸盐酸盐来制备中间体A3-a。

[0377] LCMS(方法6)：Rt＝0.13min，m/z 164.0[M+H]$^+$

[0378] 步骤B

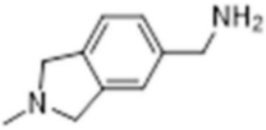
[0379] 

[0380] 5-(叠氮基甲基)-2-甲基异二氢吲哚(中间体A3-b)

[0381] 使用与用于合成中间体A2-b类似的方法，通过用中间体A3-a替代步骤b的中间体A2-a来制备中间体A3-b。

[0382] LCMS(方法6)：Rt＝0.20min，m/z 189.1[M+H]$^+$

[0383] 步骤C

[0384] 

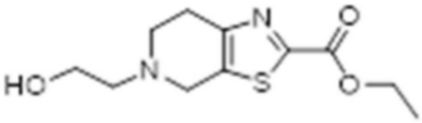
[0385] (2-甲基异二氢吲哚-5-基)甲胺(中间体A3)

[0386] 使用与用于合成中间体A2类似的方法，通过用中间体A3-b替代步骤c的中间体A2-b来制备中间体A3。

[0387] LCMS(方法6)：Rt＝0.10min，m/z 163.0[M+H]$^+$

[0388] 中间体A4

[0389] 步骤A

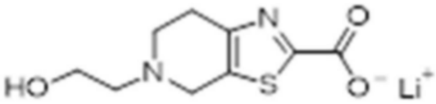
[0390] 

[0391] 5-(2-羟基乙基)-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸乙酯(中间体A4-a)

[0392] 将4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸乙酯(150mg,0.707mmol)和碳酸铯(691mg,2.120mmol)溶于乙腈(6mL),反应10min,然后添加碘化钾(58.7mg,0.353mmol)和2-溴乙醇(0.201mL,1.413mmol)。将该反应混合物在75℃搅拌7h,然后过滤,蒸发至干。通过NH-二氧化硅快速色谱法纯化得到的粗物质,用0-10%MeOH的DCM溶液洗脱。蒸发合适的级分,得到期望的产物(167mg)。

[0393] LCMS(方法6):Rt=0.16min,m/z 257.0$[M+H]^+$

[0394] 步骤B

[0395] 

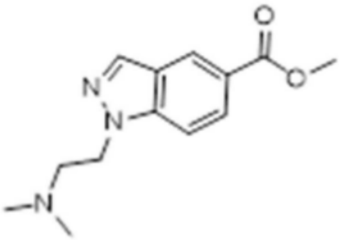
[0396] 5-(2-羟基乙基)-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸锂(中间体A4)

[0397] 将中间体A4-b溶于THF(2.5mL)和水(2.5mL),然后加入氢氧化锂(78mg),将该混合物在RT搅拌1h。真空蒸发溶剂,得到标题化合物(265mg)。

[0398] LCMS(方法6):Rt=0.14min,m/z 228.8$[M+H]^+$

[0399] 中间体A5

[0400] 步骤A

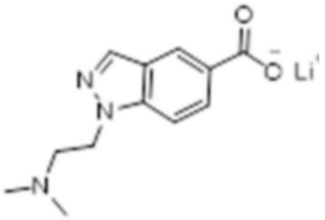
[0401] 

[0402] 1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酸甲酯(中间体A5-a)

[0403] 向1H-吲唑-5-甲酸甲酯(250mg,1.419mmol)和N,N-二甲基乙醇胺(0.289mL,2.84mmol)在甲苯(6mL)中的溶液中加入0.5M的2-(三甲基亚正膦基)乙腈的THF溶液(5.68mL,2.84mmol)。将该反应混合物在110℃搅拌18h。真空蒸发溶剂,然后将粗产物溶于EtOAc,用饱和$NaHCO_3$水溶液洗涤。真空蒸发有机相,通过NH-二氧化硅快速色谱法纯化,用1/1庚烷/EtOAc+1%三乙胺洗脱。收集合适的级分,干燥,得到标题化合物(249mg)。

[0404] LCMS(方法6):Rt=0.36min,m/z 248.2$[M+H]^+$

[0405] 步骤B

[0406] 

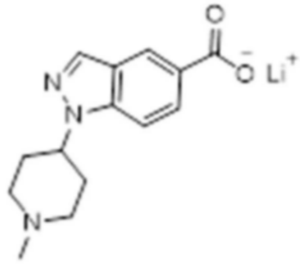
[0407] 1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酸锂(中间体A5)

[0408] 将中间体A5-a(249mg,1.01mmol)溶于MeOH(2.5mL)和水(2.5mL),然后一次性加入氢氧化锂(36.2mg,1.510mmol),将该混合物在RT搅拌1h。真空蒸发溶剂,得到期望的产物(200mg),其不经进一步纯化用于下一步。

[0409] LCMS(方法6):Rt=0.16min,m/z 234.2$[M+H]^+$

[0410] 中间体A6

[0411]



[0412] 1-(1-甲基哌啶-4-基)-1H-吲唑-5-甲酸锂(中间体A6)

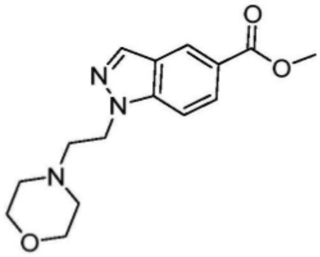
[0413] 使用与用于合成中间体A-5类似的方法,通过用1-甲基哌啶-4-醇替代N,N-二甲基乙醇胺来制备中间体A6。

[0414] LCMS(方法6):Rt=0.39min,m/z 260.0$[M+H]^+$

[0415] 中间体A7

[0416] 步骤A

[0417]



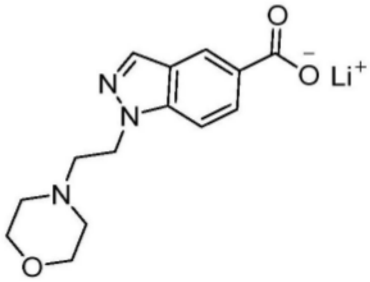
[0418] 1-(2-吗啉代乙基)-1H-吲唑-5-甲酸甲酯(中间体A7-a)

[0419] 将1H-吲唑-5-甲酸甲酯(500mg,2.84mmol)和碳酸钾(1.18g,8.51mmol)混合在DMF(10mL)中,在RT搅拌20min,然后加入4-(2-氯乙基)吗啉盐酸盐(1.205mL,5.68mmol)。将该反应混合物在70℃搅拌24h。用EtOAc(10mL)稀释该混合物,用饱和$NaHCO_3$水溶液(10mL)洗涤。用EtOAc(2x 10mL)萃取水相。真空蒸发合并的有机相。通过NH-二氧化硅快速色谱法纯化得到的粗物质,用0-50%EtOAc的己烷溶液洗脱。合并合适的级分,干燥,得到期望的产物(325mg)。

[0420] LCMS(方法6):Rt=0.38min,m/z 290.0$[M+H]^+$

[0421] 步骤B

[0422]

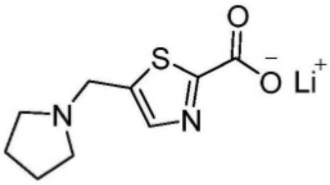


[0423] 1-(2-吗啉代乙基)-1H-吲唑-5-甲酸锂(中间体A7)

[0424] 使用与用于由中间体A5-a合成中间体A5的步骤b类似的方法，由中间体A7-a制备中间体A7。

[0425] LCMS(方法6):Rt＝0.21min,m/z 275.9$[M+H]^+$

[0426] 中间体A8

[0427] 

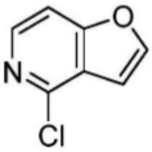
[0428] 5-(吡咯烷-1-基甲基)噻唑-2-甲酸锂(中间体A8)

[0429] 使用与用于合成中间体A7类似的方法，通过分别在步骤A中用5-(溴甲基)噻唑-2-甲酸乙酯替代4-(2-氯乙基)吗啉盐酸盐并且用吡咯烷替代1H-吲唑-5-甲酸甲酯来制备中间体A8。

[0430] LCMS(方法6):Rt＝0.14min,m/z 213.0$[M+H]^+$

[0431] 中间体B

[0432] 步骤A

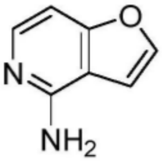
[0433] 

[0434] 4-氯呋喃并[3,2-c]吡啶(中间体B-a)

[0435] 将呋喃并[3,2-c]吡啶-4-醇(70.4g,0.52mol)在三氯氧磷(430mL)中的混合物回流加热1h。蒸馏出三氯氧磷，将残余物倾入冰/水，用饱和$NaHCO_3$水溶液中和至pH～6。用DCM将水相萃取2次，然后用饱和NaCl水溶液洗涤有机层，蒸发至干。通过硅胶柱色谱法纯化粗物质，用EtOAc-己烷洗脱，得到标题化合物(72.8g)。

[0436] LCMS(方法7):Rt＝2.71min,m/z 153.9$[M+H]^+$

[0437] 步骤B

[0438] 

[0439] 呋喃并[3,2-c]吡啶-4-胺(中间体B-b)

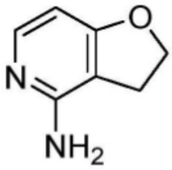
[0440] 用氩气给中间体B-a(72.8g,0.47mol)在干甲苯(730mL)中的溶液吹扫，历时20min，然后加入外消旋BINAP(17.72g,0.028mol)，三(二亚苄基丙酮)二钯(0)(8.69g,0.0095mol)和叔丁醇钾(74.50g,0.66mol)。在添加二苯甲酮亚胺(95.5mL,0.57mol)后，将该混合物在90℃加热1.5h。将该反应混合物冷却至RT，用THF稀释，通过硅藻土垫过滤，然后用THF和乙醚洗涤。蒸发合并的滤液，将残余物溶于MeOH(260mL)，滴加至预先在冰浴中用NaOH(56.91g,1.42mol)中和的羟基胺盐酸盐(98.87g,1.42mol)在MeOH(1200mL)中的溶液中。将该反应混合物在RT搅拌1h，蒸发至干。通过二氧化硅色谱法纯化粗物质，用10-100％EtOAc的己烷溶液洗脱，得到固体，其进一步通过研磨和在MTBE和DCM的混合物中过滤纯化。

通过二氧化硅色谱法进行第二次纯化，用0-10％MeOH的DCM溶液洗脱，得到纯的标题化合物(45.1g)。

[0441]　LCMS(方法8)：Rt＝0.83min，m/z 135.0[M+H]$^+$

[0442]　步骤C

[0443]



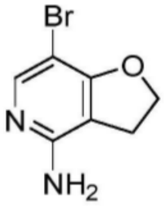
[0444]　2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体B-c)

[0445]　将中间体B-b(44.1g，0.33mol)溶于MeOH(530mL)和乙酸(56.4mL)，然后加入10％Pd/C(50％湿，17.74g)，用氩气吹扫该反应混合物，然后在10bar H_2压力下在50℃在剧烈搅拌下氢化。20h后，需要另一半当量的10％Pd/C(50％湿)和进一步3h氢化，以便实现完全转化。过滤该反应混合物，用MeOH洗涤。蒸发合并的滤液，使残余物分配在EtOAc(500mL)与水(500mL)之间。再用EtOAc(300mL)洗涤水层，用固体$NaHCO_3$中和，用NaCl饱和。用DCM(8x300mL)萃取水性混合物，用饱和NaCl水溶液(800mL)洗涤合并的有机层，用Na_2SO_4干燥，蒸发，得到标题化合物(24.57g)。

[0446]　LCMS(方法9)：Rt＝0.81min，m/z 137.1[M+H]$^+$

[0447]　步骤D

[0448]

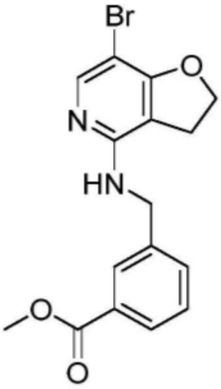


[0449]　7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体B)

[0450]　将中间体B-c(24.57g，0.180mol)溶于ACN(1230mL)，然后在-10℃在黑暗中滴加N-溴琥珀酰亚胺(35.33g，0.198mol)在ACN(490mL)中的溶液，历时3h。用饱和$NaHCO_3$水溶液(500mL)，水(500mL)，EtOAc(1000mL)和5％NaCl水溶液(500mL)使反应淬灭。分离得到的有机相和水相，再用EtOAc(1000mL)洗涤水层。用5％NaCl水溶液(7x 2000mL)洗涤合并的有机层，浓缩至干。用EtOAc(500mL)和水(200mL)的混合物处理残留固体，置于超声浴中，用10％$KHSO_4$水溶液(300mL)酸化。通过过滤采集出现的固体。分配双相滤液，用10％$KHSO_4$水溶液(各200mL)将水层洗涤2次。用EtOAc(3x 500mL)洗涤合并的水层，与在先收集的固体混合。用$NaHCO_3$将得到的水性混合物中和至pH7，用EtOAc(3x 1000mL)萃取。用饱和NaCl水溶液(500mL)洗涤合并的有机相，用无水$MgSO_4$干燥，浓缩，得到标题化合物，为固体(27.1g)。

[0451]　LCMS(方法10)：Rt＝1.69min，m/z 215.0/217.0[M+H]$^+$

[0452]　中间体C1

[0453] 

[0454] 3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酸甲酯(中间体C1)

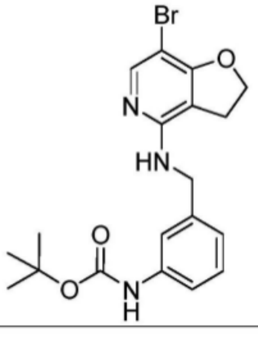
[0455] 将中间体B(15.6g,0.074mol)和3-甲酰基苯甲酸甲酯(18.1g,0.11mol)与分子筛一起溶于无水DCM(470mL),保持在惰性气体气氛中。10min后,滴加氯(三异丙氧基)钛(IV)(35.4mL,0.148mol),将得到的混合物在RT搅拌,历时2.5h。加入三乙酰氧基硼氢化钠(31.4g,0.148mol),随后加入乙酸(8.5mL,0.148mol),将该混合物在RT搅拌过夜。用甲醇使该反应混合物淬灭,蒸发溶剂。将残余物溶于EtOAc和饱和$NaHCO_3$水溶液。搅拌15min后,通过薄硅藻土垫过滤该混合物,用EtOAc洗涤。采集合并的滤液,分离有机-水相。用Na_2SO_4干燥有机层,蒸发。通过硅胶柱色谱法纯化粗物质,用20%-40%EtOAc的己烷溶液洗脱,得到标题化合物(19.3g)。

[0456] LCMS(方法6):Rt=0.85min,m/z 362.9/364.9$[M+H]^+$

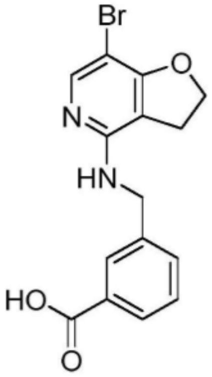
[0457] 中间体C2

[0458] 使用与用于合成中间体C1类似的方法,通过用表中指定的起始材料替代3-甲酰基苯甲酸甲酯来制备下列中间体。

[0459]

	结构	**起始材料**	**LC-MS**
C2		**(3-甲酰基苯基)氨基甲酸叔丁酯**	**Rt = 0.87min, m/z 420.2/422.4 $[M+H]^+$ (方法 6)**

[0460] 中间体D1

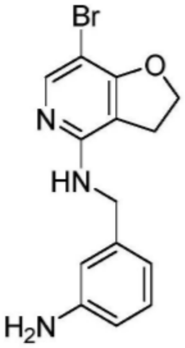
[0461] 

[0462] 3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酸(中间体D1)

[0463] 将中间体C1(100mg,0.27mmol),氢氧化锂一水合物(0.035g,0.83mmol)在THF(1mL),MeOH(1mL)和水(2mL)的溶液在RT搅拌1.5h。用水稀释得到的混合物,用EtOAc萃取。用1M HCl水溶液将水相的pH调节至pH～2-3。用Na_2SO_4干燥有机层,真空浓缩,得到产物,为固体(89mg)。

[0464] LCMS(方法1):Rt＝0.81min,m/z 348.9/350.9$[M+H]^+$

[0465] 中间体D2

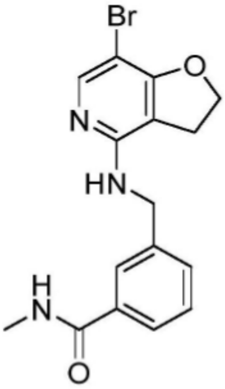
[0466] 

[0467] N-(3-氨基苄基)-7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体D2)

[0468] 将中间体C2(800mg)溶于乙腈(6mL),然后加入HCl 12M水溶液。将该溶液在RT搅拌,1h后,沉淀出现。通过过滤采集固体,得到标题化合物(550mg)。

[0469] LCMS(方法6):Rt＝0.38min,m/z 320.0/322.0$[M+H]^+$

[0470] 中间体E1

[0471] 

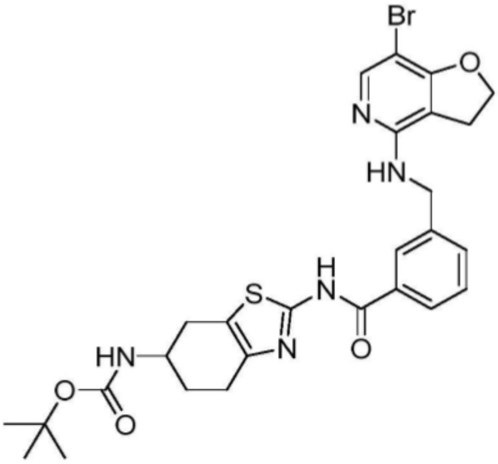
[0472] 3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-甲基苯甲酰胺(中间体E1)

[0473] 将中间体D1(40mg,0.12mmol),甲基胺盐酸盐(23mg,0.35mmol),TBTU(150mg,0.46mmol)和N,N-二异丙基乙胺(0.12mL,0.69mmol)在DCM(4mL)中的混合物在RT搅拌18h。用水稀释得到的混合物,用DCM萃取。用硫酸钠干燥有机层,真空浓缩。用MeOH稀释残余物,使其通过**Isolute®** SCX-2柱,用MeOH,然后用2M甲醇氨洗脱。真空浓缩该溶液,得到期望的产物(29mg)。

[0474] LCMS(方法1):Rt=0.73min,m/z 362.0/364.0[M+H]$^+$

[0475] 中间体E2

[0476]



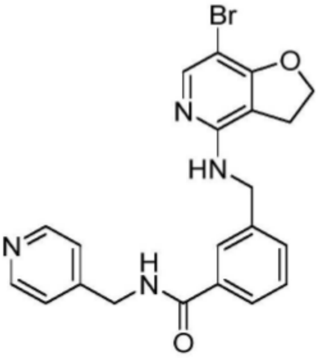
[0477] (2-(3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)-甲基)苯甲酰氨基)-4,5,6,7-四氢苯并[d]噻唑-6-基)氨基甲酸叔丁酯(中间体E2)

[0478] 将二异丙基乙胺(1.0mL,6.0mmol)加入到搅拌的3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酸(700mg,2.0mmol),(2-氨基-4,5,6,7-四氢苯并[d]噻唑-6-基)氨基甲酸叔丁酯(540mg,2.0mmol)和TBTU(837mg,2.61mmol)在DMF(12mL)中的溶液中。将该混合物在RT搅拌6h,然后使其静置16h。用EtOAc(25mL)稀释该混合物,用水(25mL)洗涤该溶液。用EtOAc(25mL)萃取水相。用饱和NaCl水溶液(2x 25mL)洗涤合并的有机相,干燥(Na_2SO_4),减压浓缩。将残余物溶于DCM,上**Isolute®** SCX-2柱,用DCM,然后用2:1DCM:MeOH洗涤,用2:1DCM:2M甲醇氨洗脱后,减压浓缩。将残余物溶于DCM,通过Si柱快速色谱法纯化,用0-50%EtOAc的DCM溶液,然后用100%EtOAc洗脱,得到期望的产物,为浅黄褐色泡沫体(775mg)。

[0479] LCMS(方法2):Rt=1.46min,m/z 600.0/601.9[M+H]$^+$

[0480] 中间体E3

[0481]



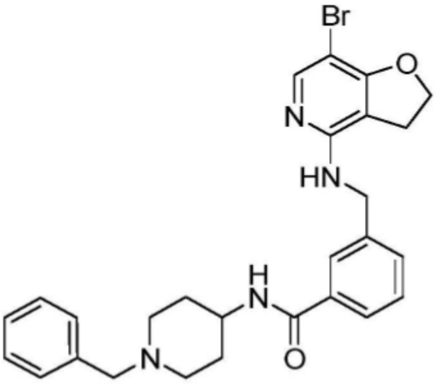
[0482] 3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-4-基甲基)苯甲酰胺(中间体E3)

[0483] 将中间体C1(250mg,0.688mmol),吡啶-4-基甲胺(0.210mL,2.065mmol)和双(三甲基铝)1,4二氮杂双环[2.2.2]辛烷加合物(529mg,2.065mmol)溶于THF(6mL),用氮气吹扫该混合物。将得到的混合物在微波照射中在120℃加热30min。用水使该反应混合物淬灭,用DCM萃取,真空蒸发有机相。通过C18-二氧化硅快速色谱法纯化得到的粗产物,用0-20%A中的B(A:水/乙腈95/5+0.1%HCOOH,B:乙腈/水95/5+0.1%HCOOH)洗脱。收集合适的级分,蒸发,得到标题化合物(164mg)。

[0484] LCMS(方法6):Rt=0.39min,m/z 439.1/441.1$[M+H]^+$

[0485] 中间体E4

[0486]



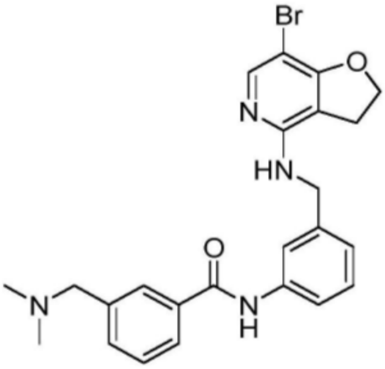
[0487] N-(1-苄基哌啶-4-基)-3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺(中间体E4)

[0488] 使用与在先用于中间体E3所述类似的方法,通过用1-苄基哌啶-4-胺替代吡啶-4-基甲胺来制备中间体E4。

[0489] LCMS(方法6):Rt=0.51min,m/z 521.2/523.1$[M+H]^+$

[0490] 中间体E5

[0491]



[0492] N-(3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-3-((二甲基氨基)甲基)苯甲酰胺(中间体E5)

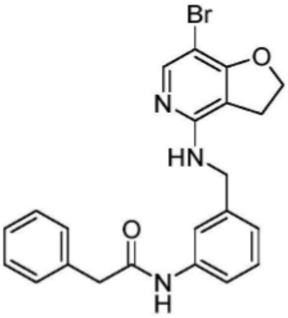
[0493] 将3-((二甲基氨基)甲基)苯甲酸盐酸盐(98mg,0.454mmol)和COMU(0.133mL,0.273mmol)溶于无水DCM(5mL),搅拌10min,然后加入中间体D2(81mg,0.23mmol)和DIEA(0.158mL,0.908mmol),将该混合物在RT搅拌2h。用DCM稀释该反应混合物,用饱和$NaHCO_3$水溶液将有机相洗涤2次,真空蒸发。通过二氧化硅快速色谱法纯化粗产物,用0-30%的80/

20DCM/MeOH(+1％三乙胺)在DCM中的溶液洗脱。合并适当的级分，真空蒸发，得到期望的产物(115mg)。

[0494]　LCMS(方法6)：Rt＝0.42min，m/z 481.0/483.0$[M+H]^+$

[0495]　中间体E6

[0496]



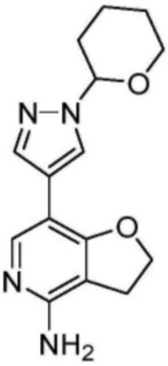
[0497]　N-(3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-苯基乙酰胺(中间体E6)

[0498]　将2-苯基乙酸(112mg，0.82mmol)和COMU(0.240mg，0.49mmol)溶于DCM(4mL)，在RT反应10min，然后加入中间体D2(150mg，0.41mmol)和DIEA(0.143mL，0.819mmol)。将该反应体系在RT搅拌2h。用DCM稀释该反应混合物，用饱和$NaHCO_3$水溶液洗涤，蒸发。通过C18-二氧化硅快速色谱法纯化得到的粗产物，用0-10％A中的B(A：水/乙腈95/5+0.1％HCOOH，B：乙腈/水95/5+0.1％HCOOH)洗脱，得到期望的产物(126mg)。

[0499]　LCMS(方法6)：Rt＝0.81min，m/z 438.0/440.0$[M+H]^+$

[0500]　中间体F

[0501]



[0502]　7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体F)

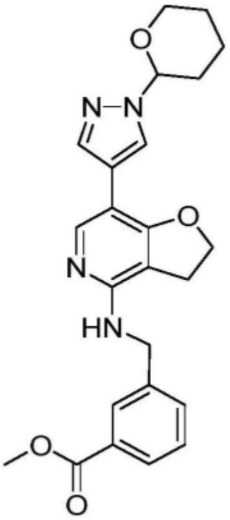
[0503]　将中间体B(1.80g，8.4mmol)，1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-硼酸(3.03g，11mmol)和碳酸铯(8.18g，25mmol)混合在DMF(72mL)和水(36mL)中。用氩气给该反应体系吹扫10min，然后加入四(三苯基膦)钯(0)(0.97g，0.8mmol)，将该反应混合物在70℃加热过夜。使该反应体系冷却至RT，用水(72mL)稀释，用EtOAc(5x 250mL)萃取。用饱和NaCl水溶液(505mL)洗涤合并的有机层，浓缩至干。用二氧化硅纯化粗产物，用0-8％MeOH的DCM溶液洗脱，得到标题化合物(1.13g)。

[0504]　LCMS(方法6)：Rt＝0.41min，m/z 287.2$[M+H]^+$

[0505]　中间体G

[0506]　步骤A

[0507]



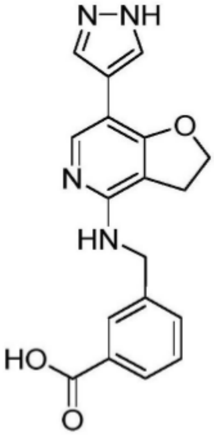
[0508]　3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酸甲酯(中间体G-a)

[0509]　将中间体C1(0.9g,2,478mmol),1-(四氢-2H-吡喃-2-基)-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑(1.378g,4.96mmol)和磷酸三钾(1.578g,7.43mmol)溶于THF(10mL)和水(10mL)的混合物。用氩气给该混合物吹扫10min,然后加入氯(2-二环己基膦基-2',4',6'-三异丙基-1,1'-联苯)[2-(2'-氨基-1,1'-联苯)]钯(II)(0.292g,0.372mmol),将该反应体系在RT搅拌6h。用水(30mL)稀释该混合物,用THF(3x25mL)萃取。用Na_2SO_4干燥有机相,浓缩至干。通过二氧化硅快速色谱法纯化粗产物,用0-10%MeOH的DCM溶液洗脱,得到期望的产物(1.08g)。

[0510]　LCMS(方法6):Rt=0.69min,m/z 435.3$[M+H]^+$

[0511]　步骤B

[0512]



[0513]　3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酸(中间体G)

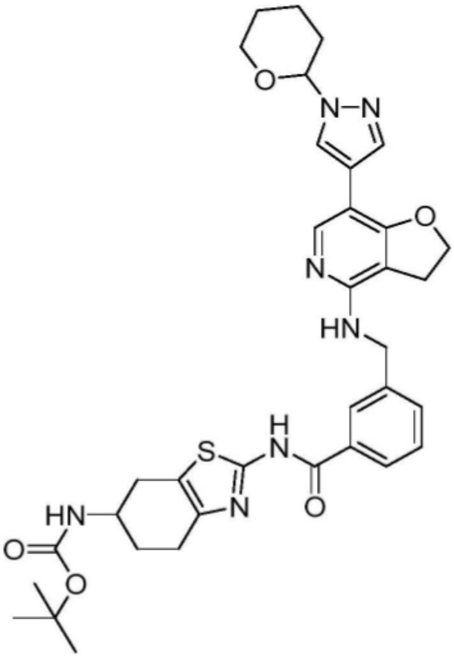
[0514]　将中间体G-a(1.26g,2.90mmol)悬浮于6M HCl水溶液(35mL,0.435mmol)。将该混合物在90℃加热30min,然后蒸发至干,得到标题化合物(1.26g),其不经进一步纯化用于下一步。

[0515]　LCMS(方法6):Rt=0.46min,m/z 337.2$[M+H]^+$

[0516]　中间体H1

[0517] 步骤A

[0518]



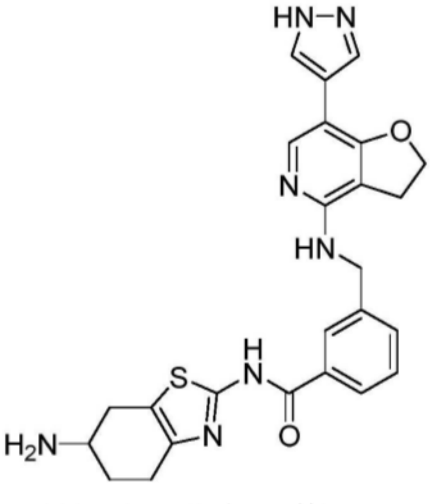
[0519] (2-(3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰氨基)-4,5,6,7-四氢苯并[d]-噻唑-6-基)氨基甲酸叔丁酯(中间体H1-a)

[0520] 将氯(2-二环己基膦基-2',4',6'-三异丙基-1,1'-联苯)[2-(2'-氨基-1,1'-联苯)]钯(II)(59mg,0.075mmol)加入到乙腈用氩气脱气的中间体E2(300mg 0.5mmol),磷酸三钾(318mg,1.5mmol),1-(四氢吡喃-2-基)-1H-吡唑-4-硼酸频哪醇酯(278mg,1.0mmol)在THF(2.0mL)和水(2mL)中的混合物中。将该混合物在80℃在微波反应器中加热1h。用EtOAc(15mL)稀释冷混合物,用水(10mL)洗涤。用EtOAc(2x 10mL)萃取水相。干燥合并的有机相(Na_2SO_4),真空浓缩。通过二氧化硅快速色谱法纯化残余物,依次用DCM,20%EtOAc的DCM溶液,50%EtOAc的DCM溶液和EtOAc洗脱,得到期望的产物(307mg)。

[0521] LCMS(方法2):Rt=1.26min,m/z 672.3[M+H]$^+$

[0522] 步骤B

[0523]



[0524] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-

氨基-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺(中间体H1)

[0525] 将中间体H1-a(305mg,0.45mmol)在1.25M氯化氢的MeOH溶液(10mL)中的溶液搅拌1.25h,然后用12M盐酸水溶液(2.0mL)处理。将得到的混合物搅拌2.5h,然后再加入等分部分的12M盐酸水溶液(1.0mL)。将该混合物再搅拌3h,然后真空浓缩。将残余物溶于MeOH(30mL),通过**Isolute®** SCX-2柱过滤该溶液。用MeOH洗涤柱,然后用20％2M甲醇氨的DCM溶液洗脱。浓缩碱性级分,得到期望的产物(150mg)。

[0526] LCMS(方法2):Rt＝0.63min,m/z 488.0[M+H]$^+$

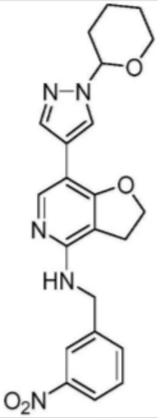
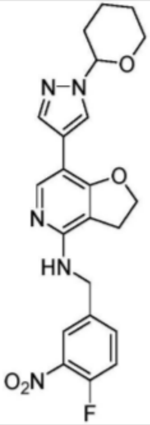
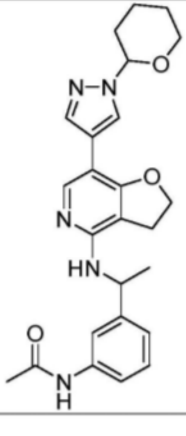
[0527] 中间体I1至I3

[0528] 使用与用于合成中间体C1类似的方法,通过分别用中间体F替代中间体B并且用表中指定的起始材料替代3-甲酰基苯甲酸甲酯来制备下列中间体。

[0529]

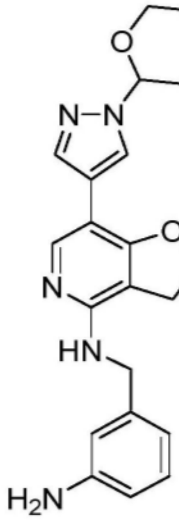
	结构	原料	LC-MS

[0530]

	结构	原料	LC-MS
I1		3-硝基苯甲醛	Rt = 0.44min，m/z 422.2 [M+H]$^+$ (方法 6)
I2		4-氟-3-硝基苯甲醛	Rt = 0.63min，m/z 439.7 [M+H]$^+$ (方法 6)
I3		N-(3-乙酰基苯基)乙酰胺	Rt = 0.56min，m/z 448.3 [M+H]$^+$ (方法 6)

[0531] 中间体J1

[0532]



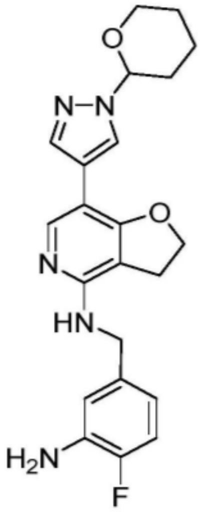
[0533] N-(3-氨基苄基)-7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体J1)

[0534] 将中间体I1(330mg,0.783mmol)溶于乙醇(7.5mL),然后加入Pd/C 5%湿(667mg,0.313mmol),将该反应体系在氢气罩内搅拌1h。过滤该反应混合物,真空蒸发溶剂,得到标题化合物(178mg),其不经进一步纯化用于下一步。

[0535] LCMS(方法6):Rt=0.44min,m/z 392.0[M+H]$^+$

[0536] 中间体J2

[0537]

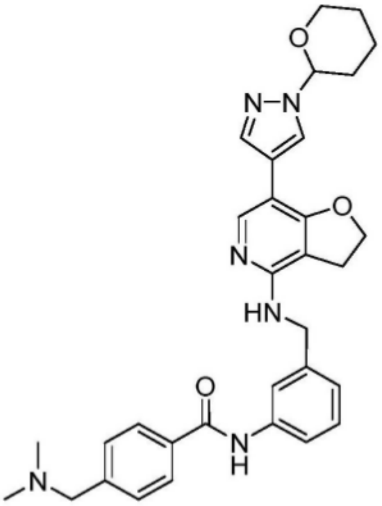


[0538] N-(3-氨基-4-氟苄基)-7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体J2)

[0539] 使用与由中间体I1合成中间体J1类似的方法,由中间体I2制备中间体J2。

[0540] LCMS(方法6):Rt=0.55min,m/z 410.0[M+H]$^+$

[0541] 中间体K1

[0542] 

[0543] 4-((二甲基氨基)甲基)-N-(3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)苯甲酰胺(中间体K1)

[0544] 将4-((二甲基氨基)甲基)苯甲酸盐酸盐(55.1mg,0.26mmol),DIEA(0.140mL,0.51mmol)和HATU(116mg,0.31mmol)溶于无水DCM(4mL),反应10min,然后加入中间体J1(50mg,0.128mmol),将该反应混合物在RT搅拌1h。用稀释DCM该反应混合物,用水(2x2.5mL)洗涤。真空干燥有机层,通过NH-二氧化硅快速色谱法纯化残余物,用0-10%MeOH的DCM溶液洗脱。合并适当的级分,真空蒸发,得到期望的化合物(16mg)。

[0545] LCMS(方法6):Rt=0.41min,m/z 553.0[M+H]$^+$

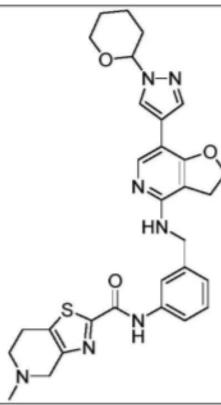
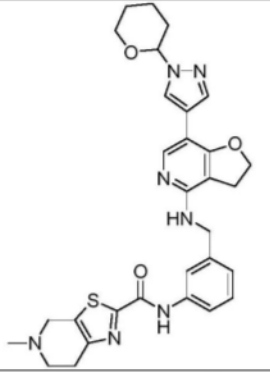
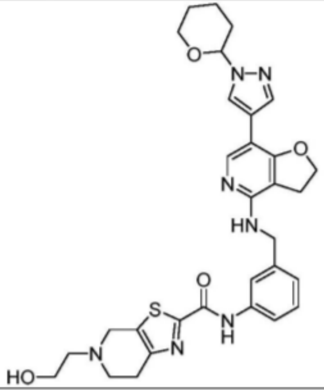
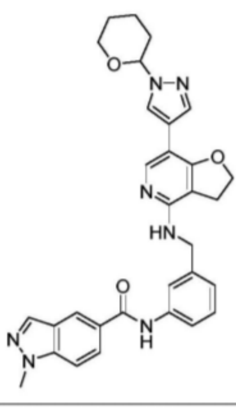
[0546] 中间体K2至K14

[0547] 使用与用于合成中间体K1类似的方法,通过用下表中指定的起始材料替代中间体J1和4-((二甲基氨基)甲基)苯甲酸盐酸盐来制备下列中间体。

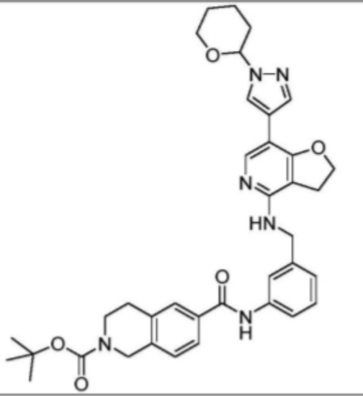
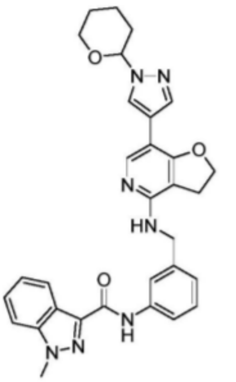
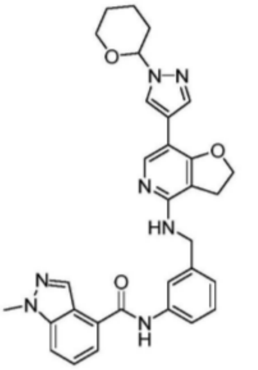
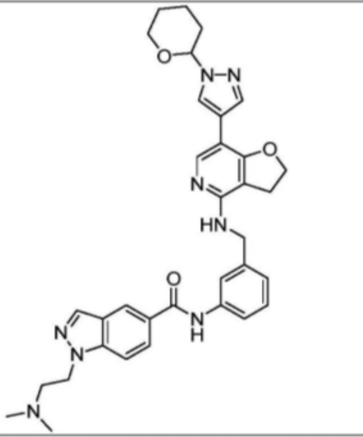
[0548]

	结构	原料	LC-MS

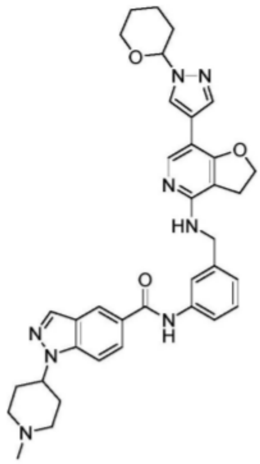
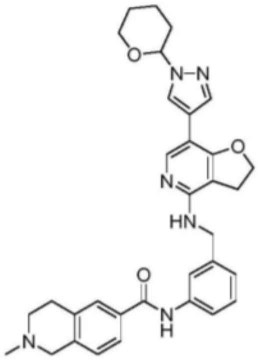
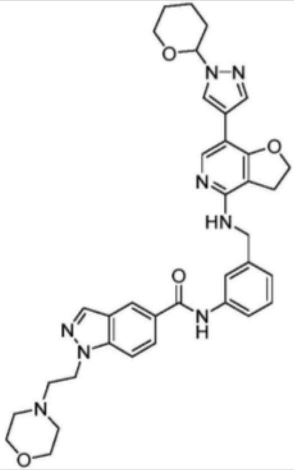
[0549]

K2		中间体 J1 和 5-甲基-4,5,6,7-四氢噻唑并[4,5-c]吡啶-2-甲酸	Rt = 0.76min，m/z 572.3 [M+H]$^+$ (方法 15)
K3		中间体 J1 和 5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酸	Rt = 0.72min，m/z 572.3 [M+H]$^+$ (方法 15)
K4		中间体 J1 和中间体 A4	Rt = 0.67min，m/z 602.1 [M+H]$^+$ (方法 15)
K5		中间体 J1 和 1-甲基-1H-吲唑-5-甲酸	Rt = 1.09min，m/z 550.1 [M+H]$^+$ (方法 15)

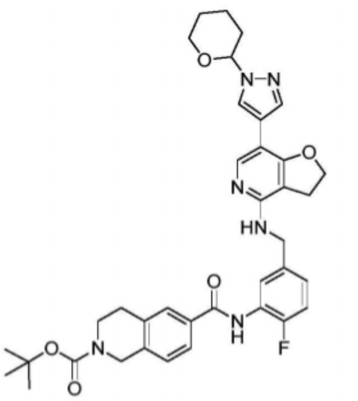
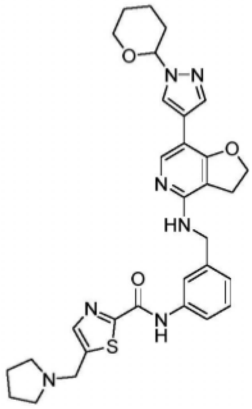
[0550]

K6		中间体 J1 和 2-(叔丁氧基羰基)-1,2,3,4-四氢异喹啉-6-甲酸	Rt = 0.87min，m/z 651.8 [M+H]$^+$ (方法6)
K7		中间体 J1 和 1-甲基-1H-吲唑-3-甲酸	Rt = 0.74min，m/z 550.1 [M+H]$^+$ (方法6)
K8		中间体 J1 和 1-甲基-1H-吲唑-4-甲酸	Rt = 1.09min，m/z 550.1 [M+H]$^+$ (方法6)
K9		中间体 J1 和中间体 A5	Rt = 0.43min，m/z 606.8 [M+H]$^+$ (方法6)

[0551]

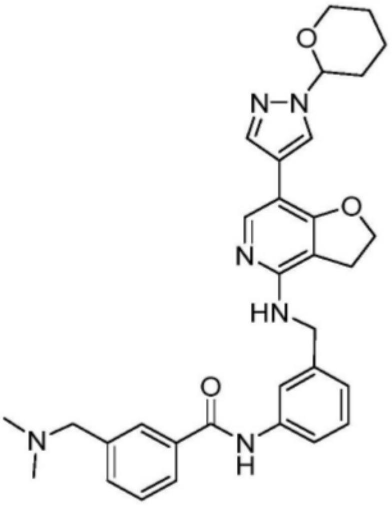
K10		中间体 J1 和中间体 A6	Rt = 0.44min，m/z 633.2 $[M+H]^+$ (方法 6)
K11		中间体 J1 和 2-甲基-1,2,3,4-四氢异喹啉-6-甲酸	Rt = 0.45min，m/z 564.9 $[M+H]^+$ (方法 6)
K12		中间体 J1 和中间体 A7	Rt = 0.52min，m/z 648.9 $[M+H]^+$ (方法 14)

[0552]

K13		**中间体 J2 和 2-(叔丁氧基羰基)-1,2,3,4-四氢异喹啉-6-甲酸**	**Rt = 0.52min，m/z 668.9[M+H]$^+$ (方法6)**
K14		**中间体 J1 和中间体 A8**	**Rt = 0.46min，m/z 585.9 [M+H]$^+$ (方法6)**

[0553] 中间体K15

[0554]



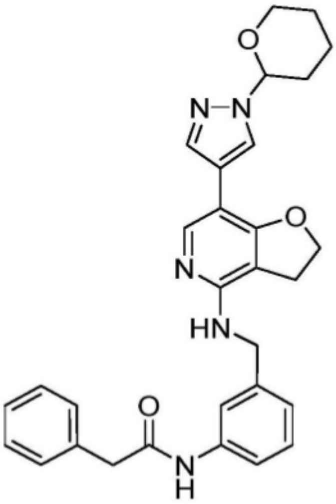
[0555] 3-((二甲基氨基)甲基)-N-(3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)苯甲酰胺(中间体K15)

[0556] 将1-(四氢-2H-吡喃-2-基)-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑(48.8mg,0.176mmol),中间体E6(65mg,0.135mmol)和碳酸铯(132mg,0.405mmol)混入DMF(2mL)和水(1mL),用氩气吹扫10min。加入四(三苯基膦)钯(0)(0.018mL,0.014mmol),将该反应体系加热至70℃2h。浓缩该反应混合物,通过C18-二氧化硅快速色谱法纯化粗产物,用0-30%A中的B(A:水/乙腈95:5+0.1%HCOOH,B:乙腈/水95:5+0.1%HCOOH)洗脱。汇集合适的级分,蒸发至干,得到标题化合物(37.5mg)。

[0557] LCMS(方法6):Rt＝0.41min,m/z 553.3$[M+H]^+$

[0558] 中间体K16

[0559]



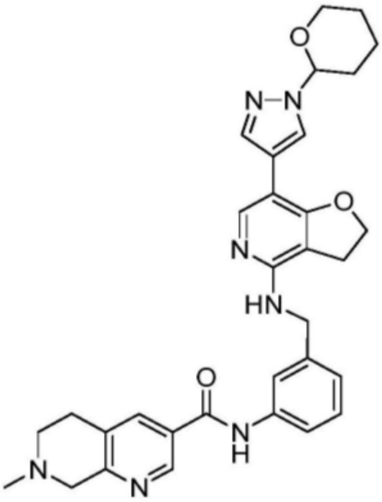
[0560] 2-苯基-N-(3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)乙酰胺(中间体K16)

[0561] 使用与用于由中间体E6合成中间体K15类似的方法,由中间体E7制备中间体K16。

[0562] LCMS(方法11):Rt＝1.2min,m/z 510.1$[M+H]^+$

[0563] 中间体K17

[0564]



[0565] 7-甲基-N-(3-(((7-(1-(四氢-2H-吡喃-2-基)-1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5,6,7,8-四氢-1,7-萘啶-3-甲酰胺(中间体K17)

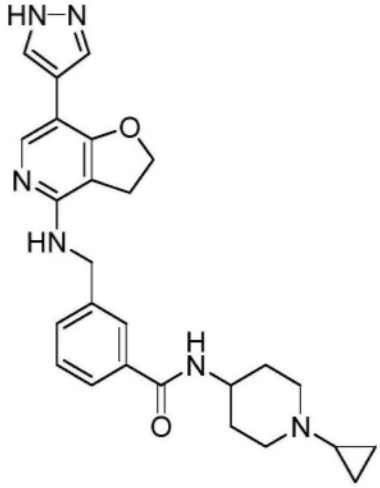
[0566] 将中间体J1(102mg,0.261mmol),双(三甲基铝)-1,4-二氮杂双环[2.2.2]辛烷加合物(134mg,0.523mmol),7-甲基-5,6,7,8-四氢-1,7-萘啶-3-甲酸乙酯(115mg,0.523mmol)和THF(3mL)加入到密封的容器中,在110℃在微波照射中加热1h。通过添加水使反应淬灭,然后用DCM稀释。分离有机相,真空蒸发。通过C18-二氧化硅快速色谱法纯化粗物质,用0-60％A中的B(A:水/乙腈95:5+0.1％HCOOH,B:乙腈/水95:5+0.1％HCOOH)洗脱,得到标题化合物(11mg)。

[0567] LCMS(方法6):Rt＝0.39min,m/z 565.9$[M+H]^+$

[0568] 实施例的制备

[0569] 实施例1

[0570]



[0571] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-环丙基哌啶-4-基)苯甲酰胺(实施例1)

[0572] 向中间体G(50mg,0.14mmol),1-环丙基哌啶-4-胺(21mg,0.149mmol),DIPEA(0.078mL,0.446mmol)和TBTU(62mg,0.193mmol)在DMF(1mL)中的混合物在RT搅拌3h。用MeOH稀释该反应混合物,上**Isolute®** SCX-2柱,用MeOH,然后用2M甲醇氨洗脱。真空浓缩相关级分,通过二氧化硅色谱法纯化粗物质,用0-10%2M甲醇氨的DCM溶液洗脱,得到标题化合物(16mg)。

[0573] LCMS(方法5)Rt=1.75min,m/z 459.4$[M+H]^+$

[0574] ^{1}H NMR(400MHz,DMSO-d6)δ12.8(s,1H),8.18(d,J=7.7Hz,1H),8.07(s,1H),7.86(s,2H),7.79(s,1H),7.65(d,7.8Hz,1H),7.46(d,J=7.8Hz,1H),7.35(t,J=7.8Hz,1H),6.71(t,J=6.7Hz,1H),4.68(t,J=8.8Hz,2H),4.60(d,J=6.2Hz,2H),3.81-3.68(m,1H),3.04(t,J=8.8Hz,2H),2.96-2.88(m,2H),2.26-2.16(m,2H),1.78-1.69(m,2H),1.62-1.55(m,1H),1.53-1.41(m,2H),0.43-0.37(m,2H),0.30-0.25(m,2H)。

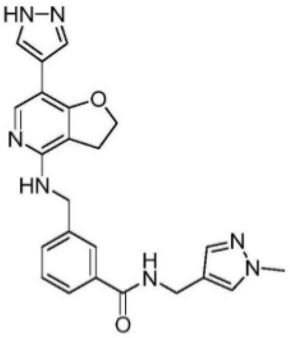
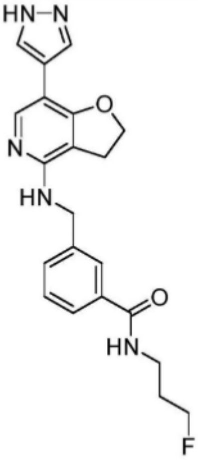
[0575] 实施例2至31

[0576] 由中间体G和按照与用于实施例1的'类似'或'相似'的方式中给出的胺制备下列化合物。这类方法可以涉及少量改变,例如反应温度,试剂/溶剂量,反应时间,后处理条件或色谱纯化条件(例如HPLC-MDAP或快速色谱法)。在一些情况中,如果改变牵涉反应溶剂(例如DCM-DMF混合物替代DMF)或偶联剂(例如HATU替代TBTU),则将这类改变报告为注意。

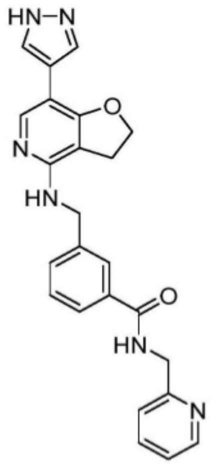
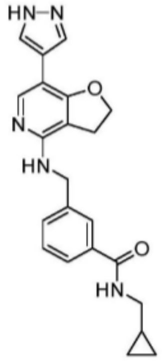
[0577]

实施例	结构	胺	^{1}H NMR	LC-MS

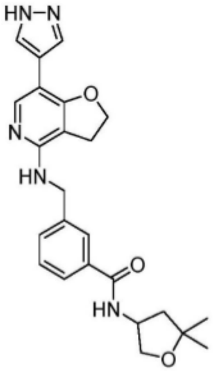
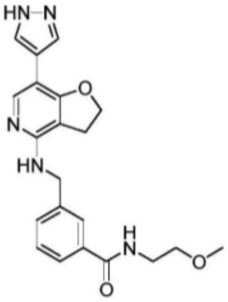
[0578]

实施例	结构	胺	^{1}H NMR	LC-MS
2	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-吡唑-3-基)甲基)苯甲酰胺	(1-甲基-1H-吡唑-4-基)甲胺	(400 MHz，DMSO-d6) δ 12.58 (s，1H)，8.50-8.39 (m，1H)，8.08 (s，1H)，7.88 (s，1H)，7.83 (s，2H)，7.71 (d，J = 7.7 Hz，1H)，7.53-7.50 (m，2H)，7.39-7.35 (m，1H)，6.32 (t，J = 6.0 Hz，1H)，6.15 (d，J = 2.1 Hz，1H)，4.70 (t，J = 8.8 Hz，2H)，4.66 (d，J = 6.2 Hz，2H)，4.44 (d，J = 5.8 Hz，2H)，3.08 (t，J = 8.9 Hz，2H)，3.04 (s，3H)。	Rt = 3.32min，m/z 430.0 [M+H]$^+$ (方法 4)
3	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-氟丙基)苯甲酰胺	3-氟丙-1-胺	(400 MHz，DMSO-d6) δ 12.58 (s，1H)，8.24-8.16 (m，1H)，8.08 (s，1H)，7.91-7.77 (m，3H)，7.68 (d，J = 7.7 Hz，1H)，7.51 (d，J = 7.3 Hz，1H)，7.40-7.35 (m，1H)，6.32 (t，J = 6.0 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.66 (d，J = 6.4 Hz，2H)，4.59 (t，J = 5.9 Hz，1H)，4.47 (t，J = 6.0 Hz，1H)，3.42-3.37 (m，2H)，3.08 (t，J = 8.7 Hz，2H)，1.96 (d，J = 51.3 Hz，2H)。	Rt = 2.35min，m/z 396.0 [M+H]$^+$ (方法 3)

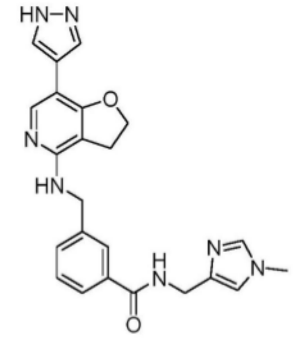
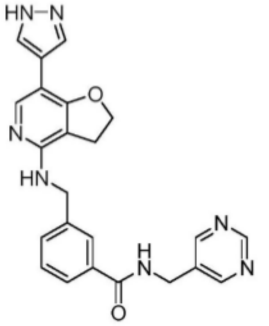
[0579]

实施例	结构	胺	^{1}H NMR	LC-MS
4	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-2-基甲基)苯甲酰胺	哌啶-2-基甲胺	(400 MHz，DMSO-d6) δ 12.74 (br s，1H)，9.02 (br t，J = 5.8 Hz，1H)，8.47 (br d，J = 4.6 Hz，1H)，8.04 (s，1H)，7.89 - 7.87 (m，1H)，7.86 (s，1H)，7.77 -7.74 (m，1H)，7.71 (br s，2H)，7.47 (br d，J = 7.7 Hz，1H)，7.39 - 7.34 (m，1H)，7.27 (d，J = 7.7 Hz，1H)，7.24 - 7.20 (m，1H)，6.66 (br t，J = 6.0 Hz，1H)，4.65 (t,J = 8.9 Hz，2H)，4.59 (br d，J = 6.1 Hz，2H)，4.52 (d，J = 5.9 Hz，2H)，4.46 - 4.43 (m，1H)，3.02 (br t，J = 8.9 Hz，2H)。	Rt = 0.44min，m/z 427.2 [M+H]$^{+}$ (方法 6)
5	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(环丙基甲基)苯甲酰胺	环丙基甲胺	(400 MHz，DMSO-d6) δ 12.58 (s，1H)，8.30 (t，J = 5.6 Hz，1H)，7.87 (s，1H)，7.65 (s，2H)，7.63-7.60 (m，1H)，7.49-7.44 (m，1H)，7.27-7.24 (m，1H)，7.18-7.13 (m，1H)，6.48 (t，J = 6.1 Hz，1H)，4.48 (t，J = 9.0 Hz，2H)，4.40 (d，J = 5.9 Hz，2H)，3.16-3.10 (m，2H)，2.91 (t，J = 6.2 Hz，2H)，2.84 (t，J = 8.9 Hz，2H)，0.85-0.77 (m，1H)，0.23-0.18 (m，2H)。	Rt = 3.75min，m/z 390.0 [M+H]$^{+}$ (方法 4)

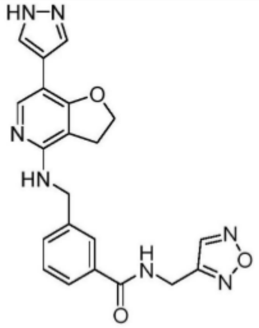
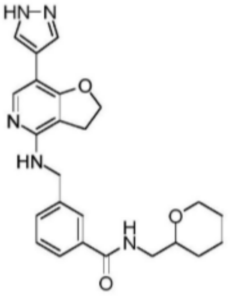
[0580]

实施例	结构	胺	^{1}H NMR	LC-MS
6	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5,5-二甲基四氢呋喃-3-基)苯甲酰胺	5,5-二甲基四氢呋喃-3-胺	(400 MHz，DMSO-d6) δ 12.81 - 12.80 (m，1H)，8.47 (d，J = 6.5 Hz，1H)，8.08 (s，1H)，7.84 - 7.81 (m，3H)，7.71 - 7.67 (m，1H)，7.50 - 7.47 (m，1H)，7.38 (t，J = 7.7 Hz，1H)，6.71 (t，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，4.54 (d，J = 8.0 Hz，1H)，4.00 (dd，J = 7.0，8.8 Hz，1H)，3.61 (dd，J = 6.4，8.8 Hz，1H)，3.10 - 3.03 (m，2H)，2.09 (dd，J = 8.3，12.5 Hz，1H)，1.82 (dd，J = 7.3，12.5 Hz，1H)，1.29 (s，3H)，1.19 (s，3H)。	Rt = 2.46min，m/z 434.2 [M+H]$^+$ (方法 3)
7	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-甲氧基乙基)苯甲酰胺	2-甲氧基乙-1-胺	(400 MHz，DMSO-d6) δ 12.6 (bs, 1H), 8.48 (m，1H)，8.17 (s，1H)，8.09 (s，1H)，7.87 (s，2H)，7.84 (s，1H)，7.70-7.67 (m，1H)，7.50-7.47 (m，1H)，7.38 (t，J = 7.7 Hz，1H)，6.73-6.68 (m，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，3.47 - 3.41 (m，4H)，3.28 (s，3H)，3.07 (t，J = 7.6 Hz，2H)。	Rt = 2.17min，m/z 394.0 [M+H]$^+$ (方法 3)

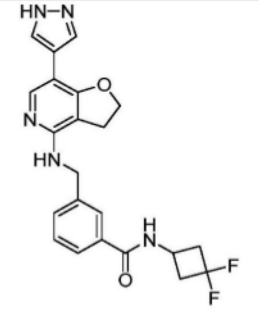
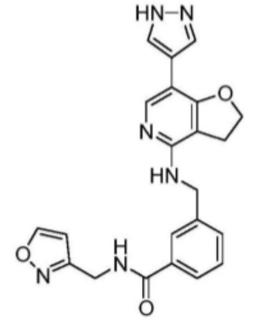
[0581]

实施例	结构	胺	^{1}H NMR	LC-MS
8	 **3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((1-甲基-1H-咪唑-4-基)甲基)苯甲酰胺**	**(1-甲基-1H-咪唑-4-基)甲胺**	**(400 MHz，DMSO-d6) δ12.80 (d，J = 0.9 Hz，1H)，8.74 (t，J = 5.6 Hz，1H)，8.09 (s，1H)，7.86 (s，3H)，7.71 (d，J = 7.8 Hz，1H)，7.47 (d，J = 5.9 Hz，2H)，7.37 (t，J = 7.7 Hz，1H)，6.93 (s，1H)，6.70 (dd，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，4.32 (d，J = 5.5 Hz，2H)，3.60 (s，3H)，3.06 (t，J = 8.9 Hz，2H)。**	**Rt = 1.64min，m/z 430.0 [M+H]$^+$ (方法 3)**
9	 **3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-5-基甲基)苯甲酰胺**	**嘧啶-5-基甲胺**	**(400 MHz，DMSO-d6) δ 12.80 (s，1H)，9.12 - 9.09 (m，2H)，8.78 (s，2H)，8.09 (s，1H)，7.88 - 7.85 (m，3H)，7.72 (ddd，J = 1.4，1.4，7.7 Hz，1H)，7.53 - 7.49 (m，1H)，7.40 (t，J = 7.7 Hz，1H)，6.71 (t，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，4.50 (d，J = 5.8 Hz，2H)，3.06 (t，J = 8.8 Hz，2H)。**	**Rt = 2.06min，m/z 428.0 [M+H]$^+$ (方法 3)**

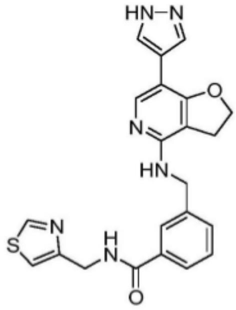
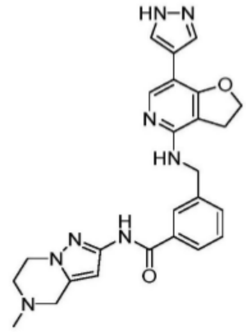
[0582]

实施例	结构	胺	^{1}H NMR	LC-MS
10	 N-((1,2,5-噁二唑-3-基)甲基)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺	(1,2,5-噁二唑-3-基)甲胺	(400 MHz，DMSO-d6) δ 13.28 (s，1H)，12.80-12.75 (m，1H)，9.06 (t，J = 5.8 Hz，1H)，8.09 (s，1H)，7.87 (s，3H)，7.74-7.70 (m，1H)，7.55-7.51 (m，1H)，7.42 (t，J = 7.7 Hz，1H)，6.73 (t，J = 6.0 Hz，1H)，4.74-4.61 (m，4H)，4.28 (d，J = 5.8 Hz，2H)，3.10-3.03 (m，2H)。	Rt = 2.3min，m/z 418.2 [M+H]$^+$ (方法 3)
11	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺	(四氢-2H-吡喃-2-基)甲胺	(400 MHz，DMSO-d6) δ 12.80 (s，1H)，8.44 (t，J = 5.8 Hz，1H)，8.09 (s，1H)，7.85-7.83 (m，2H)，7.82-7.67 (m，2H)，7.50-7.46 (m，1H)，7.37 (t，J = 7.7 Hz，1H)，6.71 (t，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，3.87 (dd，J = 2.3，10.8 Hz，1H)，3.43 (m，2H)，3.26 (m，2H)，3.06 (t，J = 8.8 Hz，2H)，1.80-1.75 (m，1H)，1.61 (d，J = 12.5 Hz，1H)，1.49-1.41 (m，3H)，1.22-1.12 (m，1H)。	Rt = 2.61min，m/z 434.2 [M+H]$^+$ (方法 3)

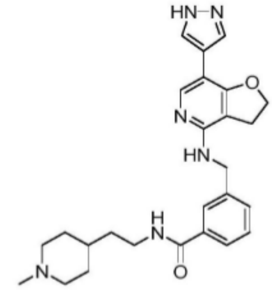
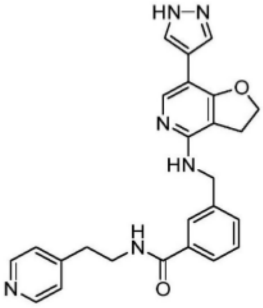
[0583]

实施例	结构	胺	^{1}H NMR	LC-MS
12	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3,3-二氟环丁基)苯甲酰胺	3,3-二氟环丁-1-胺	(400 MHz，DMSO-d6) δ 12.80-12.78 (m，1H)，8.81 (d，J = 6.5 Hz，1H)，8.09-8.08 (m，2H)，7.86-7.82 (m，2H)，7.70 (d，J = 7.7 Hz，1H)，7.53-7.49 (m，1H)，7.41 (t，J = 7.7 Hz，1H)，6.72 (t，J = 6.1 Hz，1H)，4.74-4.61 (m，4H)，4.32-4.24 (m，1H)，3.10 (m，2H)，2.83-2.68 (m，2H)，2.68 (m，2H)。	Rt = 2.68min，m/z 426.2 [M+H]$^+$ (方法 3)
13	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(异噁唑-3-基甲基)苯甲酰胺	1,2-噁唑-3-基甲胺	(400 MHz，DMSO-d6) δ 13.1 (bs，1H)，9.07 (t，J = 5.6Hz，1H)，8.34 (d，J = 1.6Hz，1H)，8.16 (s，1H)，8.09 (s，1H)，7.87 (br s，3H)，7.74-7.70 (m，1H)，7.53-7.49 (m，1H)，7.40 (t，J = 7.7Hz，1H)，6.72 (t，J = 6.2Hz，1H)，6.50 (d，J = 8.2Hz，1H)，4.70 (t，J = 8.6Hz，2H)，4.63 (d，J = 6.1Hz，2H)，4.55 (d，J = 6.1Hz，2H)，3.07 (t，J = 8.6Hz，2H)。	Rt = 2.28min，m/z 417.0 [M+H]$^+$ (方法 3)

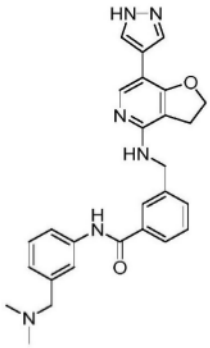
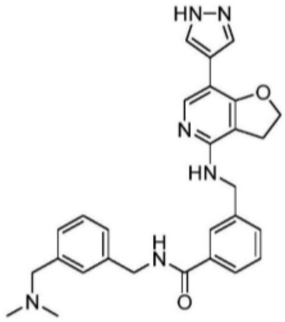
[0584]

实施例	结构	胺	^{1}H NMR	LC-MS
14	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(噻唑-4-基甲基)苯甲酰胺	噻唑-4-基甲胺	(400 MHz，DMSO-d6) δ 12.8 (s，1H)，9.07 (d，J = 2.0Hz，1H)，9.04 (t，J = 5.5Hz，1H)，8.09 (s，1H)，7.90-7.83 (m，3H)，7.77-7.73 (m，1H)，7.52-7.48 (m，1H)，7.45-7.43 (m，1H)，7.40 (t，J = 7.6Hz，1H)，6.71 (t，J = 5.9Hz，1H)，4.70 (t，J = 8.9Hz，2H)，4.62 (t，J = 5.7Hz，4H)，3.06 (t，J = 8.9Hz，2H)。	Rt = 2.29min，m/z 433.0 [M+H]$^+$ (方法 3)
15	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲基-4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-基)苯甲酰胺	5-甲基-4,5,6,7-四氢吡唑并[1,5-a]吡嗪-2-胺	(400 MHz，DMSO-d6) δ 12.81 (s，1H)，10.73 (s，1H)，8.10 (s，1H)，7.96 (s，1H)，7.87 (s，2H)，7.84 (d，J = 8.1 Hz，1H)，7.52 (d，J = 7.8 Hz，1H)，7.43 - 7.38 (m，1H)，6.71 (t，J = 6.1 Hz，1H)，6.42 (s，1H)，4.71 (t，J = 8.8 Hz，2H)，4.65 (d，J = 5.9 Hz，2H)，4.01 (t，J = 5.5 Hz，2H)，3.57 (s，2H)，3.07 (t，J = 8.8 Hz，2H)，2.85 (t，J = 5.6 Hz，2H)，2.40 (s，3H)。	Rt = 2.17min，m/z 471.6 [M+H]$^+$ (方法 13)

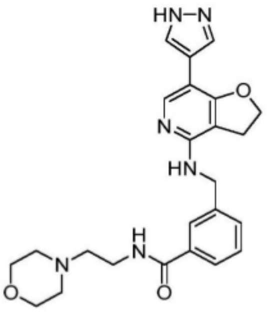
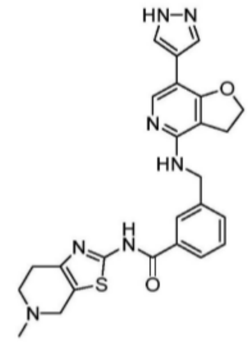
[0585]

实施例	结构	胺	^{1}H NMR	LC-MS
16	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-甲基哌啶-4-基)乙基)苯甲酰胺	1-甲基哌啶-4-基)乙胺	(400MHz，DMSO-d6) δ 12.75 (br s，1H)，8.34 (t，J = 5.7 Hz，1H)，8.05 (s，1H)，7.89 (br s，1H)，7.78 (s，2H)，7.63 (dt，J = 7.7，1.5 Hz，1H)，7.44 (dt，J = 7.7，1.5 Hz，1H)，7.34 (t，J = 7.7 Hz，1H)，6.65 (t，J = 6.0 Hz，1H)，4.67 (t，J = 8.9 Hz，2H)，4.59 (d，J = 5.7 Hz，2H)，3.27 - 3.24 (m，2H)，3.03 (t，J = 8.9 Hz，2H)，2.71 - 2.63 (m，2H)，2.09 (s，3H)，1.76 (td，J = 11.5， 2.0 Hz，，2H)，1.62 (dd，J = 11.8，2.0 Hz，2H)，1.42 (q，J = 8.0 Hz，2H)，1.18 - 1.04 (m，3H)。	Rt = 0.33min，m/z 461.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
17	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-4-基)乙基)苯甲酰胺	2-(吡啶-4-基)乙胺	(400MHz，DMSO-d6) δ 12.74 (br s，1H)，8.48 (t，J = 5.5 Hz，1H)，8.42 (d，J = 5.9 Hz，2H)，8.04 (s，1H)，7.88 (br s，1H)，7.77 (br s，1H)，7.75 (s，1H)，7.58 (dt，J = 7.7，1.0 Hz，1H)，7.43 (dt，J = 7.7，1.0 Hz，1H)，7.32 (t，J = 7.7 Hz，1H)，7.22 (d，J = 5.9 Hz，2H)，6.66 (t，J = 5.8 Hz，1H)，4.66 (t，J = 8.9 Hz，2H)，4.57 (d，J = 6.1 Hz，2H)，3.48 (q，J = 5.8 Hz，2H)，3.02 (t，J = 8.9 Hz，2H)，2.83 (t，J = 7.1 Hz，2H)。	Rt = 0.72min，m/z 441.2 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

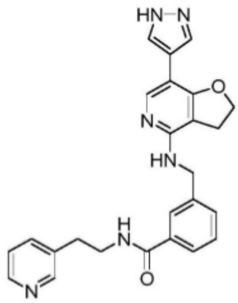
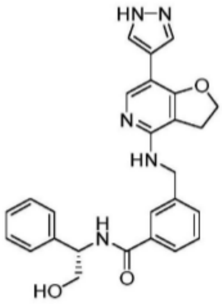
[0586]

实施例	结构	胺	^{1}H NMR	LC-MS
18	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二甲基氨基)甲基)苯基)苯甲酰胺	3-((二甲基氨基)甲基)苯胺	(400MHz，DMSO-d6) δ12.74 (br s，1H)，10.16 (s，1H)，8.05 (s，1H)，7.89 (s，2H)，7.78 (s，1H)，7.76 (s，1H)，7.71 (br s，1H)，7.65 (d，J = 8.1 Hz，1H)，7.50 (d，J = 7.7 Hz，1H)，7.40 (t，J = 7.7 Hz，1H)，7.25 (t，J = 7.8 Hz，1H)，6.98 (d，J = 7.2 Hz，1H)，6.68 (t，J = 6.0 Hz，1H)，4.66 (t，J = 8.9 Hz，2H)，4.62 (d，J = 5.9 Hz，2H)，3.34 - 3.33 (m，2H)，3.03 (t，J = 8.9 Hz，2H)，2.15 (s，6H)。	Rt = 0.39min，m/z 469.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
19	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(3-((二甲基氨基)甲基)苄基)苯甲酰胺	1-(3-(氨基甲基)苯基)-N,N-二甲基甲胺	(400MHz，DMSO-d6) δ12.74 (br s，1H)，8.95 (t，J = 5.9 Hz，1H)，8.04 (s，1H)，7.84 (s，1H)，7.69 (dt，J = 7.7，1.0 Hz，1H)，7.45 (dt，J = 7.7，1.0 Hz，1H)，7.35 (t，J = 7.7 Hz，1H)，7.27 - 7.18 (m，3H)，7.17 - 7.12 (m，1H)，7.12 - 7.09 (m，1H)，6.65 (t，J = 5.9 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.58 (d，J = 5.9 Hz，2H)，4.43 (d，J = 5.9 Hz，2H)，3.31 (s，2H)，3.01 (t，J = 8.9 Hz，2H)，2.08 (s，6H)。	Rt = 0.38min，m/z 483.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

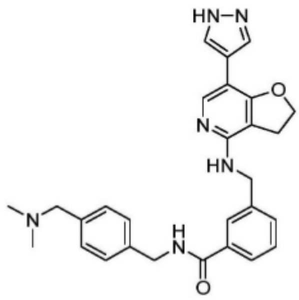
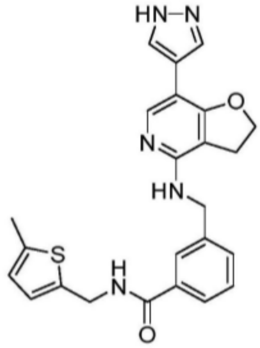
[0587]

实施例	结构	胺	^{1}H NMR	LC-MS
20	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-吗啉代乙基)苯甲酰胺	2-吗啉代乙胺	(400MHz，DMSO-d6) δ12.74 (br s，1H)，8.29 (t，J = 5.6 Hz，1H)，8.04 (s，1H)，7.88 (s，1H)，7.77 (br s，2H)，7.61 (dt，J = 7.7，1.0 Hz，1H)，7.43 (dt，J = 7.9 Hz，1H)，7.33 (t，J = 7.7 Hz，1H)，6.65 (t，J = 6.0 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.57 (d，J = 6.0 Hz，2H)，3.56 - 3.49 (m，4H)，3.33 (q，J = 6.0 Hz，2H)，3.01 (t，J = 8.9 Hz，2H)，2.42 (t，J = 6.0 Hz，2H)，2.39 - 2.34 (m，4H)。	Rt = 0.29min，m/z 449.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
21	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)苯甲酰胺	5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-胺	(400MHz，DMSO-d6) δ 12.74 (s，1H)，12.41 (s，1H)，8.04 (s，1H)，8.00 (s，1H)，7.93 - 7.85 (m，2H)，7.76 (s，1H)，7.53 (d，J = 7.7 Hz，1H)，7.41 (t，J = 7.7 Hz，1H)，6.67 (t，J = 6.1 Hz，1H)，4.66 (t，J = 8.8 Hz，2H)，4.61 (d，J = 5.9 Hz，2H)，3.48 (s，2H)，3.03 (t，J = 8.8 Hz，2H)，2.72 - 2.60 (m，4H)，2.35 (s，3H)。	Rt = 0.41min，m/z 488.1 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

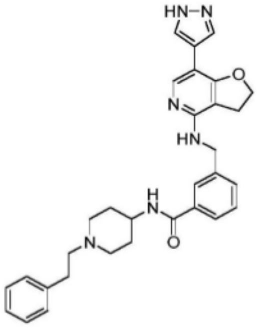
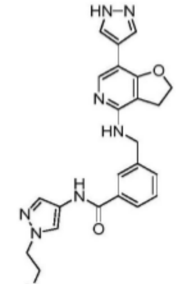
[0588]

实施例	结构	胺	^{1}H NMR	LC-MS
22	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(吡啶-3-基)乙基)苯甲酰胺	2-(吡啶-3-基)乙胺	(400MHz，DMSO-d6) δ12.74 (br s，1H)，8.48 (t，J = 5.5 Hz，1H)，8.41 (d，J = 1.8 Hz，1H)，8.37 (dd，J = 4.8，1.5 Hz，1H)，8.04 (s，1H)，7.88 (br s，1H)，7.76 (br s，1H)，7.75 (s，1H)，7.64 - 7.56 (m，2H)，7.43 (d，J = 7.7 Hz，1H)，7.32 (t，J = 7.7 Hz，1H)，7.26 (dd，J = 7.6，4.5 Hz，1H)，6.64 (t，J = 6.1 Hz，1H)，4.66 (t，J = 8.9 Hz，2H)，4.57 (d，J = 5.9 Hz，2H)，3.47 (q，J = 6.0 Hz，2H)，3.01 (t，J = 8.9 Hz，2H)，2.83 (t，J = 7.0 Hz，2H)。	Rt = 0.39min，m/z 441.2 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
23	 (S)-3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-羟基-1-苯基乙基)苯甲酰胺	(S)-2-氨基-2-苯乙醇	(400MHz，DMSO-d6) δ 12.72 (br s，1H)，8.59 (d，J = 8.1 Hz，1H)，8.04 (s，1H)，7.90 - 7.74 (m，3H)，7.71 (d，J = 7.7 Hz，1H)，7.45 (d，J = 7.7 Hz，1H)，7.39 - 7.31 (m，3H)，7.30 - 7.24 (m，2H)，7.22 - 7.16 (m，1H)，6.65 (t，J = 6.1 Hz，1H)，5.06 - 4.99 (m，1H)，4.87 (t，J = 5.9 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.59 (d，J = 6.1 Hz，2H)，3.71 - 3.58 (m，2H)，3.01 (t，J = 8.8 Hz，2H)。	Rt = 0.58min，m/z 456.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

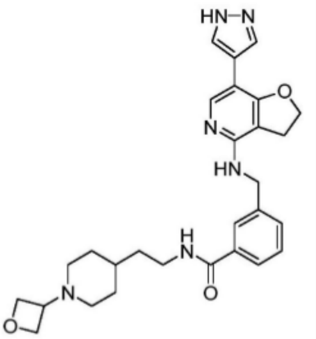
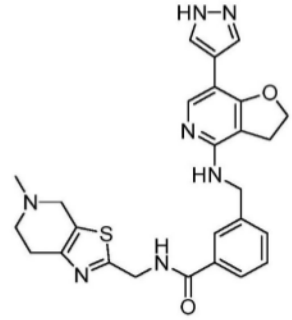
[0589]

实施例	结构	胺	^{1}H NMR	LC-MS
24	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(4-((二甲基氨基)甲基)苄基)苯甲酰胺	1-(4-(氨基甲基)苯基)-N,N-二甲基甲胺盐酸盐	(400MHz，DMSO-d6) δ 12.74 (br s，1H)，8.93 (t，J = 5.8 Hz，1H)，8.04 (s，1H)，7.87 (s，1H)，7.84 (s，1H)，7.75 (s，1H)，7.69 (d，J = 7.7 Hz，1H)，7.45 (d，J = 7.5 Hz，1H)，7.34 (t，J = 7.7 Hz，1H)，7.26 - 7.12 (m，4H)，6.64 (t，J = 5.9 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.58 (d，J = 5.9 Hz，2H)，4.42 (d，J = 5.9 Hz，2H)，3.30 (s，2H)，3.01 (t，J = 8.9 Hz，2H)，2.08 (s，6H)。	Rt = 0.31min，m/z 483.2 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
25	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基噻吩-2-基)甲基)苯甲酰胺	(5-甲基噻吩-2-基)甲胺	(400MHz，DMSO-d6) δ 12.74 (s，1H)，8.98 (t，J = 5.9 Hz，1H)，8.04 (s，1H)，7.88 (s，1H)，7.81 (s，1H)，7.76 (s，1H)，7.65 (d，J = 7.7 Hz，1H)，7.44 (d，J = 7.7 Hz，1H)，7.33 (t，J = 7.7 Hz，1H)，6.73 (d，J = 3.5 Hz，1H)，6.65 (t，J = 6.0 Hz，1H)，6.57 (dd，J = 3.5，1.1 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.57 (d，J = 6.0 Hz，2H)，4.48 (d，J = 5.9 Hz，2H)，3.01 (t，J = 8.9 Hz，2H)，2.33 (s，3H)。	Rt = 0.58min，m/z 446.3 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

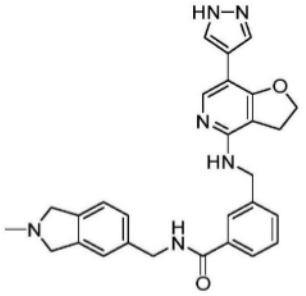
[0590]

实施例	结构	胺	^{1}H NMR	LC-MS
26	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苯乙基哌啶-4-基)苯甲酰胺	1-苯乙基哌啶-4-胺	(400MHz，DMSO-d6) δ 12.74 (s，1H)，8.15 (d，J = 7.9 Hz，1H)，8.04 (s，1H)，7.88 (br s，1H)，7.77 (s，1H)，7.76 (br s，1H)，7.63 (d，J = 7.5 Hz，1H)，7.43 (d，J = 7.7 Hz，1H)，7.32 (t，J = 7.5 Hz，1H)，7.26 - 7.11 (m，5H)，6.64 (t，J = 6.0 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.57 (d，J = 6.0 Hz，2H)，3.77 - 3.65 (m，1H)，3.01 (t，J = 8.9 Hz，2H)，2.91 (d，J = 11.8 Hz，2H)，2.72 - 2.66 (m，2H)，2.03 - 1.95 (m，2H)，1.77 - 1.70 (m，2H)，1.53 (dq，J = 11.8，3.3 Hz，2H)。	Rt = 0.46min，m/z 523.4 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU
27	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)苯甲酰胺	1-(2-(二甲基氨基)乙基)-1H-吡唑-4-胺盐酸盐	(400MHz，DMSO-d6) δ 12.74 (br s，1H)，10.33 (s，1H)，8.05 (s，1H)，8.02 (s，1H)，7.89 (br s，1H)，7.87 (s，1H)，7.76 (br s，1H)，7.74 (d，J = 7.7 Hz，1H)，7.54 (s，1H)，7.48 (d，J = 7.7 Hz，1H)，7.39 (t，J = 7.7 Hz，1H)，6.67 (t，J = 6.0 Hz，1H)，4.66 (t，J = 8.9 Hz，2H)，4.61 (d，J = 6.0 Hz，2H)，4.13 (t，J = 6.5 Hz，2H)，3.02 (t，J = 8.9 Hz，2H)，2.58 (t，J = 6.5 Hz，2H)，2.13 (s，6H)。	Rt = 0.31min，m/z 473.4 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂 HATU

[0591]

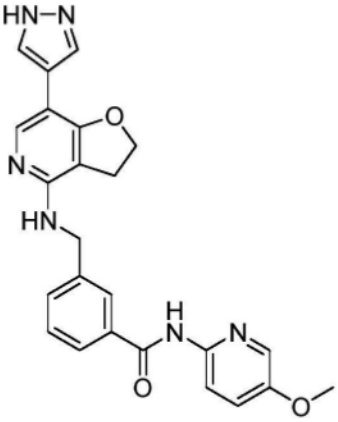
实施例	结构	胺	^{1}H NMR	LC-MS
28	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(2-(1-(氧杂环丁烷-3-基)哌啶-4-基)乙基)苯甲酰胺	中间体 A1	(400MHz，DMSO-d6) δ 12.74 (br s，1H)，8.32 (t，J = 5.5 Hz，1H)，8.03 (s，1H)，7.87 (br s，1H)，7.76 (br s，2H)，7.61 (d，J = 7.8 Hz，1H)，7.42 (d，J = 7.8 Hz，1H)，7.32 (t，J = 7.8 Hz，1H)，6.63 (t，J = 6.1 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.57 (d，J = 5.9 Hz，2H)，4.46 (t，J = 6.1 Hz，2H)，4.35 (t，J = 6.1 Hz，2H)，3.26 - 3.20 (m，3H)，3.01 (t，J = 8.9 Hz，2H)，2.63 - 2.57 (m，2H)，1.69 - 1.59 (m，4H)，1.42 (q，J = 6.9 Hz，2H)，1.29 - 1.21 (m，1H)，1.16 - 1.07 (m，2H)。	Rt = 0.29min，m/z 503.4 [M+H]$^+$ (方法 12) 注意: 反应溶剂 DCM-DMF 混合物，偶联剂 HATU
29	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-基)甲基)苯甲酰胺	中间体 A2	(400MHz，DMSO-d6) δ 12.73 (br s，1H)，9.25 (t，J = 5.8 Hz，1H)，8.04 (s，1H)，7.83 (s，1H)，7.82 - 7.74 (br s，2H)，7.68 (d，J = 7.7 Hz，1H)，7.47 (d，J = 7.7 Hz，1H)，7.36 (t，J = 7.7 Hz，1H)，6.65 (t，J = 6.1 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.62 - 4.56 (m，4H)，3.46 (s，2H)，3.02 (t，J = 8.9 Hz，2H)，2.71 - 2.61 (m，4H)，2.31 (s，3H)。	Rt = 0.25min，m/z 502.0 [M+H]$^+$ (方法 12) 注意: 反应溶剂 DCM-DMF 混合物，偶联剂 HATU

[0592]

实施例	结构	胺	^{1}H NMR	LC-MS
30	 **3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((2-甲基异二氢吲哚-5-基)甲基)苯甲酰胺**	中间体A3	(400MHz，DMSO-d6) δ 12.74 (br s，1H)，8.92 (t，J = 6.0 Hz，1H)，8.04 (br s，1H)，7.88 (br s，1H)，7.83 (s，1H)，7.76 (br s，1H)，7.68 (d，J = 7.7 Hz，1H)，7.44 (d，J = 7.7 Hz，1H)，7.34 (t，J = 7.7 Hz，1H)，7.17 - 7.02 (m，3H)，6.65 (t，J = 6.0 Hz，1H)，4.65 (t，J = 8.9 Hz，2H)，4.57 (d，J = 6.0 Hz，2H)，4.40 (d，J = 6.0 Hz，2H)，3.72 (s，4H)，3.01 (t，J = 8.9 Hz，2H)，2.41 (s，3H)。	Rt = 0.29min，m/z 480.6 [M+H]$^+$ (方法 12) 注意：反应溶剂 DCM-DMF 混合物，偶联剂

[0593] 实施例31

[0594]



[0595] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-甲氧基吡啶-2-基)苯甲酰胺(实施例31)

[0596] 将中间体G(75mg,0.22mmol),2-氨基-5-甲氧基吡啶(83mg,0.67mmol),1-(甲基磺酰基)-1H-苯并三唑(264mg,1.34mmol),三乙胺(0.31mL,2.23mmol)和THF(10mL)载入微波小瓶,在微波照射下在150℃搅拌3h。再加入1当量的2-氨基-5-甲氧基吡啶和1-(甲基磺酰基)-1H-苯并三唑和三乙胺,将该混合物在微波照射下在150℃再搅拌3h。使该反应混合物上**Isolute®** SCX-2柱,用MeOH洗涤,用7N NH_3的MeOH溶液洗脱。浓缩样品。通过MDAP纯化(Luna Phenyl-Hexyl 3x50mm,3μm 5-95%MeOH/H_2O(0.1%FA),1.7mL/min,RT),得到标题化合物(23.1mg)。

[0597] LCMS(方法3):Rt=2.68min,m/z 443.2[M+H]$^+$

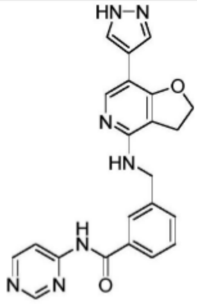
[0598] ^{1}H NMR(400MHz,DMSO-d6)δ10.61(s,1H),8.12(s,1H),8.11-8.09(m,2H),8.00(s,1H),7.90-7.85(m,3H),7.55(d,J=7.6Hz,1H),7.50(d,J=3.2Hz,1H),7.48(d,J=3.2Hz,1H),7.43(t,J=7.6Hz,1H),6.72(t,J=6.2Hz,1H),4.71(t,J=9.0Hz,2H),4.66(d,J=

6.0Hz,2H),3.85(s,3H),3.08(t,J=9.0Hz,2H)

[0599] 实施例32

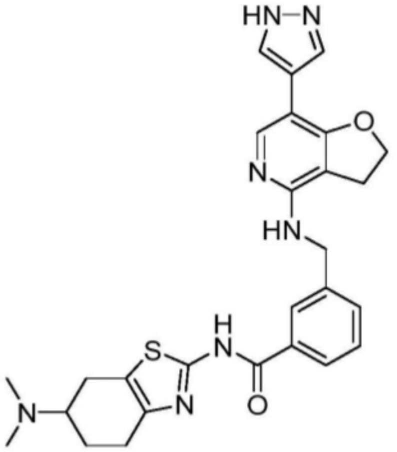
[0600] 使用与用于合成实施例31类似的方法,通过用指定的胺替代中间体G来制备下列实施例。

[0601]

实施例	结构	胺	^{1}H NMR	LC-MS
32	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(嘧啶-4-基)苯甲酰胺	4-氨基-嘧啶	^{1}H NMR (400 MHz, DMSO-d6) δ 12.78 (s, 1H), 11.19 (s, 1H), 8.95 (d, J = 1.0 Hz, 1H), 8.71 (d, J = 5.8 Hz, 1H), 8.20 (dd, J = 1.1, 5.8 Hz, 1H), 8.08 (s, 1H), 8.01-7.97 (m, 1H), 7.90-7.84 (m, 3H), 7.60-7.55 (m, 1H), 7.47-7.42 (m, 1H), 6.72 (t, J = 6.1 Hz, 1H), 4.69 (t, J = 8.8 Hz, 2H), 4.65 (d, J = 6.1 Hz, 2H), 3.06 (t, J = 8.9 Hz, 2H)。	Rt = 2.28min, m/z 414.3 [M+H]$^+$ (方法 5)

[0602] 实施例33

[0603]



[0604] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(二甲基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺(实施例35)

[0605] 将多聚甲醛(13mg,0.43mmol)和氰基硼氢化钠(27mg,0.43mmol)加入到搅拌的中间体H1(70mg,0.14mmol)在MeOH(2.0mL)和DMF(0.5mL)中的悬浮液中。将得到的混合物搅拌20h,然后用1M NaOH水溶液(5.0mL)处理。用DCM(2x 10mL),然后用10%MeOH的DCM溶液(4x 5mL)萃取该混合物。使合并的有机相通过**Isolute®** SCX-2柱。然后用1:1DCM:MeOH洗涤,用20%2M甲醇氨的DCM溶液洗脱。真空浓缩,得到粗产物,通过MDAP纯化(Luna Phenyl hexyl 21.2x150mm,10μm 5-60%MeOH/H_2O(0.1%FA)20mL/min),得到期望的产物,为甲酸盐(21.6mg)。

[0606] LCMS(方法3):Rt=2.05min,m/z 516.4[M+H]$^+$

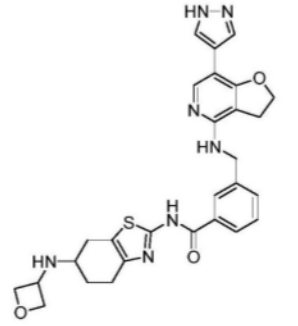
[0607] ^{1}H NMR(400MHz,DMSO-d6)δ12.40(br s,2H),8.18(s,1H),8.09(s,1H),8.04(s,1H),7.93(d J=7.4Hz,1H),7.87(s,2H),7.57(d J=7.9Hz,1H),7.45(t J=7.7Hz,1H),6.73(t J=6.0Hz,1H),4.71(t J=8.9Hz,2H),4.65,(d J=6.0Hz,2H),3.08(t J=8.9Hz,2H),2.90-2.60(m,6H),2.32(s,6H),2.09-2.01(m,1H),1.76-1.64(m,1H)。

[0608] 实施例34

[0609] 使用与用于制备实施例33类似的方法，由中间体H1和氧杂环丁烷-3-酮制备下列实施例。

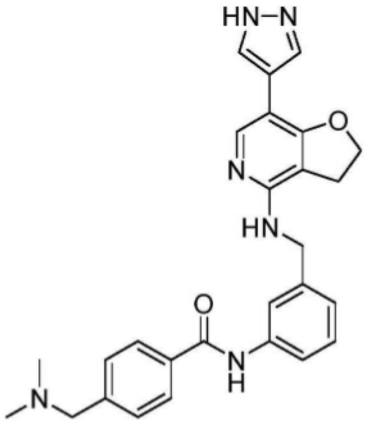
[0610]

[0611]

实施例	结构	^{1}H NMR	LC-MS
34	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(6-(氧杂环丁烷-3-基氨基)-4,5,6,7-四氢苯并[d]噻唑-2-基)苯甲酰胺	^{1}H NMR (400 MHz，DMSO-d6) δ 12.82 (s，1H)，8.10 (s，1H)，8.05 (s，1H)，7.93 (d，J = 7.7 Hz，1H)，7.87 (s，1H)，7.53 (d，J = 7.4 Hz，1H)，7.44 - 7.39 (m，1H)，6.72 (dd，J = 6.0，6.0 Hz，1H)，4.74 - 4.62 (m，5H)，4.41 (s，2H)，4.35 (m，2H)，4.06 - 3.98 (m，3H)，3.07 (t，J = 8.8 Hz，2H)，2.92 - 2.79 (m，2H)，2.70 - 2.57 (m，2H)，2.39 - 2.33 (m，1H)，1.95 - 1.83 (m，1H)，1.61 - 1.56 (m，1H)。	Rt = 2.02min，m/z 544.0 [M+H]$^+$ (方法 3)

[0612] 实施例35

[0613]



[0614] N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-4-((二甲基氨基)甲基)苯甲酰胺(实施例35)

[0615] 将中间体K1溶于乙腈(2mL)，然后加入12M HCl水溶液(2mL)。将该溶液在RT搅拌1h，直至完全转化。减压干燥该反应混合物，通过使用C18-硅胶的快速色谱法纯化得到的粗产物，用0-20%含有A的B(A:水/乙腈95/5+0.1%HCOOH,B:乙腈/水95/5+0.1%HCOOH)洗脱，得到期望的产物(3.8mg)。

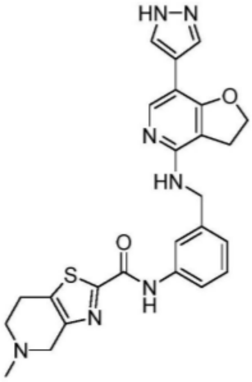
[0616] LCMS(方法13):Rt=3.24min,m/z 469.2[M+H]$^+$

[0617] ^{1}H NMR(400MHz,DMSO-d6)δ10.25(s,1H),8.13(s,1H),8.08(s,1H),7.95-8.00(d,J=7.9Hz,2H),7.85(s,2H),7.73(s,1H),7.51-7.68(m,3H),7.27(t,J=7.9Hz,1H),7.09(d,J=7.9Hz,1H),6.67(br s,1H),6.50(s,1H),4.71(t,J=4.7Hz,2H),4.60(d,J=4.6Hz,2H),3.06(br t,J=9.0Hz,2H),2.60(s,6H)。

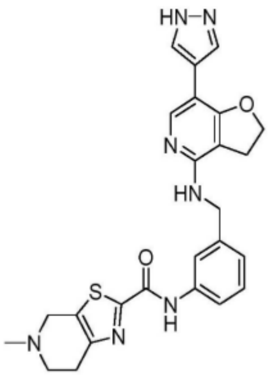
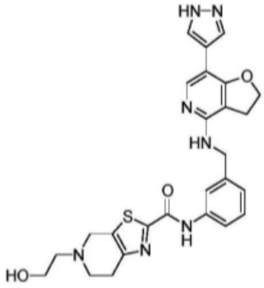
[0618] 实施例36至52

[0619] 按照与实施例35类似的方式,通过用下表中指定的中间体替代中间体K1来制备下列实施例。

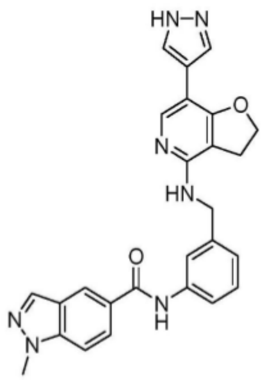
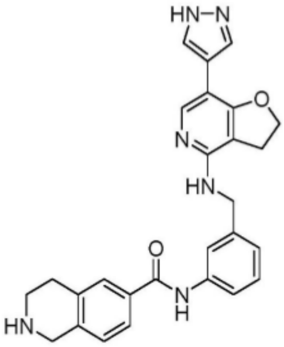
[0620]

实施例	结构	中间体	^{1}H NMR	LC-MS
36	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[4,5-c]吡啶-2-甲酰胺**	**中间体K2**	**(400 MHz，DMSO-d6) δ 10.54 - 10.59 (m，1H)，8.16 (s，1H)，8.06 - 8.10 (m，1H)，7.80 - 7.89 (m，3H)，7.61 - 7.68 (m，1H)，7.26 (t，J = 7.8 Hz，1H)，7.09 (d，J = 7.7 Hz，1H)，6.63 (t，J = 6.0 Hz，1H)，4.64 - 4.73 (m，2 H)，4.57 (d，J = 5.9 Hz，2H)，3.61 (s，2H)，3.05 (br t，J = 8.9 Hz，2 H)，2.95 (br t，J = 5.59 Hz，2H)，2.68 - 2.73 (m，2H)，2.42 (s，3H)。**	**Rt = 3.24min，m/z 488.2 $[M+H]^+$ (方法 13)**

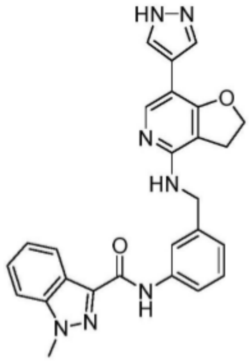
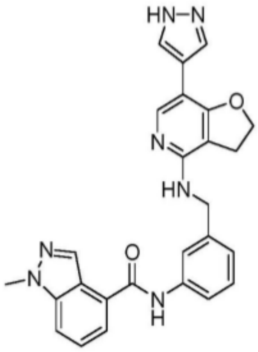
[0621]

37	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-甲基-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺**	**中间体 K3**	**(400 MHz，DMSO-d6) δ 10.58 (s，1H)，8.15 (s，1H)，8.07 (s，1H)，7.78 - 7.92 (m，3H)，7.64 (d，J = 7.9 Hz，1H)，7.25 (t，J = 7.7 Hz，1H)，7.09 (d，J = 7.9 Hz，1H)，6.58 - 6.73 (m，1H)，4.68 (t，J = 8.8 Hz，2H)，4.56 (d，J = 5.7 Hz，2H)，3.69 (s，2H)，3.05 (t，J = 9.0 Hz，2H)，2.83 - 2.96 (m，2H)，2.68 - 2.83 (m，2H)，2.39 (s，3H)。**	**Rt = 3.19min，m/z 488.1 [M+H]$^+$ (方法 13)**
38	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(2-羟基乙基)-4,5,6,7-四氢噻唑并[5,4-c]吡啶-2-甲酰胺**	**中间体 K4**	**(400 MHz，DMSO-d6) δ 13.31 (br s，1H)，11.17 (br s，1H)，10.83 (s，1H)，8.63 (br t，J = 6.1 Hz，1H)，8.07 (s，2 H)，7.99 (s，1H)，7.89 (s，1H)，7.77 (br d，J = 8.3 Hz，1H)，7.37 (t，J = 7.9 Hz，1H)，7.17 (br d，J = 7.89 Hz，1H)，4.97 (br t，J = 9.2 Hz，2H)，3.15 - 4.89 (m，14 H)。**	**Rt = 3.12min，m/z 518.2 [M+H]$^+$ (方法 13)**

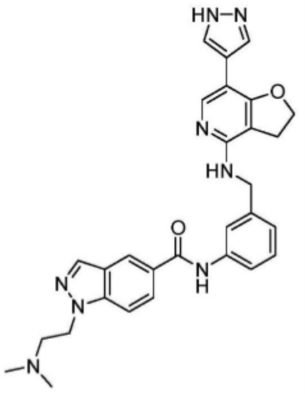
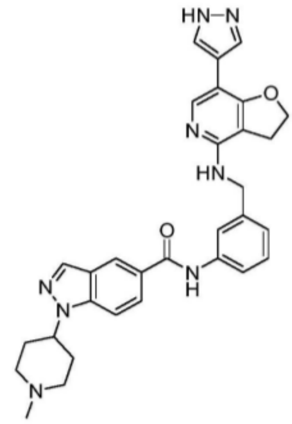
[0622]

39	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-5-甲酰胺**	**中间体 K5**	**(400 MHz，DMSO-d6) δ 12.77 (s，1H)，10.22 (s，1 H)，8.45 (s，1H)，8.23 (d，J = 0.9 Hz，1H)，8.09 (s，1H)，7.58 - 8.02 (m，6H)，7.27 (t，J = 7.7 Hz，1H)，7.07 (d，J = 7.5 Hz，1H)，6.64 (t，J = 5.9，1H)，4.69 (t，J = 9.0 Hz，2H)，4.59 (d，J = 4.6 Hz，2H)，4.09 (s，3 H)，3.06 (t，J = 9.0 Hz，2H)。**	**Rt = 4.03min，m/z 466.2 [M+H]$^+$ (方法 13)**
40	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺**	**中间体 K6**	**(400 MHz，DMSO-d6) d ppm 13.24 (br s，1H)，10.33 (s，1H)，9.46 (br s，2H)，8.62 (br s，1H)，7.99 - 8.07 (m，3H)，7.80 - 7.90 (m，3H)，7.68 (d，J = 9.2 Hz，1H)，7.23 - 7.49 (m，2H)，6.87 - 7.23 (m，1H)，4.97 (t，J = 9.0 Hz，2H)，4.74 (d，J = 6.1 Hz，2H)，4.27 - 4.47 (m，2H)，3.40 (d，J = 6.1 Hz，2H)，3.25 (t，J = 9.2 Hz，2H)，3.09 (t，J = 6.1 Hz，2H)。**	**Rt = 3.45min，m/z 467.1 [M+H]$^+$ (方法 13)**

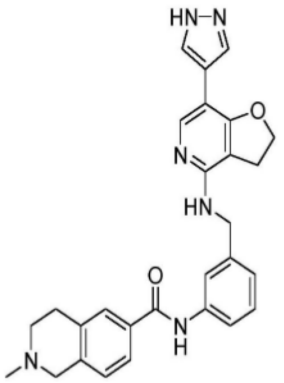
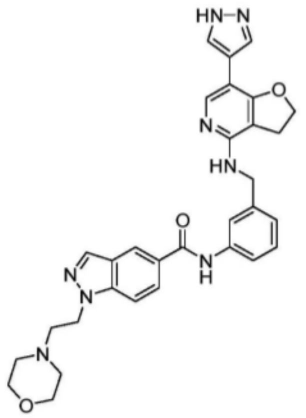
[0623]

41	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-3-甲酰胺**	**中间体 K7**	**(400 MHz，DMSO-d6) δ 10.20 (s，1H)，8.22 (d，J = 7.9 Hz，2H)，8.09 (s，1H)，7.80 - 7.85 (m，3H)，7.78 (d，J = 8.8 Hz，1H)，7.70 (d，J = 8.3 Hz，1H)，7.50 (t，J = 7.5 Hz，1H)，7.32 (t，J = 7.5 Hz，1H)，7.26 (t，J = 7.9 Hz，1H)，7.07 (d，J = 7.5 Hz，1H)，6.63 (t，J = 6.1 Hz，1H)，4.69 (t，J = 8.8 Hz，2H)，4.59 (d，J = 6.14 Hz，2H)，4.19 (s，3 H)，3.07 (t，J = 8.8 Hz，2H)。**	**Rt = 4.74min，m/z 466.4 $[M+H]^+$ (方法 13)**
42	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-甲基-1H-吲唑-4-甲酰胺**	**中间体 K8**	**(400 MHz，DMSO-d6) δ 12.16 - 12.95 (br s，1H)，10.34 (s，1H)，8.32 (s，1H)，8.09 (s，1H)，7.82 - 7.90 (m，3H)，7.79 (s，1H)，7.75 (d，J = 7.0 Hz，1H)，7.66 - 7.76 (m，1H)，7.52 (dd，J = 8.3，7.5 Hz，1H)，7.28 (t，J = 7.9 Hz，1H)，7.09 (d，J = 7.5 Hz，1H)，6.66 (m，1H)，4.69 (t，J = 8.8 Hz，2H)，4.60 (d，J = 6.1 Hz，2H)，4.10 (s，3 H)，3.06 (t，J = 9.0 Hz，2H)。**	**Rt = 4.07min，m/z 466.1 $[M+H]^+$ (方法 13)**

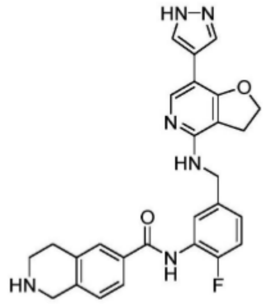
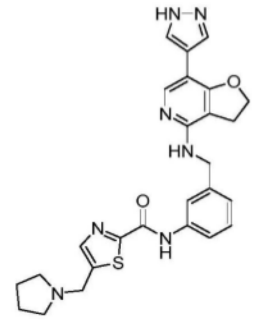
[0624]

43	 N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-(二甲基氨基)乙基)-1H-吲唑-5-甲酰胺	中间体K9	(400 MHz，DMSO-d6) δ 12.77 (br s，1H)，10.21 (s，1H)，8.39 - 8.49 (m，1H)，8.24 (s，1H)，8.09 (s，1H)，7.86 - 8.01 (m，2H)，7.71 - 7.86 (m，3H)，7.67 (m，J = 7.89 Hz，1H)，7.27 (t，J = 7.89 Hz，1H)，7.07 (m，1H)，6.65 (t，J = 6.14 Hz，1H)，4.69 (t，J = 8.99 Hz，2H)，4.48 - 4.63 (m，4H)，3.06 (t，J = 8.77 Hz，2H)，2.77 (br s 2H)，2.20 (br s，6H)。	Rt = 3.36min，m/z 523.0 [M+H]$^+$ (方法 13)
44	 N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(1-甲基哌啶-4-基)-1H-吲唑-5-甲酰胺	中间体K10	(400 MHz，DMSO-d6) δ 10.21 (s，1H)，8.46 (s，1H)，8.27 (s，1H)，8.14 (s，1H)，8.09 (s，1H)，7.98 (dd，J = 9.0，1.5 Hz，1H)，7.78 - 7.89 (m，3H)，7.75 (s，1H)，7.60 - 7.70 (m，1H)，7.27 (t，J = 7.9 Hz，1H)，7.07 (d，J = 7.5 Hz，1H)，6.65 (t，J = 6.1 Hz，1H)，4.60 - 4.70 (m，3H)，4.59 (d，J = 5.7 Hz， 2H)，2.98 - 3.16 (m，5H)，2.37 - 2.47 (m，4H)，2.23 (dq，J = 12.1，3.5 Hz，2H)，2.00 (br s，2H)。	Rt = 3.43min，m/z 549.2 [M+H]$^+$ (方法 13)

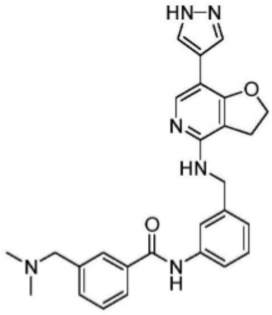
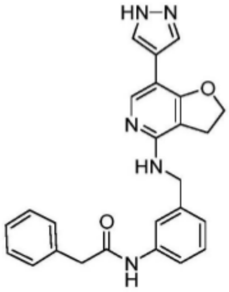
[0625]

45	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-甲基-1,2,3,4-四氢异喹啉-6-甲酰胺**	**中间体 K11**	**(400 MHz，DMSO-d6) δ 12.16 - 13.09 (br s，1H)，10.23 (s，1H)，8.07 (s，1H)，7.88 (br s，2H)，7.83 (s，2H)，7.73 - 7.77 (m，1H)，7.64 (d，J = 8.3 Hz，1H)，7.23 - 7.37 (m，2H)，7.09 (d，J = 7.5 Hz，1H)，4.73 (t，J = 8.1 Hz，2H)，4.61 (d，J = 5.7 Hz，2H)，4.38 (br s，2H)，3.35 - 3.61 (m，2H)，3.01 - 3.24 (m，4H)，2.89 (s，3H)。**	**Rt = 3.19min，m/z 481.2 [M+H]$^+$ (方法 13)**
46	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-1-(2-吗啉代乙基)-1H-吲唑-5-甲酰胺**	**中间体 K12**	**(400 MHz，DMSO-d6) δ 12.76 (br s，1H) 10.23 (s，1H) 8.44 (s，1H) 8.22 - 8.30 (m，1H)，8.13 (s，1H)，8.08 (s，1H)，7.97 (d，J = 8.8 Hz，1H)，7.85 - 7.90 (m，2H)，7.70 - 7.80 (m，2H)，7.67 (d，J = 7.9 Hz，1H)，7.28 (t，J = 7.7 Hz，1H)，7.08 (d，J = 7.5 Hz，1H)，4.73 (t，J = 8.6 Hz，2H)，4.58 - 4.68 (d，J = 6.1 Hz，4H)，3.40 - 3.50 (br s，4H)，3.09 (t，J = 8.8 Hz，2H)，2.80 (br s，2H)，2.40 - 2.50 (br s，2H)，1.30 - 1.50 (m，2H)。**	**Rt = 3.40min，m/z 565.2 [M+H]$^+$ (方法 13)**

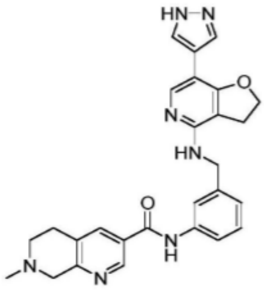
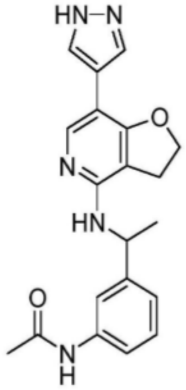
[0626]

47	 N-(5-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-2-氟苯基)-1,2,3,4-四氢异喹啉-6-甲酰胺	中间体K13	(400 MHz，DMSO-d6) δ 9.97 (s，1H)，8.21 (s，2H)，8.08 (s，1H)，7.85 (s，2H)，7.68 - 7.76 (m，2H)，7.45 - 7.53 (m，1H)，7.10 - 7.26 (m，3H)，6.68 (t，J = 6.1 Hz，1H)，4.68 (t，J = 8.8 Hz，2H)，4.56 (d，J = 6.1 Hz， 2H)，4.03 (s，2H)，2.96 - 3.18 (m，4H)，2.85 (t，J = 5.9 Hz，2H)。	Rt = 3.21min，m/z 485.1 [M+H]$^+$ (方法 13)
48	 N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-5-(吡咯烷-1-基甲基)噻唑-2-甲酰胺	中间体K14	(400 MHz，DMSO-d6) δ 13.30 (br s，1H)，11.53 - 11.63 (m，1H)，10.85 (s，1H)，8.65 (br t，J = 6.0 Hz，1H)，8.26 (s，1H)，8.07 (s，2H)，8.02 (s，1H)，7.88 (s，1H)，7.78 (br d，J = 8.3 Hz，1H)，7.38 (t，J = 7.9 Hz，1H)，7.18 (d，J = 7.7 Hz，1H)，4.98 (br t，J = 9.1 Hz，2H)，4.74 (br dd，J = 9.2, 6.1 Hz，4H)，3.34 - 3.39 (m，2H)，3.25 (br t，J = 9.1 Hz，2H)，3.04 - 3.16 (m，2H)，1.85 - 2.08 (m，4H)。	Rt = 3.24min，m/z 502.3 [M+H]$^+$ (方法 13)

[0627]

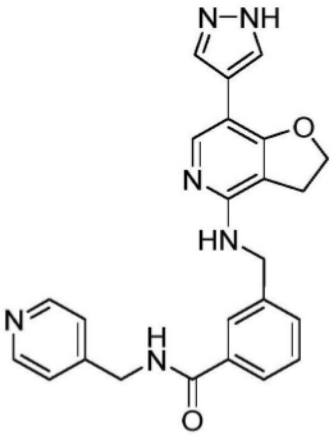
49	 N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-3-((二甲基氨基)甲基)苯甲酰胺	中间体 K15	(400 MHz，DMSO-d$_6$) δ 10.26 (s，1H)，8.13 (s，1H)，8.08 (s，1H)，8.03 (s，1H)，7.98 (d，J = 7.5 Hz，1H)，7.85 (s，2H)，7.72 (s，1H)，7.65 (s，2H)，7.53-7.61 (m，1H)，7.28 (t，J = 7.9 Hz，1H)，7.09 (d，J = 7.5 Hz，1H)，6.61-6.76 (br s，1H)，4.69 (m，2H)，4.59 (d，J = 6.1 Hz，2H)，4.12 (br s，2H)，3.06 (m，2H)，2.58 (br s，6H)。	Rt = 3.06min，m/z 469.2 [M+H]$^+$ (方法 13)
50	 N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-2-苯基乙酰胺	中间体 K16	(400 MHz，DMSO-d6) δ 12.27 - 13.05 (br s，1H)，10.33 (s，1H)，8.05 (s，1H)，7.76 - 7.97 (m，2H)，7.43 - 7.59 (m，2H)，7.20 - 7.34 (m，7H)，6.93 - 7.07 (m，1H)，4.65 - 4.87 (m，2H)，4.56 (d，J = 6.1 Hz，2H)，3.61 (s，2H)，2.90 - 3.19 (m，2H)。	Rt = 4.08min，m/z 426.1 [M+H]$^+$ (方法 13)

[0628]

51	 **N-(3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯基)-7-甲基-5,6,7,8-四氢-1,7-萘啶-3-甲酰胺**	**中间体 K17**	**(400 MHz，DMSO-d6) δ 13.31 (br s，1H)，11.47 (br s，1H)，10.60 (s，1H)，8.97 (d，J = 2.2 Hz，1H)，8.64 (t，J = 6.1 Hz，1H)，8.24 (d，J = 1.8 Hz，1H)，8.07 (s，2H)，8.02 (s，1H)，7.85 (s，1H)，7.69 (d，J = 8.3 Hz，1H)，7.37 (t，J = 7.9 Hz，1H)，7.15 (d，J = 7.9 Hz，1H)，4.97 (t，J = 9.2 Hz，2H)，4.76 (d，J = 6.1 Hz，2H)，4.32 - 4.58 (m，4H)，3.30 - 3.45 (m，2H)，3.25 (t，J = 9.2 Hz，2H)，2.95 (d，J = 4.4 Hz，3 H)。**	**Rt = 3.03min，m/z 482.1 [M+H]$^+$ (方法 13)**
52	 **N-(3-(1-((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)乙基)苯基)乙酰胺**	**中间体 I3**	**(400 MHz，DMSO-d6) δ 9.83 (s，1H)，8.02 (s，1H)，7.83 (s，2 H)，7.51 (s，1H)，7.43 (br d，J = 8.1 Hz，1H)，7.18 (t，J = 7.8 Hz，1H)，7.06 (d，J = 7.7 Hz，1H)，6.33 (d，J = 7.9 Hz，1H)，5.17 - 5.26 (m，1H)，4.68 (t，J = 9.0 Hz，2H)，3.08 (t，J = 8.9 Hz，2H)，2.01 (s，3H)，1.44 (d，J = 7.0 Hz，3H)。**	**Rt = 0.41min，m/z 364.3 [M+H]$^+$ (方法 6)**

[0629] 实施例53

[0630]



[0631] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(吡啶-4-基甲基)苯甲酰胺(实施例53)

[0632] 将中间体E3(90mg,0.205mmol),1-(四氢-2H-吡喃-2-基)-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)-1H-吡唑(114mg,0.410mmol),磷酸三钾(130mg,0.615mmol)溶于THF(1mL)和水(1mL)。用氩气给该反应体系吹扫10min,然后加入氯(2-二环己基膦基-2’,4’,6’-三异丙基-1,1’-联苯)[2-(2’-氨基-1,1’-联苯)]钯(II)(24.18mg,0.031mmol),将得到的混合物在95℃加热1h。用水使反应淬灭,用DCM萃取得到的混合物。用饱和NaCl水溶液洗涤有机相,使其通过相分离器,真空蒸发溶剂。通过C18-二氧化硅快速色谱法纯化得到的粗产物,用0-30%A中的B(A:水/乙腈95/5+0.1%HCOOH,B:乙腈/水95/5+0.1%HCOOH)梯度洗脱。汇集合适的级分,用1M HCl水溶液处理,减压干燥,得到标题化合物(32mg)。

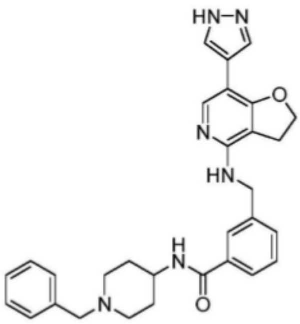
[0633] LCMS(方法6):Rt=0.27min,m/z 427.2$[M+H]^+$

[0634] ^{1}H NMR(400MHz,DMSO-d6)δ13.02-13.85(br s,1H),9.53(br s,1H),8.83(d,J=6.6Hz,2H),8.53-8.73(m,1H),7.99-8.16(m,4H),7.85-7.98(m,3H),7.62-7.64(d,1H),7.44-7.56(m,1H),4.96(t,J=9.2Hz,2H),4.83(d,J=6.1Hz,2H),4.73(d,J=5.7Hz,2H),3.25(t,J=9.2Hz,2H)。

[0635] 实施例54

[0636] 使用用于制备实施例53类似的方法,由中间体E4制备下列实施例。

[0637]

Ex	结构	¹H NMR	LC-MS
54	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(1-苄基哌啶-4-基)苯甲酰胺	(400 MHz，DMSO-d6) δ 12.28 - 12.93 (br s，1H)，8.20 (d，J = 7.9 Hz，1H)，8.14 (s，1H)，8.07 (s，1H)，7.85 (s，2H)，7.80 (s，1H)，7.65 (d，J = 7.5 Hz，1H)，7.46 (d，J = 7.5 Hz，1H)，7.17 - 7.39 (m，6H)，6.67 (t，J = 5.9 Hz，1H)，4.68 (t，J = 8.8 Hz，2H)，4.60 (d，J = 5.7 Hz，2H)，3.68 - 3.85 (m，1H)，3.52 (br s，2H)，3.04 (t，2H)，2.85 (d，J = 11.0 Hz，2H)，2.09 (br s，2H)，1.78 (d，J = 10.5 Hz，2H)，1.50 - 1.68 (m，2H)	Rt = 3.24min， m/z 509.1 [M+H]$^+$ (方法 13)

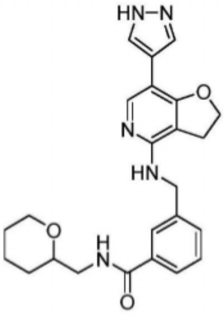
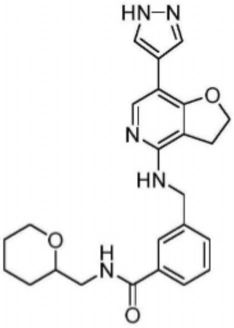
[0638] 实施例55和56

[0639] 由外消旋实施例11为原料，使用下列手性色谱条件以对映异构体方式拆分实施例55和实施例56：YMC Cellulose-C 5μm，洗脱液：30/70IPA(0.5%DEA)/CO$_2$，流速15mL/min，120bar，柱温40℃。分离两种级分，表征为实施例55(对映异构体1)和实施例56(对映异构体2)。

[0640]

实施例	结构	¹H NMR	LC-MS	手性 LC

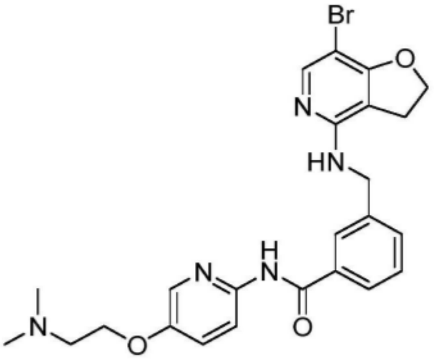
[0641]

55	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体 1)	(400 MHz，d6-DMSO) δ 12.80 (s，1H)，8.44 (t，J = 5.8 Hz，1H)，8.09 (s，1H)，7.85-7.83 (m，2H)，7.82-7.67 (m，2H)，7.50-7.46 (m，1H)，7.37 (t，J = 7.7 Hz，1H)，6.71 (t，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，3.87 (dd，J = 2.3，10.8 Hz，1H)，3.46 - 3.39 (m，1H)，3.29 - 3.23 (m，2H)，3.06 (t，J = 8.8 Hz，2H)，1.80-1.75 (m，1H)，1.61 (d，J = 12.5 Hz，1H)，1.49-1.41 (m，3H)，1.22-1.12 (m，2H)。	Rt = 2.68min，m/z 434.0 $[M+H]^+$ (方法 3)	Rt = 8.62min 条件: YMC Cellulose-C 30/70 IPA (0.1%DEA)/ CO_2
56	 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-((四氢-2H-吡喃-2-基)甲基)苯甲酰胺(对映异构体 2)	(400 MHz，d6-DMSO) δ 12.80 (s，1H)，8.44 (t，J = 5.8 Hz，1H)，8.09 (s，1H)，7.85-7.83 (m，2H)，7.82-7.67 (m，2H)，7.50-7.46 (m，1H)，7.37 (t，J = 7.7 Hz，1H)，6.71 (t，J = 6.1 Hz，1H)，4.70 (t，J = 8.9 Hz，2H)，4.62 (d，J = 6.0 Hz，2H)，3.87 (dd，J = 2.3，10.8 Hz，1H)，3.45 - 3.40 (m，1H)，3.30 - 3.23 (m，2H)，3.06 (t，J = 8.8 Hz，2H)，1.80-1.75 (m，1H)，1.61 (d，J = 12.5 Hz，1H)，1.49-1.41 (m，3H)，1.22-1.12 (m，2H)。	Rt = 2.68min，m/z 434.0 $[M+H]^+$ (方法 3)	Rt = 10.10min 条件 YMC Cellulose-C 30/70 IPA (0.1%DEA)/ CO_2

[0642] 实施例57

[0643] 步骤A

[0644]



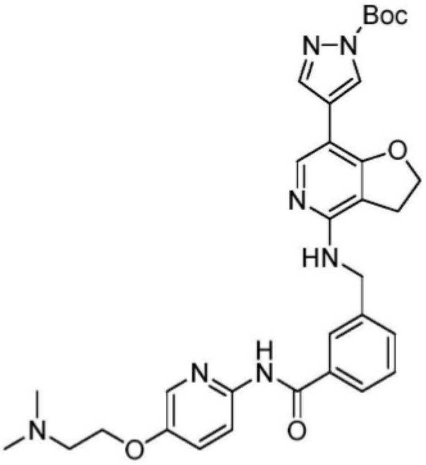
[0645] 3-(((7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-(2-(二甲基氨基)乙氧基)哌啶-2-基)苯甲酰胺(中间体57A)

[0646] 向中间体D1(400mg,1.15mmol),5-(2-二甲基-氨基乙氧基)吡啶-2-基胺(230mg,1.26mmol)和TBTU(440mg,1.37mmol)在DCM(12mL)中的溶液中加入DIPEA(0.60mL,3.44mmol)。将该反应混合物在室温搅拌18h。再加入一定量的TBTU(369mg,1.15mmol),将该混合物搅拌48h。用DCM稀释该反应混合物,用水萃取。用硫酸镁干燥有机相,过滤,真空浓缩,得到标题化合物(380mg)。

[0647] LCMS(方法2):Rt＝1.46min,m/z 512.3/514.3$[M+H]^+$

[0648] 步骤B

[0649]



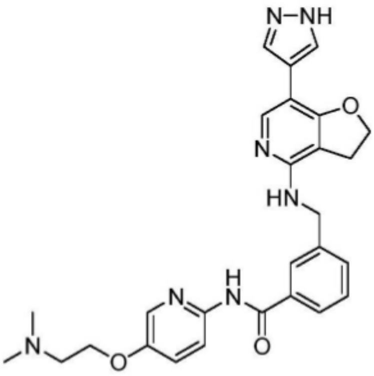
[0650] 4-(4-((3-((5-(2-(二甲基氨基)乙氧基)哌啶-2-基)氨基甲酰基)-苄基)氨基)-2,3-二氢呋喃并[3,2-c]吡啶-7-基)-1H-吡唑-1-甲酸叔丁酯(中间体57B)

[0651] 向脱气的中间体57A(100mg,0.195mmol),4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡唑-1-甲酸叔丁酯(63mg,0.215mmol)和碳酸铯(95mg,0.293mmol)在1,4-二噁烷(3mL)和水(0.3mL)中的混合物中加入[1,1'双(二苯基膦基)二茂铁]二氯钯(II)与二氯甲烷的复合物(16mg,0.0195mmol),将该反应混合物加热,在80℃搅拌1h。冷却该反应混合物,通过**Celite®**垫过滤,浓缩。使粗化合物上**Isolute®** SCX-2柱,用2N氨的MeOH溶液洗脱。浓缩碱性级分,得到标题化合物(81mg)。

[0652] LCMS(方法2):Rt＝1.50min,m/z 600.5$[M+H]^+$

[0653] 步骤C

[0654]



[0655] 3-(((7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)-N-(5-(2-(二甲基氨基)乙氧基)吡啶-2-基)苯甲酰胺(实施例57)

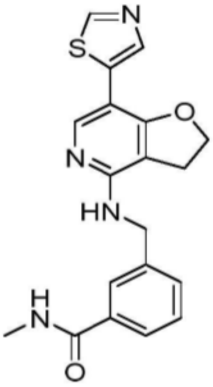
[0656] 向中间体57B(60%,80mg,0.080mmol)在二氯甲烷(2mL)中的溶液中加入三氟乙酸(0.25mL,3.20mmol),将该反应混合物在室温搅拌2h。将该反应混合物浓缩至干,进行MDAP(Sunfire C18 3x50mm,3μm 5-95%ACN/H_2O(10mM NH_4CO_3),1.7mL/min,RT,然后Luna Phenyl-Hexyl 21.2x150mm,10μm 5-60%MeOH/H_2O+0.1%FA,20mL/min,RT)。得到期望的产物,为黄白色固体(15mg)。

[0657] LCMS(方法3):Rt=1.98min,m/z 500$[M+H]^+$

[0658] ^{1}H NMR(400MHz,DMSO-d6)δ10.60(s,1H),8.18(s,1H),8.12-8.08(m,3H),7.99(s,1H),7.90-7.85(m,3H),7.54(d,J=7.7Hz,1H),7.50(dd,J=3.1,9.2Hz,1H),7.42(t,J=7.7Hz,1H),6.75-6.70(m,1H),4.71(t,J=8.9Hz,2H),4.66(d,J=5.9Hz,2H),4.14(t,J=5.7Hz,2H),3.07(t,J=8.8Hz,2H),2.66(t,J=5.8Hz,2H),2.25(s,6H)。

[0659] 实施例A

[0660]



[0661] N-甲基-3-(((7-(噻唑-5-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺(实施例A)

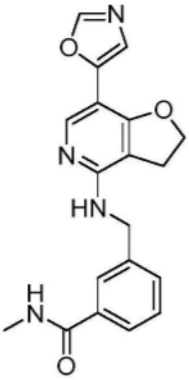
[0662] 将脱气的中间体E1(29mg,0.08mmol),5-(三丁基甲锡烷基)噻唑(33mg,0.09mmol),四(三苯基膦)钯(0)(4.6mg,0.004mmol)和噻吩-2-甲酸铜(I)(1.5mg,0.008mmol)在二噁烷(5mL)中的混合物在150℃在微波照射中加热1h。用MeOH稀释该反应混合物,使其通过**Isolute®** SCX-2柱,用MeOH,然后用2M甲醇氨洗脱。真空浓缩该溶液,通过MDAP纯化残余物(Sunfire乙腈碱性5-60,Sunfire C1819x150mm,10μm,5-60%乙腈/H_2O(10mM NH_4CO_3),20mL/min,RT),得到期望的产物(7.8mg)。

[0663] LCMS(方法3):Rt=2.29min,m/z 367.0$[M+H]^+$

[0664] ^{1}H NMR(400MHz,DMSO-d6)δ8.96(s,1H),8.45-8.35(m,1H),8.16(s,1H),8.15(d,J=0.7Hz,1H),7.83-7.80(m,1H),7.68-7.66(m,1H),7.49-7.46(m,1H),7.41-7.36(m,1H),7.11-7.06(m,1H),4.77(t,J=8.9Hz,2H),4.65(d,J=6.0Hz,2H),3.10(t,J=8.9Hz,2H),2.78(d,J=4.5Hz,3H)。

[0665] 实施例B

[0666]



[0667] N-甲基-3-(((7-(噁唑-5-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-基)氨基)甲基)苯甲酰胺(实施例B)

[0668] 用氩气给中间体E1(75mg,0.21mmol),5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)噁唑(48mg,0.25mmol),四(三苯基膦)钯(0)(24mg,0.021mmol)和碳酸铯(0.20g,0.62mmol)在DMF(4mL)和水(0.4mL)中的混合物脱气,在100℃加热18h。通过**Celite®**过滤该反应混合物,真空浓缩,通过MDAP纯化残余物(Luna Phenyl-Hexyl3x50mm,3μm 5-95%MeOH/H_2O(0.1%FA),1.7mL/min,RT),得到产物(13.4mg)。

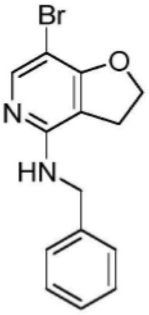
[0669] LCMS(方法3):Rt=2.16min,m/z 351.0$[M+H]^+$

[0670] ^{1}H NMR(400MHz,DMSO-d6)δ8.43-8.38(m,1H),8.33(s,1H),8.13(s,1H),7.82(s,1H),7.68(ddd,J=1.5,1.5,8.0Hz,1H),7.47(d,J=7.9Hz,1H),7.39(t,J=7.7Hz,1H),7.18(s,1H,),7.12(t,J=6.1Hz,1H),4.78(t,J=9.0Hz,2H),4.67(d,J=6.0Hz,2H),3.09(t,J=8.9Hz,2H),2.78(d,J=4.5Hz,3H)。

[0671] 实施例C

[0672] 步骤A

[0673]

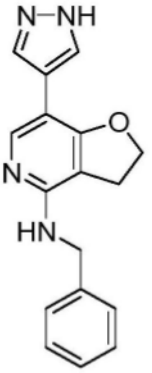


[0674] N-苄基-7-溴-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(中间体CA)

[0675] 使用与用于合成中间体C1类似的方法,通过用苯甲醛替代3-甲酰基苯甲酸甲酯来制备中间体CA。

[0676] LCMS(方法16):Rt=1.57min,m/z 305.1/307.1$[M+H]^+$

[0677] 步骤B

[0678] 

[0679] N-苄基-7-(1H-吡唑-4-基)-2,3-二氢呋喃并[3,2-c]吡啶-4-胺(实施例C)

[0680] 将脱气的中间体CA(50mg,0.164mmol),4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡唑-1-甲酸叔丁酯(58mg,0.197mmol),[1,1'-双(二苯基膦基)-二茂铁]二氯钯(II)与DCM的复合物(14mg,0.0164mmol),碳酸铯(53mg,0.164mmol)在1,4-二噁烷(1.5mL)和水(0.15mL)中的混合物在90℃加热20h。再加入部分4-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡唑-1-甲酸叔丁酯(58mg,0.197mmol),[1,1'-双(二苯基膦基)-二茂铁]二氯钯(II)与二氯甲烷的复合物(14mg,0.0164mmol)和碳酸铯(53mg,0.164mmol),将得到的混合物再搅拌2h。使该反应混合物上**Isolute®** SCX-2柱,用DCM,然后用MeOH洗涤,然后用MeOH/NH_3 2N洗脱产物,真空浓缩。通过MDAP纯化残余物(Sunfire C18 19x150mm,10μm 20-80%ACN/H_2O(10mM NH_4CO_3),20mL/min,RT),得到产物(10.74mg)。

[0681] LCMS(方法3)RT=2.59min,m/z 293.3$[MH]^+$

[0682] ^1H NMR(400MHz,DMSO-d6)δ12.79(s,1H),8.09(s,1H),7.91(s,1H),7.83(s,1H),7.36-7.27(m,4H),7.20(tt,J=1.7,7.1Hz,1H),6.67-6.62(m,1H),4.70(t,J=8.9Hz,2H),4.59(d,J=6.0Hz,2H),3.05(t,J=8.9Hz,2H)。

[0683] 本发明的化合物的药理学活性

[0684] 体外抑制活性测定描述ROCK1和ROCK2

[0685] (方法A)

[0686] 本发明的化合物抑制Rho激酶活性的有效性可以使用ADP-Glo试剂盒(Promega)在包含40mM Tris pH7.5,20mM $MgCl_2$ 0.1mg/mL BSA,50μM DTT和2.5μM肽底物(髓磷脂碱性蛋白)的10μL测定法中测定。将化合物溶解在DMSO中,使得DMSO的最终浓度在本测定中为1%。所有反应/温育均在25℃进行。将化合物(2μL)和Rho激酶1或2(4μl)混合并温育30min。通过添加ATP(4μL)启动反应,使得测定中ATP的最终浓度为10μM。温育1小时后,加入10μL ADP-Glo试剂,再温育45分钟后,加入20μL激酶检测缓冲液,将混合物再温育30分钟。在光度计上测量发光信号。对照由不含化合物的测定孔组成,使用不添加酶的测定孔测定背景。以剂量-反应形式测试化合物,并在化合物的每个浓度下计算激酶活性的抑制。确定IC_{50}(抑制50%酶活性所需的化合物浓度)使用具有可变斜率的S形拟合将数据拟合到%抑制对log10化合物浓度的图中,并将最大值固定为100%,最小值固定为0%。为了确定Ki值,使用Cheng-Prusoff方程($Ki=IC_{50}/(1+[S]/Km)$)。

[0687] 体外抑制活性测定描述ROCK1和ROCK2

[0688] (方法B)

[0689] 本发明的化合物抑制Rho激酶活性的有效性可以使用ADP-Glo试剂盒(Promega)在含有40mM Tris pH7.5,20mM $MgCl_2$ 0.1mg/mL BSA,50μM DTT和2.5μM肽底物(髓磷脂碱性蛋白)的10μL测定法中测定。将化合物溶解在DMSO中,使得DMSO的最终浓度在本测定中为1%。所有反应/温育均在25℃进行。将化合物(2μL)和Rho激酶1或2(4μl)混合并温育30min。通过添加ATP(4μL)启动反应,使得测定中ATP的最终浓度为200μM。在1小时温育后,加入10μL ADP-Glo试剂,并且再经过45分钟温育后,加入20μL激酶检测缓冲液,将该混合物再温育30分钟。在发光计上测量发光信号。对照由不含化合物的测定孔组成,使用不添加酶的测定孔测定背景。以剂量-反应形式测试化合物,并在化合物的每个浓度下计算激酶活性的抑制。为了确定IC_{50}(抑制50%酶活性所需的化合物浓度),使用具有可变斜率的S形拟合将数据拟合至%抑制与log_{10}化合物浓度关系的图,并将最大值固定为100%,最小值固定为0%。为了确定Ki值,使用Cheng-Prusoff方程($Ki=IC_{50}/(1+[S]/Km)$)。

[0690] 用方法A和用方法B获得的Ki值是一致的。

[0691] 本发明的化合物对两种同种型显示出低于500nM的Ki值。

[0692] 实施例的各个化合物的结果在下表1中提供,并表示为活性范围。

[0693] PKA的体外抑制活性测定描述

[0694] 本发明的化合物抑制PKA活性的有效性可以使用ADP-Glo试剂盒(Promega)在包含40mM Tris pH 7.5,20mM $MgCl_2$,0.1mg/mL BSA,50μM DTT和260μM肽底物(Kemptide)的10μL测定法中测定。将化合物溶解在DMSO中,使得DMSO的最终浓度在本测定中为1%。所有反应/温育均在25℃进行。将化合物和PKA酶(6μL)混合并温育30min。通过添加ATP(4μL)启动反应,使得测定中ATP的最终浓度为10μM。在30min温育后,加入10μL ADP-Glo试剂,并且再经过1小时温育后,加入20μL激酶检测缓冲液,并将该混合物再温育45分钟。在光度计上测量发光信号。对照由不含化合物的测定孔组成,使用不添加酶的测定孔测定背景。以剂量-反应形式测试化合物,并在化合物的每个浓度下计算激酶活性的抑制。为了确定IC_{50}(抑制50%酶活性所需的化合物浓度),使用具有可变斜率的S形拟合将数据拟合至%抑制与log_{10}化合物浓度关系的图,并将最大值固定为100%,最小值固定为0%。为了确定Ki值,使用Cheng-Prusoff方程($Ki=IC_{50}/(1+[S]/Km)$)。

[0695] PKA的体外抑制活性以相对于ROCK2的选择性比率报告。通过将PKA的Ki值除以ROCK2的Ki值(方法B)计算选择性比率PKA/ROCK2,并报告在表1中。

[0696] 表1.

[0697]

实施例编号	方法 A		方法 B		Ki PKA/ROCK2比率
	ROCK 1	ROCK 2	ROCK 1	ROCK 2	
1			+++	+++	***
2			++	+++	***
3			++	++	***
4			++	++	
5			++	++	***
6			++	++	***
7			++	+++	
8			++	+++	***
9			++	++	
10			+++	+++	***
11			+++	+++	***
12			++	++	***
13			++	+++	
14			+++	+++	
15	+++	+++	+++	+++	***
16	+++	+++	+++	+++	***
17	+++	+++			
18	+++	+++			
19	+++	+++			
20	+++	+++			
21	+++	+++			
22	+++	+++			
23	+++	+++			
24	+++	+++			
25	+++	+++			

[0698]

26	+++	+++			
27	+++	+++			
28	+++	+++	+++	+++	***
29	++	+++			
30	+++	+++			
31			+++	+++	***
32			+++	+++	***
33	+++	+++	+++	+++	***
34	+++	+++	+++	+++	***
35	+++	+++			
36	+++	+++			
37	+++	+++			
38	+++	+++			
39	+++	+++			
40	+++	+++			
41	+	++			
42	++	+++			
43	+++	+++	+++	+++	
44	+++	+++	+++	+++	
45	+++	+++	+++	+++	
46	+++	+++	+++	+++	
47	+++	+++			
48	+++	+++	+++	+++	
49	+++	+++			
50	++	++			
51	+++	+++			
52	++	++			
53	+++	+++			

[0699]

54	+++	+++			
55			+++	+++	***
56			+++	+++	***
57			+++	+++	***
A			+	+	
B			+	++	***
C			+	+	*

[0700] 其中所述化合物根据其对ROCK1和ROCK2同种型的抑制活性的效力根据以下分类标准进行分类：

[0701] +++:Ki≤3nM

[0702] ++:3<Ki≤30nM

[0703] +:Ki>30nM

[0704] 本发明的化合物有利地显示至少对ROCK2的Ki值等于或低于30nM，优选甚至等于或低于3nM；对两种同种型进一步优选低于30nM，优选甚至等于或低于3nM。本发明的化合物比对比例A和B更有效。

[0705] 此外，本发明的优选化合物表现出相对于PKA的显著选择性。本发明的化合物在ROCK2选择性相对于PKA方面的选择性为至少5倍，优选等于或大于10倍。总之，本发明的化合物比对比例C更具有选择性。

[0706] 根据以下分类标准，就PKA对ROCK2同种型的抑制活性(Ki)的比率而言，根据选择性对化合物进行分类：

[0707] ***:比率≥10

[0708] **:5<比率<10

[0709] *:比率≤5